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The Role of Genetic Instability in Familial Cancer Syndromes

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Abstract

Familial cancer syndromes have been model diseases in order to understand the mechanisms and process of neoplastic transformation in a number of solid tumors, including colorectal, breast, ovarian, gastric and others. Basic experimentation in hereditary cancer genetics has been interpolated into important hypotheses about carcinogenesis in humans. Overtime, evolution of molecular genetics and clarification of the functional structure of the human genome has led to the identification of familial cancer-causing germline mutations. At present, approximately 100 genes (corresponding to 0.5% of all genes in the human genome) exhibit mutations with low or high penetration, which underlie hereditary cancer syndromes. Furthermore, sequencing of complete cancer genomes across a wide range of human tumors has shown that common human cancers possess numerous somatic mutations in their genomes that might contribute to the neoplastic process. This review discusses the role of genomic instability in tumorigenesis through the model of familial cancer syndromes and their potential implications in the clinic.

Keywords: Genetic instability; Familial cancer syndromes; DNA repair

Introduction

Familial cancer syndromes constitute invaluable research tools for understanding the nature and origin of cancer. Recent advances in cancer genetics involve the identification of novel genes with moderate risk to cause cancer, after synergism with particular environmental factors, and therefore reinforcing the genetic component in relation to cancer predisposition. The identification of specific genes associated with hereditary cancer risk has provided the necessary information for the complete characterization of familial cancer syndromes and enabled their direct diagnosis through genetic analysis. The most common cancers for which such diagnostic tests are available include hereditary tumors of the colon, breast, ovary, endometrium and melanoma. More specifically, the most prevalent hereditary syndromes correlated with these tumors are hereditary nonpolyposis colorectal cancer (HNPCC), which is linked to pathogenic mutations in one of the mismatch repair (MMR) genes *MLH1, MSH2, MSH6* and *PMS2*, Familial Adenomatous Polyposis (FAP) caused by high-penetrant mutations within the *APC* gene, Hereditary Breast/Ovarian Cancer linked to mutations within *BRCA1* and *BRCA2* genes and familial melanoma, associated with the *CDKN2A* gene [1-2]. Apart from these susceptibility genes associated with specific types of cancer, systematic screening of the entire genome through new high throughput technologies has identified some 400 genes that are somatically mutated in cancer and are likely to contribute to carcinogenesis [3].

Genetic basis of familial cancer syndromes

Cancer arises through mutations that occur in critical genes within a single cell, allowing it to escape normal controls of growth and proliferate until it becomes a clinically evident tumor. It is well known that the vast majority of cancers present as isolated cases (sporadically). In patients with sporadic cancer, multiple common alleles can increase cancer risk, but each one of them has a weak effect [4]. In sporadic tumor progression, an early mutation usually presents as the initial event; however, it is unlikely that it will affect multiple molecular pathways of intracellular signaling or inactivation of regulatory systems, which constitute hallmarks of cancer [5]. Following this event, additional mutations occur and result in uncontrolled proliferation of affected cells. During tumor progression, cells with the most competing mutations predominate. Over time, mutations in genes responsible for genomic integrity promote tumor progression. Typically, a tumor arises through a series of multiple alterations in the genome with various effects on the cell, which lead to loss of normal cellular functions. Most of the genes responsible for the development of a malignancy fall into two categories: oncogenes and tumor suppressor genes. When a mutated copy of a gene confers a growth advantage to a cell even in the presence of a normal (wild-type) copy of the gene, it has the potential to act as an oncogene [6]. Conversely, when carcinogenesis results from loss of the normal function of a gene, it is considered a tumor suppressor gene. A mutation in a single tumor suppressor gene is not by itself deleterious to the cell because there are two copies of each chromosome. Since each tumor suppressor gene, therefore, has a "backup" copy to provide its function if the other copy is inactivated by a mutation, both copies must be inactivated for the function of the gene to be lost and for malignant transformation to proceed [5,7].

On the other hand, familial cancer syndromes represent disease entities where affected members inherit a defective copy of one of the genes responsible for the maintenance of genomic integrity [6]. In a normal cell of such a member, once the corresponding non defective allele undergoes a mutation or a functional reduction due to amplification of the inherited defective allele, the process of destabilization of the genome commences. Consequently, the rate of accumulation of genomic damage in daughter cells is much higher than the one which occurs with environmental damage alone. Therefore, what distinguishes familial form sporadic cancer is that in familial cancer, one additional event is adequate to trigger genomic destabilization; on the contrary, in normal individuals, two separate events are necessary for the elimination of the function of

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both the maternal and the paternal alleles. Interestingly, inherited mutations in oncogenes are relatively uncommon; such mutations, by removing normal controls over cell growth, are usually lethal during embryogenesis. However, there is much less selective pressure against germline mutations in tumor suppressor genes, because a wild-type copy from the other parent allows the embryo to develop normally. It is only later in a person's lifetime, when the remaining copy is lost or mutated, that a cell is subjective to malignancy. Thus, most familial cancer syndromes are the result of inherited mutations in tumor suppressor genes rather than proto-oncogenes [6,8].

Familial cancer syndromes are directly or indirectly associated with genomic instability. Diverse processes contribute to the maintenance of genomic integrity, DNA repair mechanisms, activation of checkpoint systems that are necessary for temporary cell cycle arrest until DNA repair is completed and activation of programmed cell death,

Hereditary breast cancer also known as apoptosis, in case of inefficient repair of DNA damage. Therefore, genes responsible for familial cancer syndromes code for proteins-components of complex regulatory pathways that participate in cell response to DNA damage and prevention of chromosomal rearrangements throughout the cell cycle [9]. Familial cancer syndromes progress through networks initially driven by the specific genetic effect; this in turn selects for later routes amenable to the defect. DNA damage cell response and DNA repair mechanisms are illustrated in more detail in Figures 1 and 2. In this review, we aim to describe in detail the most frequent familial cancer syndromes and their association with genetic instability.

The two genes most commonly mutated in hereditary breast cancer are tumor suppressor genes *BRCA1* and *BRCA2*. Affected individuals inherit one mutated allele and do not display apparent phenotypic abnormalities beyond increased lifetime risk for cancer, which is estimated to be as high as 85% for breast cancer. Several studies suggest the prevalence of *BRCA1/2* mutations in general population to be 1:400 [10-11]. However, founder mutations exist in certain populations, for example those of Ashkenazi Jewish descent, in whom the prevalence of three specific mutations (185delAG and 5382insC in *BRCA1* and 6174delT in *BRCA2*) is as high as 1:40 [12].

The *BRCA1* gene is located on chromosome 17q21 and *BRCA2* on chromosome 13q12.3. They encode very large proteins, which are found in the nucleus of proliferating cells in most tissues. *BRCA1* and *BRCA2* proteins are fundamental components of DNA damage response machinery; their role involves enabling the accurate repair of the most hazardous DNA lesions, named DNA double-strand breaks (DSBs) by Homologous Recombination (HR-Figure 1), [4,5]. Cells deficient in either gene accumulate characteristic cytogenetic abnormalities indicative of deficiency in HR mediated DNA repair. In addition, *BRCA1* protein participates in cell checkpoint control, chromatin remodeling, centrosome duplication, transcriptional regulation and protein ubiquination. The various domains of *BRCA1* allow it to integrate signals from upstream DNA-damage-sensing proteins such as *ATM* and *Chk2*, and to recruit phosphoproteins such as *BACH1* and *PALB2* [13]. On the other hand, *BRCA2* protein forms a complex with *RAD51* enzyme, which binds to the break of one DNA strand at the damaged lesion and mediates base recombination. However, it does not appear to have the same damage-sensing and recruitment capabilities as *BRCA1* suggesting that *BRCA2* is an effector, whereas *BRCA1* is more of a coordinator that mediates various responses to DSBs.

BRCA1 and *BRCA2* mutations increase the relative risk of breast cancer by 10-20-fold, whereas cumulative breast cancer risk penetrance

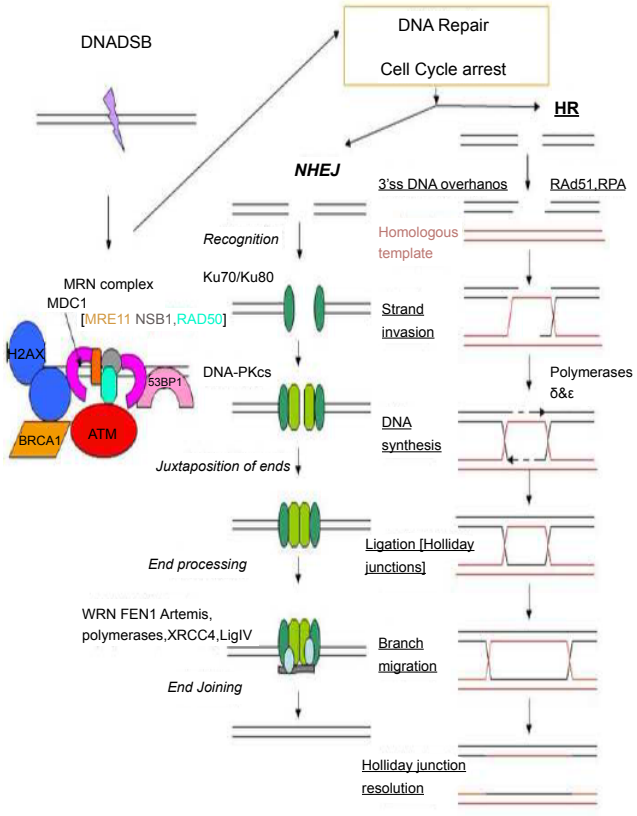

Figure 1: Model for initial response of the cell to a Double Strand Break (DSB). A DNA DSB is initially recognized by the proteins ATM, MDC1, 53BP1, BRCA1 and the damage recognition complex MRN, which consists of the subunits Mre11, NBS1 and RAD50. Those proteins activate complex signal transduction pathways that lead to cell cycle arrest and repair of DNA damage by Homologous Recombination (HR) or Non Homologous End Joining (NHEJ) mechanisms.

up to the age of 75 has been found to be 57% for *BRCA1* and 49% for *BRCA2* gene [14]. In some studies, breast cancer lifetime risk is reported as high as 60-80%, which is substantially higher than the lifetime risk of general population in western countries (12%) [15].

Several studies focus on the differences in pathology between breast cancer caused by *BRCA* mutations and its sporadic counterpart [16-17]. More specifically, research has shown that the hitological subtype of medullary carcinoma with high-grade features is associated with a more favorable prognosis in *BRCA1* carriers. There is also a higher prevalence of invasive lobular or tubular carcinoma in *BRCA2* familial settings. Differences are also evidenced in *BRCA1* and *BRCA2* mutation-positive breast cancers, given the fact that breast cancers of *BRCA1* mutation carriers are frequently estrogen receptor negative, in contrast to *BRCA2* mutation breast cancers that are more frequently estrogen receptor positive [18]. Interestingly, the 10-year survival rates for *BRCA1* and *BRCA2* mutation carriers are similar to those of women with sporadic breast cancer.

Of note, *BRCA* mutations are not encountered in sporadic breast cancer, even though loss of Wild Type (WT) allele and *BRCA* protein are frequent events. On the contrary, epigenetic alterations, such as hypermethylation of *BRCA1* promoter, are implicated in the *BRCA1* gene inactivation process [15].

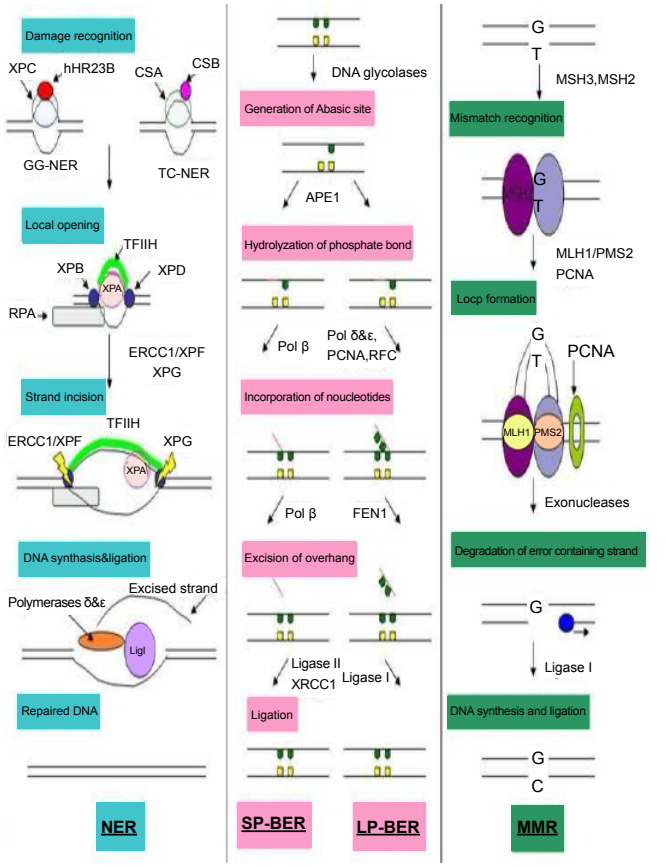

Figure 2: Model for DNA repair mechanisms Nucleotide Excision Repair (NER), Base Excision Repair (BER) and Mismatch Repair (MMR). NER removes mutations resulting from UV induced DNA damage, BER is responsible for removal of small base lesions and MMR corrects errors arising during DNA replication.

Other hereditary breast cancer syndromes

TP53 mutations: *TP53* gene is located on chromosome 17p13.1 and the encoding protein plays a crucial role in cell cycle regulation. *P53* protein, which is frequently referred as 'guardian of the genome', serves as a check point control, helping to determine whether damaged cells undergo cell cycle arrest for repair or apoptosis. Consequently, *TP53* mutations may result in damaged cells bypassing this checkpoint and potentially going on to proliferate, colonize and become a malignant tumor [19].

TP53 mutations are implicated in the Li-Fraumeni syndrome (LFS), a rare autosomal dominant condition. Although most patients with documented *TP53* mutations have an extensive family history of cancer, including childhood cancer, de novo mutations are not infrequent. Founder mutations may exist in certain populations, most notably the R337H mutation in Brazil, which may be seen in up to 0.3% of the population [20]. Germline mutations in the *TP53* gene are thought to account for only a small fraction of hereditary breast cancers cases and for less than 1% of all breast cancer cases. Unlike cases of sporadic breast cancer, which most commonly occur in postmenopausal women, the vast majority of patients with germline *TP53* mutations who develop breast cancer do so by age 50, with a mean age of 37. A woman with LFS is thought to have a lifetime breast cancer risk of 90% [21-22].

PTEN mutations: The *PTEN* gene is located on chromosome 10q23.3. The exact function of the gene is unknown, but it is known that the *PTEN* protein is a phosphatase that down-regulates the phosphatidylinositol-3-kinase *(PI3K)* signal transduction cascade, acting as a tumor suppressor and growth regulator [23]. Dysfunctional *PTEN* leads to the inability to activate cell cycle arrest and apoptosis, resulting in abnormal cell survival. Recent studies have shown that loss of *PTEN* sensitizes tumors to the inhibition of *mTOR* (Mammalian Target Of Rapamycin) and clinical trials with *mTOR* inhibitors are very promising for breast cancer [24].

PTEN mutations are the cause of Cowden syndrome (CS). CS is an autosomal-dominant, highly penetrant genetic disorder. About half of the 20% of patients who have CS without a detectable *PTEN* mutation may instead have a mutation in the *PTEN* promoter. More than 90% of individuals with *PTEN* mutations are believed to manifest some feature of the syndrome (although rarely cancer) by age 20, and by age 30 nearly 100% of carriers are believed to have developed at least some of the mucocutaneous signs. Women with CS have approximately a 67% to 76% risk for benign breast disease, such as fibroadenomas and fibrocystic breast disease, and a 25% to 50% lifetime risk for breast cancer. The peak incidence of breast cancer in women with CS occurs between the ages of 38 and 46 years. CS, though undoubtedly rare (it is estimated that fewer than 1% of hereditary breast cancer families are caused by CS), may be under-recognized, as women who present with breast cancer and subtle skin findings or common associated features (ie, fibroids or fibrocystic breast disease) may not be recognized as potentially part of the Cowden's spectrum. In patients with a *PTEN* gene mutation and breast cancer, risk of bilateral and multifocal cancer is increased [25].

ATM mutations: *ATM* is a serine/threonine kinase that mediates checkpoint regulation and HR by phosphorylating a number of proteins; without it, cells display aberrant cell-cycle progression and increased chromosomal breakage, especially when exposed to ionizing radiation. It delays cell cycle progression between phases G1 and G2 in the presence of DNA damage. In addition, it phosphorylates protein *p53* and the *BRCA1* tumor suppressor gene [26].

ATM mutation is responsible for the Ataxia-Telangiectasia (AT) disorder, which is characterized by neurological deficits and immunodeficiency [27]. It is known that 10-20% of patients with homozygous *ATM* defect develop malignancies, such as lymphomas and leukemias. Case control studies have shown that carriers of the mutant *ATM* allele do not usually display the classic manifestations of AT, but they have an increased by 2-fold risk of breast cancer, which also presents at a younger age. More specific, Renwick et al. identified 12 deleterious mutations in 443 affected cases compared to two out of 521 controls resulting in an estimated relative risk of 2.37. Overtime, several studies have identified numerous variants of AT mutation that increase breast cancer risk [28].

BRIP1 and PALB2 mutations: The *BRIP1* gene, which is located on chromosome 17, encodes a DNA-dependent ATPase and helicase which binds directly to *BRCA1*. *PALB2* protein, located on chromosome 16, regulates stabilization of *BRCA2* protein. Furthermore, like *BRCA2*, it is involved in HR, which includes the exchanging of nucleotide sequences between the two DNA strands [29].

The *BRIP and PALB2* genes are two out of 13 genes associated with Fanconi anemia, an autosomal recessive disorder, which is characterized by developmental abnormalities, bone marrow failure and increased risk of malignancy. It is estimated that heterozygous carriers of BRP1 mutation have a 2-fold risk of breast cancer, especially

for women younger than 50 years of age. Heterozygous carriers of *PALB2* mutation have been found to have a 2 to 6-fold breast cancer risk. However, a mutation in those genes does not always involve breast cancer development [30].

CHEK2 mutations: *CHEK2* is a firmly established moderate-penetrant predisposition gene for breast cancer, as well as for a number of other malignancies, including prostate and colon. *CHEK2* encodes a threonine/serine kinase responsible for arresting mitosis in response to DNA damage by phosphorylating a number of proteins involved in checkpoint control including *BRCA1, p53* and *Cdc25c*. A founder mutation, 1100delC, which abrogates the kinase domain, was discovered in Northern European populations [31].

The 1100delC mutation of the *CHEK2* gene is associated with a 2 to 3-fold increased risk of breast cancer [30]. Additionally, some data suggest that *CHEK2* mutation carriers have a higher risk of breast cancer relapse and worse prognosis. Although responsible for 1% of familial breast cancer, *CHEK2* mutations have been identified in approximately 5% of breast cancer cases that do not belong to the *BRCA* family [32].

Hereditary ovarian cancer

BRCA1 and BRCA2 genes: Mutations in genes *BRCA1* and *BRCA2 (BRCA1/2)* are implicated in the majority of hereditary ovarian cancer cases [33]. The proportion of ovarian carcinoma that is hereditary for a specific population varies based on the frequency of the responsible genes [34].

Family history of ovarian cancer is one of the strongest risk factors for the development of ovarian cancer and a genetic predisposition caused by a mutation in *BRCA1* can confer up to a 39–46% lifetime chance of developing the disease (as compared to 1.4% in the general population). *BRCA2* penetrance for ovarian cancer is lower, since lifetime risk approaches 12-25%, with an average age of diagnosis at 60 years [15]. Approximately 8–13% of women diagnosed with epithelial ovarian cancer have a germline mutation in either *BRCA1* or *BRCA2* [3–5].

The majority of ovarian cancer cases associated with *BRCA1/2* mutations is diagnosed at an advanced stage and has usually high-grade histological features. Histological subtype varies and includes serous, endometrioid and clear cell carcinomas [35]. Furthermore, it has been shown to have a more favorable prognosis over sporadic cases, probably related to higher sensitivity to platinum chemotherapy [36]. In addition, several studies have demonstrated that targeted therapy with *PARP* inhibitors is more efficacious in *BRCA*-deficient patients [37-38]. More specifically, exposure of tumor cells to *PARP* inhibitors will lead to the accumulation of spontaneously occurring single-strand DNA breaks which cannot be repaired by *PARP*-dependent base excision repair (BER-Figure 1). After DNA replication, these single-strand breaks will be converted to double-strand DNA breaks which are usually repaired by HR. However, cells missing both working alleles of *BRCA1* or *BRCA2*, as is seen in *BRCA*-associated tumors, are incapable of performing HR, causing accumulation of multiple double-strand DNA breaks that ultimately result in cancer cell death.

Genes associated with Fanconi anemia and breast cancer: As previously mentioned, *BRCA* genes are involved in HR. Specifically, they are integral for double strand DNA repair process that occurs during the G2 phase of the cell cycle. Apart from *BRCA* genes, mutations in other genes, such as components of the Fanconi anemia pathway also result in cells with defective homologous recombination similar to that in cells with *BRCA* mutations [23]. At a cellular level, FA is associated with a high degree of genomic instability such as chromosomal fragility and chromatid interchanges [22]. FA cells are highly sensitive to DNA crosslinking drugs, including mitomycin C and cisplatin. This hallmark is currently used as a clinical diagnostic test and implies a defect in the DNA repair pathway due to the germinal genetic alteration. There are 14 genes associated with FA; proteins encoded by these genes take part in recognition and repair of damaged DNA [39]. In 2002, Howlett et al. identified the *FANCD1* gene as the *BRCA2* gene, establishing an important connection between the FA genes and ovarian cancer. Biallelic mutations in the *FANCD1* gene would result in a FA phenotype, while individuals with heterozygous mutations were associated to familial breast and ovarian cancer. Biallelic *BRCA1* mutations have not been described. Consequently, *BRCA1* is not a FA gene, but a key component of the FA pathway.

PALB2 gene: The *PALB2* gene, which is associated with elevated cancer risk, is also implicated in ovarian cancer. Casodei et al. sequenced the *PALB2* gene in high risk breast cancer families, identifying mutations in 33 of 972 of them [40]. Out of these 33 families, 18 had a family member with ovarian cancer, who was a *PALB2* mutation carrier. Although ovarian cancer was more common among relatives of *PALB2* carriers, these results were not statistically significant [40]. Therefore, *PALB2* gene penetrance for ovarian cancer has not been confirmed.

RAD51C gene: *RAD51C* gene is a substantial HR component and a biallelic mutation causes a FA-like phenotype [41]. *RAD51C* gene has been studied as a possible breast and ovarian susceptibility gene in 1100 high risk families negative for *BRCA1/2* mutations [42]. Genetic mutations have been found in 1.3% of the families with both breast and ovarian cancer, but in none of the families with breast cancer only. Within the *RAD51C* mutation-associated pedigrees, mean age at cancer diagnosis was 60 years for ovarian cancer and 53 years for breast cancer [42].

RAD51D gene: The *RAD51D* gene was recently investigated in 911 families with breast and ovarian cancer which were *BRCA1/2* negative. Inactivating mutations were found in 0.9% of studied families. Of note, a higher prevalence of mutations was observed in families with more cases of ovarian cancer. The relative risk of ovarian cancer in women with *RAD51D* mutations was 6.3, whereas the relative risk for breast cancer was not significantly increased [43].

BRIP1 gene: Similarly to breast cancer, *BRIP1* gene mutations have been also found to increase ovarian cancer risk. A rare frameshift mutation in *BRIP1* gene, c.2040_2041insTT, confers an increased risk of ovarian cancer, but not of breast cancer. On the contrary, another rare frameshift mutation, c.1702_1703del, has been associated with an elevated risk of both ovarian and breast cancer [44].

Familial colorectal cancer syndromes

Among common malignancies, colorectal cancer is characterized by a large proportion of familial cases. It has been estimated that almost 30% of colon cancer cases arise in the setting of familial colorectal cancer (CRC) syndromes. Approximately 5% of cases are associated with highly penetrant inherited mutations and well-characterized clinical presentations, whereas 20-30% of inherited CRCs are not completely understood [45].

Lynch Syndrome or Hereditary Non Polyposis Colorectal Cancer (HNPCC): Lynch syndrome is an autosomal dominant disorder which predisposes to several types of cancer, especially colon and endometrial

cancer. It accounts for 2-4% of all CRCs [46]. It usually involves only single colorectal adenomas or carcinomas that cannot be clinically distinguished from sporadic tumors [47]. HNPCC patients frequently develop colorectal cancer before the age of 50, and approximately one-third of patients develop another HNPCC-typical tumor within 10 years. Histologically, neoplasms are poorly differentiated, mucinous and with a high proportion of infiltrating lymphocytes [48].

Lynch Syndrome is a result of germline mutations in a class of genes involved in DNA Mismatch Repair (MMR), a DNA repair mechanism responsible for correcting errors arising during DNA replication. These genes include *hMSH2*, *hMLH1*, *hMSH6* and *hPMS2*. MMR is crucial for the maintenance of genomic integrity by correcting single base mismatches and insertion-deletion loops that are formed during DNA replication. Evidence of disrupted DNA repair in malignant cells includes lengthening of short DNA replication sequences, known as microsatellites. The biomarker for DNA repair deficiency is the presence of widespread frameshift mutations evidenced by replication errors (RERs) in microsatellite markers, and known also as DNA microsatellite instability (MSI). Cancers with instability in less than 30–40% of markers are termed as MSI-L and those with higher levels as MSI-H [49].

hMSH2 and *hMLH1* gene mutations account for 90% of cancer cases attributed to Lynch syndrome. On the contrary, *hMSH6* mutations are responsible for 10% of cases and *hPMS2* mutations are rare [50]. Differences in relative cancer risk have been reported among MMR gene mutation carriers. For instance, patients with *hMSH6* mutation are more likely to present with endometrial cancer [51]. The most striking difference is found in *hPMS2* mutation carriers; it has been recently demonstrated that colon cancer risk reaches 15-20% and endometrial cancer risk approaches 15%. These risk estimates are substantially lower compared to other MMR genes [52].

Recently, germline mutations of the *EpCAM* gene, upstream of *hMSH2* gene and responsible for epithelial cell adhesion, were found in a subgroup of patients with Lynch syndrome. These patients develop multiple cancers at a young age, similarly to *hMSH2* mutation carriers; although no MMR gene mutations have been identified. In addition, hypermethylation of *hMSH2* promoter has been detected, which is an uncommon finding for CRC. This subgroup of patients was subsequently found to have germline deletions in the 3' region of *EPCAM* gene, which results in gene *EpCAM-hMSH2* fusion transcripts. It has been estimated that these deletions are responsible for 6.3% of cases with Lynch syndrome [53-54].

Familial Adenomatous Polyposis (FAP*):* Familial adenomatous polyposis (FAP) is an autosomal dominant condition and the second most common type of inherited CRC. It accounts for less than 1% of all CRC cases. Classic FAP is characterized by hundreds to thousands of colonic adenomas beginning in adolescence. There is a near 100% lifetime risk of CRC in untreated individuals at an average age of 39 years. Attenuated FAP is a less severe form of the condition, characterized by fewer adenomatous polyps, a later age of onset of adenomas and CRCs, and a lower lifetime risk of developing CRC [55].

Classic and attenuated FAP arise from germline mutations of the adenomatous polyposis coli *(APC)* gene located on chromosome 5q21-q22. More than 1,000 unique *APC* variants have been identified that generally because a mutated gene product, because of either frames shifts or premature stop codons. *APC* protein is a tumor suppressor protein, component of *WNT* pathway. New or *de novo* mutations in *APC* are implicated in approximately 25% of cases with FAP. Additionally, 20% of patients with *de novo APC* mutations display somatic mosaicism (the condition where >2 cell lines in an individual differ genetically) [56]. The location of the mutation within the *APC* has been associated with the severity of colonic polyposis and the degree of cancer risk [57].

Peutz-Jeghers syndrome (PJS) and Juvenile Polyposis Syndrome (JPS): PJS and JPS are hamartomatous polyposis conditions that are both associated with an increased risk for CRC and other malignancies. They are characterized by the presence of hamartomatous polyps throughout the GI tract [58].

PJS is caused by mutations in the *STK11* gene; JPS results from mutations in *SMAD4* and *BMPR1A* genes. Disease associated mutations have been found in as many as 70% of patients with PJS, but in only 40% of patients with JPS. Patients with PJS have an 81-93% lifetime risk of cancer, including a 70% risk of GI cancer and a 50% risk of breast cancer [59]. The lifetime risk of CRC in individuals with JPS is estimated to be approximately 40% [60].

Other familial colorectal cancers: Overtime, several different groups of less penetrant but more common causes of susceptibility to CRC have been identified, based on family history and population studies. These include high risk familial, non- syndromic colon cancers and common familial risk colon cancers defined by family history. Population studies have also detected genetic factors associated with increased risk for CRC that include low-penetrant susceptibility loci (identified in genome studies) and specific polymorphisms. Interestingly, low-penetrant susceptibility loci have additive effects on CRC risk, whereas CRC risk associated with polymorphisms is affected by gene-gene and gene-environmental interactions [45].

High risk familial non-syndromic colon cancers include colon cancers that meet the criteria for Lynch syndrome but lack MMR deficiency; they have therefore been termed familial colorectal cancer type X. Studies have shown that CRC risk is lower than in Lynch syndrome and that CRC diagnosis averages 10 years later [61]. Additionally, tumors do not exhibit MSI, and there is no increased incidence of extracolonic malignancies. Identification of relevant genes responsible for CRC type X will allow the development of genetic testing and surveillance guidelines for these patients.

Individuals who have a first-degree relative with CRC diagnosed after age 50 years have a 2–3-fold increased risk for this malignancy. Population-based studies have demonstrated that approximately 20% of all CRC cases occur in a higher risk setting; CRC before age 50 or a first-degree relative pair with CRC [62]. Furthermore, having one first-degree relative with CRC before age 45 years, or having two first-degree relatives affected with CRC confers a 3–6-fold CRC risk compared to the general population [63].

Variants identified at low-penetrant susceptibility loci are not mutations that would be predicted to code for non-functional proteins. They may affect gene expression through non-coding changes or lead to linkage disequilibrium with other genes implicated in CRC risk [64]. Polymorphisms associated with CRC have been found in genes such as *APC-11307K, MTHFR* and genes encoding the N-acetyl transferases 1 and 2 (*NAT1, NAT2*) and the glutathione-S transferases Mu, Theta and Pi. The risk conferred by variants of these genes is modest, but their high incidence in general population could affect overall CRC risk [65].

Hereditary gastric cancer

The only gastric cancer syndrome with a proven inherited defect is

hereditary diffuse gastric cancer and is caused by germline E-cadherin-*CDH1* alterations. Its molecular basis was identified in 1998 by Guilford, who reported three cases of diffuse gastric cancer with a germilne mutation in *CDH1* gene [66].

Germline *CDH1* alterations are not restricted to specific sites of the *CDH1* gene or specific E-cadherin protein domains, as they are distributed throughout the coding regions and include splice-site sequences and UTRs (5'- and 3'-untranslated regions) of the gene, as well as throughout all protein functional domains [67]. Penetrance in proven mutation carriers is incomplete, with an estimated lifetime risk for DGC of >80% in both men and women by age 80 and of 60% for lobular breast cancer in women by the age of 80 [67].

Familial melanoma

Approximately 5-10% of melanomas present in families with a genetic predisposition for the disease [68]. It is known that 10-20% of those families display mutations in *CDKN2A* gene, which is located on chromosome 9p21 and encodes two different proteins, *p16INK4* and *p14RF*. These proteins are involved in cell cycle regulation and senescence. In *CDKN2A* mutation carriers, melanoma lifetime risk varies between populations based on sun exposure and melanoma prevalence in the general population. Several *CDKN2A* mutations have been associated not only with melanoma, but also with an increased risk for other malignancies, mainly pancreatic cancer. A subgroup of families with familial melanoma exhibits genetic mutations in *CDK4 g*ene, which is located on chromosome 12q14 and encodes a kinase that interacts with the *p16INK4A* protein [69].

Conclusions

Through the years, we have witnessed a rapid evolution in familial cancer syndrome genetics. These syndromes constitute paradigms for investigation and understanding of the neoplastic process. They are directly or indirectly associated with disruption of genomic integrity. Inherited defects in DNA repair allow an increase in mutational burden and genetic instability. There are numerous pathways and genes participating in the maintenance of genomic integrity. Defects in only a few of them are currently established to represent familial cancer syndromes. As to the rest of the above, reductions in function of these genes might impact the probability of cancer development. Defining complex networks involved in DNA repair and maintenance of genomic integrity will be a prerequisite for the understanding of familial cancer syndromes but, most importantly, for the better understanding of cancer.

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