Hereditary Cancer Genes and Related Risks

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KEYWORDS: hereditary cancer, cancer syndromes, Lynch syndrome, clinical features

INTRODUCTION

The recent explosion of knowledge in the field of cancer genetics dates to 1961 when Henry Lynch described an autosomal dominant pattern of gastrointestinal and gynecological cancers in two large families, coining the condition as "Lynch syndrome" as we know it today. Lynch syndrome affects 1 in 279 individuals, representing the most common cause of hereditary colorectal cancer.[1] It then took another 30 years for the discovery of the two, now well-known genes responsible for the majority of inherited breast and ovarian cancers named BRCA1 and BRCA2. Hundreds of ancient pathogenic variants have been discovered to alter BRCA1/2, which have been established to grossly increase cancer risks and cause the familiar condition known as Hereditary Breast and Ovarian Cancer Syndrome (HBOC). Over the last three decades, there has been an exponential growth of knowledge in how genetics can lead to cancer development, and more recently how genetics can help inform specific treatment for a cancer patient. It began with common cancers striking younger patients with strong cancer family histories, which allowed genetic mapping to identify candidate genes and the establishment of what are now well-known cancer syndromes (i.e., Lynch syndrome, HBOC, Li-Fraumeni). Early genetics work led to the identification of genes associated with hereditary cancer conditions such as Cowden Syndrome, Peutz-Jeghers syndrome, and Hereditary Diffuse Gastric Cancer, among others. Over the past 15 years, we have continued to discover more about cancer genetics and have identified other high and moderate risk genes, such as PALB2, ATM, CHEK2, BRIP1, RAD51C, RAD51D, and BARD1. Our understanding of the early discovered tumor suppressor genes such as BRCA1 and BRCA2 has evolved over time, with risk predictions and disease management being constantly refined as our understanding deepens. The National Comprehensive Cancer Network (NCCN) guidelines have come to reflect this changing landscape of cancer care with recent editions more closely tailoring management based on genetic profile.[2]

The rapidly evolving nature of cancer genetics makes writing a comprehensive review elusive because as data is reported, new research is constantly refining what is known. Therefore, the purpose of this article is to highlight well-established genetic cancer syndromes as well as novel hereditary oncology genes, to review the associated cancer risks, and to emphasize the field's rapid evolution. It should be noted that because the terms "pathogenic" and "likely pathogenic" are clinically interchangeable, for brevity, only the term pathogenic is used throughout this overview.

LYNCH SYNDROME

Some of the most well-established tumor suppressor genes result in a condition called Lynch syndrome when pathogenic variants are present. Also known as hereditary nonpolyposis colorectal cancer (HNPCC), Lynch syndrome is inherited in an autosomal dominant fashion, and therefore commonly evident in each family generation. This hereditary condition is caused by the inheritance of a germline pathogenic variant in one of five mismatch repair genes, MLH1, MSH2, MSH6, PMS2, or less commonly an EPCAM variant which silences MSH2.[1] These pathogenic variants result in increased cancer risks of various types.[3,4] Initially, our understanding of this condition was limited such that medical management recommendations were identical regardless of the altered mismatch repair gene. Continual research over the past decades, with an even greater focus over the past 10 years, helped clarify the unique cancer risks associated with each Lynch syndrome gene. Depending on the gene, the cancer risks can include colorectal (10% to 61%), endometrial (13% to 57%), ovarian (general population to 38%), gastric (general population to 9%), small bowel (general population to 11%), hepatobiliary (general population to 4%), renal pelvis and/or ureter (general population to 28%), pancreatic (general population to 6%), and central nervous system (general population to possibly as high as 7.7%).[5–9] These wide risk ranges are reflective of the varying levels of cancer risk among the five mismatch repair genes. Following the discovery of MSH2 in 1993, cancer risks were initially reported to be the same among Lynch syndrome genes. However, over time it was discovered that each mismatch repair gene results in unique cancer risks or degree of risk. For example, MLH1 carries a colon cancer risk that is

three times that of PMS2[10,11] and as a result of the increased risk of ovarian cancer in MLH1 carriers there are clinical recommendations for prophylactic ovary removal while the evidence remains insufficient in those who carry variants within MSH6 and PMS2.[2,5–9] Fortunately, due to the specific genotype-phenotype relationship among Lynch syndrome genes, medical management recommendations are tailored to each Lynch gene, preventing unnecessary medications, screenings, and surgeries.[2]

Although rare, these genes are also associated with an autosomal recessive conditional known as constitutional mismatch repair deficiency (CMMRD). Biallelic pathogenic variants in MLH1, MSH2, MSH6, or PMS2 cause this childhood cancer predisposition syndrome. Colorectal cancer and cancer of the small intestine have been seen in individuals with this condition prior to age 20 and cutaneous findings are like that seen in individuals with neurofibromatosis type I (café au lait macules). Counseling regarding CMMRD is part of the informed consent process, especially for those who are of reproductive age having a partner with a cancer history suspicious for HNPCC.

HEREDITARY BREAST AND OVARIAN CANCER SYNDROME (HBOCS)

HBOCS is also relatively common and caused by well-established tumor suppressor genes, BRCA1 and BRCA2, which were discovered in 1994 and 1995, respectively. Although reported rates vary, breast cancer risk by age 80 for BRCA1 carriers is estimated to be 72% and 69% for BRCA2 carriers in a 2017 cohort study.[12] Additionally, the same study found the risk of contralateral breast cancer to be approximately 40% for BRCA1 carriers and 26% for BRCA2 carriers.[12] Interestingly, the probability of developing cancer varies within each individual BRCA1/BRCA2 carrier (even within the same family) which is likely attributable to other yet to be identified factors including epigenetic modification or environmental factors that are influencing cancer penetrance. Breast cancer risk has also been discovered to be influenced by polygenic risk scores (PRS), which are a collection of single nucleotide polymorphisms (relatively common genetic variants) that together serve to either increase or decrease risk. Individually, these genetic variants have little impact. However, collectively, the impact may someday be determined large enough to alter medical management recommendations. Current research is also investigating how PRS may modify cancer risks, even within those already found to carry an altered cancer predisposition gene such as BRCA1, BRCA2 or CHEK2.[13] Although identified as the BReast CAncer (BRCA) gene by name, pathogenic BRCA1 and BRCA2 variants are known to increase the risk of additional cancers including ovarian (also fallopian tube and peritoneal cancers) prostate, pancreatic, and cutaneous melanoma. Approximately 48% of BRCA1 and 20% of BRCA2 female carriers will develop ovarian cancer by age 70.[14] BRCA1 and BRCA2 male carriers have an estimated 29% and 60% lifetime risk of prostate cancer, respectively.[15] Patients diagnosed with pancreatic cancer are more likely than the general population(1.6%) to have a pathogenic variant in BRCA1 (11%) and BRCA2 (17%).[16,17] BRCA2 may have a link in patients with cutaneous melanoma although studies have produced conflicting results.[18]

Pathogenic variants in BRCA2 gene in their recessive form have important reproductive implications as well. In addition to the gene's association with autosomal dominant HBOCS, this gene is also linked to autosomal recessive Fanconi anemia.[19] Far less common, but still reported, Fanconi anemia is also connected to pathogenic variants in the BRCA1 gene.[20]

Different types of autosomal recessive Fanconi anemia are linked to other hereditary cancer genes; however, the type associated with biallelic pathogenic BRCA2 variants, Fanconi anemia type D (FANCD1), is particularly severe in comparison. Characteristics include bone marrow failure, short stature, abnormal skin pigmentation, developmental abnormalities in multiple organ systems, and early-onset cancers (acute leukemia and solid tumors). The cumulative probability for malignancy is estimated to be up to 97% by age 6.[19,21-24] Therefore, discussions with a mutation carrier of reproductive age include the option of testing his/her partner to clarify their future children's risk of Fanconi anemia.

COWDEN SYNDROME

This is a rare autosomal dominant disorder with an incidence of approximately 1 in 200,000 resulting from germline variants in the PTEN gene.[25] It is notably associated with hamartomas,[26] along with a higher incidence of breast cancer (60%),[27] thyroid disease (30–68%),[28,29] thyroid cancer (3–10%),[26] and other malignant and nonmalignant features. One study found the cumulative lifetime risk of any type of cancer in patients diagnosed with Cowden syndrome was 85% overall, with females found to have an increased cancer risk compared with males.[30]

LI-FRAUMENI SYNDROME (LFS)

LFS is another well studied but rare genetic cancer syndrome and is caused with a germline pathogenic variant in the TP53 gene.[31] This cancer syndrome is generally associated with a devastating lifetime cancer risk of essentially 100% and often strikes at a young age.[32] The breadth of associated cancer risk spans from soft tissue sarcomas, breast cancer, colon cancer, adrenocortical carcinoma, brain tumors,[33] gastric cancer,[34] acute lymphoblastic leukemia,[35] and possibly melanoma.[36] Red flags for this condition include breast cancer diagnosed prior to the age of 31, a diagnosis or family history of LF associated tumors before age 45, or pediatric

acute lymphoblastic leukemia.[37] Interestingly, large panel testing is uncovering families who do not fit this expected phenotype, highlighting the value in multi-gene panel testing as well as ongoing research of what are thought to be rare cancer syndromes.

PALB2

Similar to BRCA1/2 genes, PALB2 is considered a high-risk gene in its association with hereditary breast cancer. It was originally identified as a BRCA2-interacting protein critical for BRCA2 function and subsequently discovered to encode proteins involved in BRCA1 and RAD51 pathways. It is a partner and localizer of BRCA2, and deleterious PALB2 variants increase similar cancer risks.[38] Inherited in an autosomal dominant fashion, loss of function variants are associated with an approximate 35% increased risk of breast cancer by the age of 70 compared to women without a pathogenic variant in this gene.[38] There is strong evidence that pathogenic PALB2 variants are also associated with a small increased lifetime risk of ovarian cancer (up to 5%) as well as pancreatic cancer (5–10%).[39] There is also emerging evidence for the increased risk of male breast, prostate, and possibly colorectal cancer.[40] However, more research is needed. Pathogenic variants in the PALB2 gene are also associated with autosomal recessive Fanconi anemia type N (FANCN), giving it the same reproductive considerations as BRCA1 and BRCA2 carriers.[38]

ATM

Research shows pathogenic ATM variants are associated with moderately increased risk for the development of breast cancer in women. A meta-analysis suggests the lifetime risk for breast cancer by age 80 in those with pathogenic ATM variants is 33%.[41] Pancreatic cancer risk is also increased in ATM carrier to a lifetime risk of approximately 5% to 10% compared to the 1.6% general population risk.[42] Lastly, studies connect this gene with an elevated risk of ovarian cancer (2–3%); however, in comparison, this is much lower than the 20–48% risk associated with pathogenic variants found in BRCA1 and BRCA2.[43]

ATM variants can result in the development of autosomal recessive ataxia telangiectasia, which is typically identified in early childhood with the development of progressive cerebellar ataxia. Ataxia telangiectasia is also associated with oculomotor apraxia, telangiectasias of the conjunctiva, and frequent illness due to immunodeficiency. Childhood leukemia and lymphoma are the most common malignancies.[44]

CHEK2

Inherited in an autosomal dominant fashion, pathogenic variants in the cell cycle checkpoint kinase 2 (CHEK2) gene have a cumulative lifetime risk for breast cancer estimated to range from 28% to 37%, categorizing it as another moderate risk gene.[43,45] Although the risks remain unclear, studies have shown CHEK2's possible connection with colon, thyroid, and prostate cancers, among others.[46,47]

BRIP1

Pathogenic variants in this gene have a clear association with autosomal dominant risk for ovarian cancer and type J autosomal recessive Fanconi anemia (FANCJ).[48] Breast cancer risk has been suggested, but not supported by subsequent research. The lifetime risk for developing ovarian cancer by age 80 is estimated to be 5% to 10%.[49]

RAD51C/RAD51D

These genes are involved in homologous recombination and DNA repair. Pathogenic variants in RAD51C and RAD51D were initially identified as causing an increased risk for ovarian cancer, which is estimated to be 10–15% and 10–20% respectively. More recent studies have shown a strong association with an increased lifetime risk of female breast cancer (20–40%) changing breast screening recommendations.[50] RAD51C also has reproductive implications given its association with type O autosomal recessive Fanconi anemia (FANCO).[51]

BARD1

Pathogenic variants in the BRCA1-associated RING domain 1 (BARD1) gene are known to be associated with an increased risk of breast cancer. The risks were recently refined to 20–40%.[52]

CONCLUSION

We acknowledge this review does not include descriptions of all hereditary cancer syndromes and genes. Therefore, a more exhaustive list is summarized in **Table 1,** which includes inherited cancer genes associated with hereditary colorectal polyposis (APC, MUTYH, and others) as well as genes related to rare inherited cancer syndromes such as Hereditary Diffuse Gastric Cancer Syndrome (CDH1), Birt-Hogg-Dube Syndrome (FLCN), and Von Hippel-Lindau Syndrome (VHL).

The progression of knowledge surrounding hereditary cancer syndromes continues to change our understanding of cancer risk for all those affected. As a result, there are positive influences on clinical management. Through genetic awareness and targeted screening cancers can be diagnosed earlier, intervened on, and even prevented.[53] As cancer genetic testing becomes more common due to increased media and medical attention, as well as from the rapid

Table 1. Hereditary Cancer Syndromes

Gene	Disorder	MOI	Associated Cancers/Clinical Features
MLH1, MSH2, MSH6, PMS2, EPCAM	Lynch syndrome	AD	**Cancers:** CRC, endometrial, ovarian, gastric, renal pelvis and/or ureter, bladder, small bowel, pancreas, biliary tract, CNS, skin
APC	Familial adenomatous polyposis (FAP) Attenuated-FAP (AFAP)	AD	**Clinical Features:** Polyposis **Cancers:** CRC, small intestine, stomach, hepatoblastoma, pancreatic, thyroid, brain Other manifestations (FAP only): desmoid tumors, osteomas, CHRPE
MUTYH	Polyposis syndrome	AR	**Clinical Features:** Colorectal and extracolonic polyps **Cancers:** CRC, duodenal
AXIN2, BMPR1A, GREM1, POLE, POLD1	Polyposis syndromes	AD	**Clinical Features:** polyposis **Cancers:** CRC
NTHL1	Polyposis syndrome	AR	**Clinical Features:** polyposis **Cancers:** CRC
BRCA1, BRCA2	HBOC	AD	**Cancers:** Breast, ovarian, pancreatic, prostate, melanoma
TP53	Li Fraumeni syndrome	AD	**Cancers:** premenopausal breast, soft-tissue sarcoma, osteosarcoma, CNS tumor, adrenocortical carcinoma
PTEN	Cowden syndrome		**Clinical features:** macrocephaly, thyroid lesions, hamartomatous polyps, lipomas, cutaneous lesions **Cancers:** breast, endometrial, thyroid, renal
CDH1	HDGC	AD	**Cancers**: diffuse gastric, lobular breast
PALB2	HBOC	AD	**Cancers**: breast, ovarian, pancreatic
ATM	HBOC	AD	**Cancers**: breast, ovarian, pancreatic
CHEK2	Hereditary breast	AD	**Cancers:** breast, colon
BRIP1	Hereditary ovarian	AD	**Cancers:** ovarian
RAD51C	HBOC	AD	**Cancers**: breast, ovarian
RAD51D	HBOC	AD	**Cancers**: breast, ovarian
BARD1	Hereditary breast	AD	**Cancers:** breast
FLCN	Birt-Hogg-Dube	AD	**Clinical features:** lung cysts, pneumothorax, renal tumors, skin lesions (fibrofolliculomas/trichodiscomas) **Cancers**: renal
MEN1	MEN1	AD	**Clinical features:** endocrine tumors
RET	MEN2	AD	**Cancers:** medullary thyroid
SDHx	PGL/PCC	AD	**Clinical features:** paraganglioma, pheochromocytoma
VHL	von Hippel-Lindau syndrome		**Clinical features:** hemangioblastoma, pheochromocytoma, renal cysts, pancreatic cysts, endolymphatic sac tumors. **Cancers**: renal

MOI: Mode of Inheritance; AD: autosomal dominant; AR: autosomal recessive; CRC:colorectal cancer; CNC:central nervous system; GI: gastrointestinal; HBOC: Hereditary breast and ovarian cancer syndrome; HDGC: Hereditary Diffuse Gastric Cancer; MEN1; Multiple Endocrine Neoplasia type 1; MEN2: Multiple Endocrine Neoplasia type 2; PGL/PCC: Hereditary paraganglioma-pheochromocytoma syndrome

influx of direct-to-consumer genetic testing, the greater the demand on healthcare practitioners to increase their knowledge and resources to access genetic services. Although access to updated national guidelines greatly assist practitioners in understanding who is at risk for an inherited cancer syndrome and how to manage those testing positive, the interpretation and management are nuanced and complex. Therefore, additional methods of service delivery for pre-test education continue to be investigated to accommodate the increasing number of individuals qualifying for genetic testing with the small number of trained professionals available. As this gap widens it becomes more important to stay current in this rapidly advancing field to fulfill the duty of best clinical care and to address practice limitations with education, available resources, and patient referral if deemed necessary.

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Disclosures

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