Chirurgia (2023) 118: 584-595
No. 6, November-December

http://dx.doi.org/10.21614/chirurgia.2023.v.118.i.6.p.584

New Insights into Lynch Syndrome: A Narrative Review

Cosmin Victor Ene[1,2], Catalin Andrei Bulai[1,2], Petrisor Geavlete[1,2], Razvan Ionut Popescu[1,3], Ileana Adela Vacaroiu[1,4], Dragoș Eugen Georgescu[1,5]*, Isabela Voichita Isaconi[6], Madalina Andreea Munteanu[1], Corina Daniela Ene[1,7], Adrian Militaru[1,2], Bogdan Geavlete[1,2], Razvan Multescu[1]

[1]Carol Davila University of Medicine and Pharmacy, 050474, Bucharest, Romania
[2]Department of Urology, Sf. Ioan Clinical Emergency Hospital, 042122, Bucharest, Romania
[3]Department of Urology, Prof. Dr. Th. Burghele Clinical Hospital, 050659, Bucharest, Romania
[4]Department of Nephrology, Sf. Ioan Clinical Emergency Hospital, 042122, Bucharest, Romania
[5]Department of Surgery, Dr. I. Cantacuzino Clinical Hospital, 030167, Bucharest, Romania
[6]Department of Animal Productions and Public Health, University of Agronomic Sciences and Veterinary Medicine of Bucharest, 011464, Bucharest, Romania
[7]Department of Nephrology, Carol Davila Clinical Hospital of Nephrology, 010731, Bucharest, Romania

*Corresponding author:
Dragoș Eugen Georgescu, MD, PhD
Department of Surgery
Dr. I. Cantacuzino Clinical Hospital
030167, Bucharest, Romania
E-mail: gfdragos@yahoo.com

Received: 20.10.2023
Accepted: 15.12.2023

Rezumat

Noi perspective asupra sindromului Lynch: recenzie descriptivă a literaturii

Sindromul Lynch, caracterizat prin mutații în genele de reparare a erorilor de potrivire a bazelor, este unul dintre sindroamele ce predispun la cancer, fiind asociat cu un risc crescut de cancer colorectal şi endometrial. Acest studiu îşi propune să analizeze în detaliu conexiunile specifice şi să cerceteze mecanismele moleculare fundamentale ale acestui sindrom. Modificările genetice la nivelul genelor de reparare a erorilor de potrivire a bazelor ale ADN-ului, precum MLH1, MSH2, MSH6, PMS2 şi EPCAM, predispun indivizii afectați la multiple tipuri de cancer. Prezenta lucrare de cercetare examinează în mod exhaustiv metodele actuale de screening şi măsurile preventive adaptate pentru indivizii diagnosticați sau cu risc de a dezvolta sindromul Lynch. Integrarea tehnologiilor avansate de secvențiere şi a dispozitivelor sofisticate de bioinformatică a îmbunătățit semnificativ precizia detectării mutațiilor, facilitând identificarea precisă a purtătorilor de mutații şi a rudelor expuse la risc. În plus, în acest studiu se subliniază evoluția tehnicilor diagnostice, revoluționând identificarea potențialilor purtători de mutații. Algoritmul diagnostic care integrează criterii clinice, teste tumorale şi analize genetice, joacă un rol esențial în identificarea şi gestionarea sistematică a pacienților cu sindrom Lynch. Deşi asocierea bine-cunoscută a

sindromului Lynch cu cancerul colorectal şi endometrial este recunoscută, dovezi recente sugerează un risc crescut pentru alte tipuri de cancer. Un aspect cheie al acestei recenzii de literatură este analiza detaliată a corelației dintre sindromul Lynch şi cancerele de prostată sau testiculare. Înțelegerea acestor conexiuni este deosebit de importantă pentru elaborarea protocolelor de screening personalizate şi a strategiilor preventive pentru indivizii purtători de mutații genetice. Evaluarea completă a acestui spectru divers de neoplasme subliniază necesitatea unor strategii de supraveghere personalizate şi a abordărilor multidisciplinare pentru gestionarea şi reducerea riscurilor la indivizii la care se suspectează modificări asociate sindromului Lynch.

Cuvinte cheie: sindrom Lynch, MMR, testare germinativă, carcinogeneza, cancer colorectal

Abstract

Lynch syndrome, characterized by DNA mismatch repair deficiency, represents a significant paradigm among cancer predisposition syndromes and is notably associated with heightened susceptibility to various cancers, particularly colorectal and endometrial malignancies. The primary aim of this research paper is to scrutinize specific associations and delve into the underlying molecular mechanisms of Lynch syndrome. Genetic alterations in MMR genes, including MLH1, MSH2, MSH6, PMS2, and EPCAM, compromise DNA repair mechanisms, predisposing affected individuals to a spectrum of malignancies. This paper comprehensively investigates current screening methodologies and preventive measures tailored for individuals identified or at risk of Lynch syndrome. The integration of advanced sequencing technologies and refined bioinformatics tools has significantly improved mutation detection accuracy, facilitating precise identification of mutation carriers and their at-risk relatives. Moreover, this review emphasizes the evolving diagnostic landscape, which have revolutionized the identification of potential mutation carriers. The structured diagnostic algorithm, incorporating clinical criteria, tumor testing, and genetic analysis, plays a pivotal role in systematically identifying and managing individuals with Lynch syndrome. While the well-established association of Lynch syndrome with colorectal and endometrial cancers is recognized, emerging evidence suggests an increased risk for other types of malignancies. A crucial aspect of this literature review is to extensively analyze the less commonly acknowledged correlation between Lynch syndrome and prostate or testicular malignancies. Understanding these correlations holds significant importance in guiding tailored screening protocols and preventive strategies for individuals carrying Lynch syndrome-associated genetic mutations. The comprehensive assessment of this diverse spectrum of cancers underscores the necessity for tailored surveillance strategies and multidisciplinary approaches to effectively manage and mitigate risks in individuals harboring Lynch syndrome-associated genetic alterations.

Key words: Lynch syndrome, MMR, germline testing, carcinogenesis, colorectal cancer

Introduction

Lynch syndrome (LS), also known as hereditary non-polyposis colorectal cancer (HNPCC), is a genetic disorder that increases an individual's risk of developing various types of cancer, including colorectal, endometrial, ovarian and stomach cancer. Lynch syndrome is caused by mutations in one of several genes involved in DNA mismatch repair (MMR). Constitutional pathogenic variations (previously known as inherited mutations) in the MMR genes MLH1, MSH2, MSH6, PMS2, and EPCAM distinguish LS from other diseases. Previously, only a small

number of carefully chosen individuals with a CRC diagnosis were provided with LS testing (1).

Tumor markers are substances in tumor cells or in response to tumor growth. They can be used to detect the presence of neoplasia, monitor the progression of cancer and assess the response to treatment (2).

In Lynch syndrome, tumor markers can be useful for several purposes. First, tumor markers can be used to screen individuals with Lynch syndrome for cancer development. For example, individuals with Lynch syndrome are at an increased risk of developing colorectal cancer, so that they may undergo regular screening with colonoscopy. Tumor markers such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) can help detect colorectal cancer early when it is more easily treatable. Second, tumor markers can be used to monitor individuals with Lynch syndrome who have been diagnosed with cancer. CEA and CA 19-9 are commonly used to monitor the progression of colorectal cancer and to assess the response to treatment. Third, tumor markers can help distinguish between sporadic malignancies and those associated with Lynch syndrome. For example, neoplasm associated with Lynch syndrome are more likely to have defects in MMR, so testing for MMR status can help identify individuals with Lynch syndrome. However, immunohistochemistry (IHC) finds over 90% of LS instances (3).

Additionally, checkpoint inhibitor immunotherapy, which is relatively new and has recently been authorized in standard clinical practice, may be effective against MMR – deficient tumors (4). Then, if IHC is abnormal for proteins other than MLH1 in the tumors with loss of MLH1 expression of MSI, the tumors may be immediately qualified for genetic testing without waiting for a subsequent test to identify methylation of the MLH1 promotor. The patient is qualified for genetic testing for LS if the tumor is deficient in mismatch repair (dMMR), has abnormal IHC or Microsatellite Instability Testing (MSI) results, and does not show evidence of MLH1 promotor methylation. All in all, there are currently two main methods for diagnosing Lynch syndrome: (1) molecular screening of colorectal and endometrial tumor samples for evidence of impaired MMR function (MMR-D) or high-level MSI (MSI-H) to identify cancer patients who should undergo germline testing for pathogenic MMR gene variants; or (2) direct germline testing carried out on patients who are personal and/or family histories of cancer are suspicious for Lynch syndrome (5).

Regarding the diagnosis of Lynch syndrome, four primary pathology studies can help with the molecular identification of cancer patients who are likely to have Lynch syndrome: 1) MSI testing based on polymerase chain reaction (PCR); 2) immunohistochemical staining (or immunohistochemistry (IHC)) for the MMR proteins; 3) analysis of MLH1 promoter methylation (or analysis of somatic BRAF V600E mutant); and 4) next-generation somatic (and/or germline) sequencing assays (5).

Recently, it has been demonstrated that MSI status may be accurately determined by next-generation sequencing (NGS) of malignancies, either by directly evaluating many microsatellite loci or by evaluating the overall mutational load of a tumor as a proxy for MSI status (6,7). Nowadays, all patients with colorectal and endometrial cancers can now reliably get screening for underlying Lynch syndrome thanks to developments in molecular testing and NGS technology, while advances in immuno-oncology promise to revolutionize the treatment of Lynch-associated cancers further (8).

Despite this critically important body of knowledge, there are still several questions concerning the epidemiology, pathogenesis, clinical phenotype, and cancer risk reduction of LS. This review offers a comprehensive review of recent advancements in these domains, acknowledging the scarcity of studies published annually due to the rarity of this pathology.

This literature review comprehensively examined the currently available information concerning genetic markers linked to Lynch Syndrome. Moreover, it investigated the

varieties of these markers associated with Lynch Syndrome, the methodologies for their identification and their implications concerning diagnosis and treatment. Additionally, we will discuss the current research gaps and limitations in the field. A separate investigation was conducted in well-known genetically associated tumors such as colorectal, endometrial, gastric, kidney, and uroepithelial cancers.

This research provides thorough insights into the current state of the field. It highlights the need for further research in the area to determine the exact nature of the relationships between genetic markers and cancer development. Furthermore, it can inform future clinical and research decisions. The article concludes by deliberating on the challenges and prospects offered by the ongoing research in the field.

Materials and Methods

A comprehensive literature search was conducted by the authors using Scopus, Medline and PubMed data-bases between January 2015 and January 2023. Several combinations of keywords such as genetic markers, Lynch Syndrome, hereditary cancers, kidney, colon, gastric, uroepithelial, MMR, MSH, MSI, MLH, PMS, and DNA were employed. The initial stage of our study involved identifying and examining 253 articles consisting of observational research, review articles, systematic reviews and randomized controlled trials. Upon screening the title/abstract and conducting a thorough evaluation of full-text articles, a subset of 100 articles conformed to our inclusion criteria and were selected for detailed analysis. These studies were included based on specific prerequi-sites: implementation of germline testing, explicit diagnostic methodologies and the examination of a substantial patient cohort. Texts in languages other than English were excluded.

Furthermore, a meticulous examination of these articles aimed to discern the predominant genetic markers utilized in Lynch Syndrome research. The outcomes of this analysis yielded critical insights into the current landscape of Lynch Syndrome investigations, ultimately identifying 19 articles that furnished comprehensive results warranting detailed elucidation.

In our modest perspective, the implications derived from this research possess the potential to significantly impact clinical and research-related deliberations concerning hereditary cancers and Lynch Syndrome. The identification of prevalent genetic markers and the insights garnered from these studies contribute substantively to the ongoing discourse and decision-making processes in this domain.

Results

Genetic Data in Lynch Syndrome

There is a strong correlation between point mutations in tumor suppressor genes like p53 and APC and sporadic cases of colon cancer. However, LS tends to have a lower incidence of these mutations. After the onset of MMR in LS, it is usual for mutations to develop in the KRAS gene, which is then followed by mutations in the APC gene (9,10). The syndrome is responsible for a diverse array of oncological cancer forms. The underlying mechanism of this condition is a germline mutation of DNA mismatch repair (MMR) genes, which can be discovered in 88–95% of people who have been diagnosed with this condition (11,12). In addition, approximately three percent of instances of LS are caused by EPCAM, a gene located nearby MSH2 that, when altered, can potentially render MSH2 inactive (13). MMR is one of the essential factors in preventing the development of cancer in a biological system. As a result, it repairs mismatched DNA insertions and replication errors. Additionally, it acts as a checkpoint to maintain vital genomic stability by restoring improperly assembled single-base matches during replication (14). Furthermore, the damage caused by oxidation or alkylation can be identified and either corrected or driven to cause death in the cell.

Individuals diagnosed with Lynch syndrome must initially meet the condition of having a

germline mutation present in one of the two MMR genes. In most cases, inactivation of the second healthy allele results from the presence of minor pathogenic variations in addition to gene loss, which ultimately fails in the MMR system (15).

To this day, research has pinpointed four primary MMR genes as being involved in developing cancer linked to LS. These predisposing genes are called mutL homolog 1 (MLH1) and mutS homolog 2 (MSH2), which are then followed by mutS homolog 6 (MSH6) and postmeiotic segregation increased 2 (PMS2). It has been demonstrated that MSH2 can create the MSH2-MSH6 heterodimer, which detects base-base mismatches. The MSH2 and MLH1 proteins are required to form their respective dimer to function properly (16-19). MutL⊚ then stimulates the excision of the mismatched locus, which is carried out by proteins such as exonuclease-1 and DNA polymerase. DNA ligase then resynthesizes and binds the DNA strand (20,21).

Any deficiency in these proteins results in an inactive DNA repair mechanism, which raises pathogenic modification rates in genes of the cell growth cycle, hence causing abnormalities in tumor suppressor genes and oncogenes and a subsequent rise in cancer risk (22). Inadequate MMR and the consequent change in the number of nucleotides in a microsatellite region, characterized as short repeating DNA sequences, are known as microsatellite instability (MSI), and it is present in roughly 95% of all cancers associated with LS (16). In contrast, MSI is uncommon in colorectal cancer (CRC) that arises sporadically. Tumor mutational burden (TMB) was consistently high in colorectal cancer cases with MMR gene inactivation (23).

The Diagnostic Algorithm in LS

It has been demonstrated that it is cost-effective for some institutions to routinely test patients for LS who are at a 5% or higher risk (24). It is also a regular practice to screen patients with colon cancer under 50 years of age. The three stages of evaluation – clinical criteria, tumor tissue testing, and genetic testing are available to aid in diagnosing LS.

Clinical

The diagnosis of HNPCC is made using the Amsterdam criteria I and II (25), but the diagnosis of Lynch syndrome (including suspected Lynch syndrome variations such as Lynch-like syndrome) requires the discovery of a mutation in the MMR gene.

Tissue testing

Immunohistochemistry and multiplex sequence-independent polymerase chain reaction (MSI-PCR) assays must be performed initially when a tissue sample is available for analysis. Immunohistochemistry can be used to distinguish the protein by-products of the MMR genes MLH1, MSH2, MSH6, and PSM2. When the MMR proteins are absent, certain genetic testing is run. Polymerase chain reaction (MSI-PCR) measures the variance in microsatellite length. A high MSI suggests MMR insufficiency and supports the suspicion of Lynch syndrome; however, testing five marker panels of microsatellite alleles is indicated to determine the genuine MSI status (26).

Genetic

When MMR gene abnormalities are detected, germline genetic testing is required to diagnose Lynch syndrome. The universal testing strategy establishes who is eligible for genetic testing. The analysis may involve IHC testing for the proteins MLH1/MSH2/MSH6/PMS2 and/or MSI analysis. Loss of MLH1 in cancers indicates the need for BRAF testing or research into MLH1 promoter hypermethylation (27).

Once a patient meets the Amsterdam I/II criteria and is determined to have MSI-high tumors or a loss of protein expression on IHC, LS is typically suspected. This is done after consulting with a genetic counselor. However, assertions made by certain researchers suggest that the strict Amsterdam II criteria might potentially overlook a considerable segment of individuals with LS (28).

The index patient and any future descendants with a 50% probability of inheriting the mutation would benefit from discovering a diagnosis for LS.

Evolution of diagnostic criteria over time

Several recognized clinical models and methods can be used to identify patients who are very susceptible to LS. The Amsterdam Criteria I, or the initial set of guidelines, was released in 1990. These standards were revised to reflect the Amsterdam II standard, as shown in *Table 1* (25).

Finding those who do not meet the Amsterdam criteria but may still be at risk for LS is still challenging. Consequently, Bethesda Guidelines were established in 1997. These guidelines recommend identifying mutation carriers by looking for replication defects and MSI. An updated version of the Bethesda recommendations may be seen in *Table 2* (29) and was made in 2004.

The Bethesda Guidelines are simplified by the MIPA criteria, published in 2005 and shown in *Table 3*, by leaving out the details of family history, which are frequently unnecessary in clinical practice (30).

Table 1. Amsterdam II criteria for Lynch syndrome

For identifying individuals at risk of being MMR mutation carriers, where all criteria must be met:
• Three or more relatives with histologically verified Lynch syndrome-related cancers (colorectal, endometrial, small intestinal, renal pelvic, ureter). One of which should be a first-degree relative of the other two.
• Involvement of two or more successive generations should be affected
• One or more cancers diagnosed before age 50
• Exclusion of familial adenomatous polyposis

Table 2. Revised Bethesda Guidelines as a current recommendation for LS identification

Patients meeting any one of the following should undergo microsatellite instability (MSI) testing:
• CRC is diagnosed in an individual under the age of 50 years.
• Presence of synchronous, metachronous colorectal, or other LS-associated tumors *, re-gardless of age.
• CRC with the MSI-H (high-frequency MSI) histology ‡, in a patient <60 years of age.
• CRC is diagnosed in 2 or more first- or second-degree relatives with LS-related tumors *, regardless of age.
• CRC in 1 or more first-degree relatives with an LS-related tumor *, with 1 of the cancers being diagnosed under age 50 years.

Table 3. MIPA Criteria. Identifying LS in patients without a known family history

Patients meeting any one of the following should undergo MSI analysis:
• CRC before the age of 50 years.
• Two LS-associated tumors, including synchronous or metachronous CRCs or
• LS-associated tumors.
• Adenoma before the age of 40 years.

Types of Cancer Associated with Lynch Syndrome

Colorectal cancer

The two most frequently observed cancer forms in LS are CRC and endometrial cancer (31). However, it has been demonstrated that several other malignancies, including stomach cancers, ovarian, biliary system, small bowel, and brain tumors, are more common in LS than in the general community (32). According to research, there are differences between the cancer traits linked to MLH1, MSH2, and MSH6 gene mutations. As an illustration, Vasen et al. (33) discovered that MSH2 mutation bearers were more likely to develop extracolonic cancers than MLH1 mutation carriers. This syndrome is linked with several clinical traits common to colonic tumors. Female MSH6 mutation carriers have a significantly lower chance of developing CRC than do MLH1 and MSH2 mutation carriers, according to Hendriks et al. (34). For LS mutation carriers, colonoscopic monitoring has been advised to stop the growth of cancer. Jarvinen et al. (35) compared colonoscopic screening (done at three-year intervals) with no screening of at-risk LS family members in a long-term controlled trial. The findings demonstrated that screening greatly decreased overall mortality (8% in screened patients versus 22% in controls) as well as the incidence of CRC (6% in screened patients versus 16% in controls). The National Institute of Health and Care Excellence has suggested "universal" testing for all new CRC diagnoses since 2017 (4). Mismatch repair deficiency testing on the tumor specimen is recommended for all CRCs,

ideally on colonoscopic biopsies when practical (36). Fecal immunochemical testing (FIT) was introduced as a stopgap measure to risk stratify patients with LS owing to surveillance endoscopy. An emergent colonoscopy was prioritized with a 10 g/g cut-off of feces (37). By checking for the existence of somatic BRAF V600E mutations, which serve as a stand-in for the methylation state of MLH1, promoter methylation in colorectal cancers can also be evaluated indirectly (38). BRAF mutation has a strong negative predictive value because somatic BRAF V600E mutations are only found in a small percentage of colorectal cancers overall, but they are found in 69% to 78% of colorectal cancers with MLH1 promoter methylation and hardly ever in cancers linked to Lynch syndrome (39).

Endometrial cancer

Patients are diagnosed at an average age of 49 years, notably lower than the general community's average value of 60 years at the time of diagnosis (40). According to studies, MSH6 mutation families have a greater risk of developing endometrial cancer (64–71%) than MSH2 or MLH1 mutation families (40–50%) (41). For MLH1, MSH2, MSH6 variant bearers, and PMS2 variant carriers, the lifetime risk of endometrial cancer ranges from 20% to 70%, with a slightly lower but elevated risk of ovarian cancer. However, monitoring for uterine or ovarian cancer has not been shown to lower mortality in LS (42). 94% of endometrial cancer cases without MLH1 or PMS2 are due to methylation of the MLH1 promoter (43). Due to the prevalence of MLH1 promoter methylation, patients with MSI-H tumors and/or tumors that show no expression of the MLH1 and PMS2 proteins on IHC typically rule it out before germline genetic testing.

Gastric cancer

Chronic gastritis brought on by Helicobacter pylori is strongly linked to developing the intestinal form of gastric cancer. Therefore, research has indicated that H. pylori infection and atrophic gastritis may indicate a higher risk of gastric cancer in people with LS. However, according to a Finnish survey, only 20% of gastric cancers in LS were H. Pylori positive (44). In a group of 73 mutation carriers, Renkonen-Sinisalo et al. (45) assessed the utility of gastroscopic surveillance. LS families with a cluster of stomach cancer and in nations with a high prevalence of the disease are encouraged to get screened for gastric cancer, according to a group of collaborative European specialists in hereditary gastro-intestinal cancer. Serological biomarkers like pepsinogen I and II and H. pylori antibodies have also been proposed as a non-endoscopic screening technique in LS for determining individual risk for gastric cancer (46).

Uroepithelial and kidney cancer

Particularly in MSH2 mutation carriers, Van der Post et al. (47) found an elevated risk for bladder cancer. Similarly, MSH2 mutation carriers had a sevenfold greater lifetime risk of developing urological tumors than did MLH1 mutation carriers, according to Watson et al.'s research (48). It has been demonstrated that urine cytology is ineffective in detecting bladder and ureter cancers in LS mutation bearers (49). On the other hand, abdomen ultrasound, urinalysis, and urine cytology are suggested for detecting urological lesions by European authorities on hereditary gastro-intestinal cancer. Ages 30 to 35 should be the starting point for screening, with gaps of one to two years. This plan is particularly designed for families with urological tumor clusters (46).

Prostate cancer

In men, prostate cancer is the most frequent form of malignancy and the second highest cause of fatalities attributed to cancer (50). Although spontaneous adenocarcinomas of the prostate make up the majority of cases, a tiny percentage can be attributed to hereditary factors, most notably the BRCA2 gene (51). Recent epidemiological research shows a link between Lynch syndrome and prostate cancer. Even if the molecular genetic pathways involved in prostate cancer are not well known, there is a link between Lynch syndrome and prostate cancer (52).

The idea that prostate cancer should be included in the Lynch syndrome spectrum has been supported by a systematic review and meta-analysis that was published in 2014 by Ryan et al. (52). It found a total of 23 research, including six molecular investigations and 18 risk studies, that analyzed data on prostate cancer in people who carried the MMR gene mutation. It was discovered that MMR deficiency was present in 74 percent of prostate tumors among mutation carriers, with a range of 57 – 85 percent (especially MSH2 mutations). Those individuals with the gene alterations had a relative risk of having prostate cancer that was 3.67 times higher (95% confidence interval (CI), 2.32 – 6.67). The scientists also showed that patients with Lynch syndrome had an epidemiological risk of prostate cancer that was significantly enhanced by two to three times compared to people without Lynch syndrome. These findings corroborate a 2016 research of 288 Danish Lynch syndrome families, which found that nearly 10% of the group acquired prostate cancer. Sixty-nine percent of patients were found to lack MMR (53).

As the protein products of BRCA1 and BRCA2 are involved in DNA repair and other associated functions to stabilize DNA, similar to MMR proteins, the fact that carriers of BRCA mutations are more likely to develop prostate cancer adds an intriguing new twist to this story (54).

The clinical implications concerning screening and surveillance are not yet clearly evident. PSA testing should be tried out in MSH2 mutation carriers between the ages of 40 and 50, according to the recommendations of Barrow et al. (55).

The most common form of cancer in men is prostate cancer, and it is the second leading cause of cancer-related death (50). Even though spontaneous prostate adenocarcinomas account for most cases, a small percentage can be traced to hereditary factors, most notably the BRCA2 gene (51). In recent epidemiological studies, a link has been found between Lynch syndrome and prostate cancer. Even though the molecular genetic pathways involved in prostate cancer are not well understood, it is known that Lynch syndrome is associated with prostate cancer (52).

Testicular cancer

It is unclear whether LS is associated with testicular cancer. This association has been demonstrated in studies examining refractory rather than primary testicular tumors (56). One-third of refractory tumors and 0% to 6% of unselected germ cell tumors were found to exhibit MSI with reduced expression of MLH1 and MSH2 (57) and a higher risk of relapse and death following chemotherapy (58). This suggests that refractory tumors, which are tumors that don't respond to chemotherapy, are more likely to have reduced expression of certain proteins associated with DNA mismatch repair. Therefore, this could be why refractory tumors have a higher risk of relapse and death following chemotherapy (57).

However, other possible explanations exist for why refractory tumors have a higher relapse rate. For example, it could be that the cancer cells in refractory tumors are more resistant to the effects of chemotherapy. Conversely, a possibility exists that cancer cells within refractory tumors exhibit heightened aggressiveness and accelerated growth compared to those within tumors responsive to chemotherapy. Interestingly, some studies have failed to demonstrate a correlation between the expression of MLH1 or MSH2 and primary testicular cancer (56). This association needs to be further explored before any conclusions can be formulated.

Others cancers

In a notable study across four LS research facilities, Watson et al. identified a seven percent lifetime risk for ovarian cancer (48). Additionally, they discovered that the risk for ovarian cancer peaked between the ages of 40 and 55 and that MSH2 family members had an occurrence rate that was almost twice as high as that of MLH1 family members. LS ovarian cancer appears to have a better prognosis than ovarian cancer in the general

community or in people who carry the BRCA1/2 mutation (59).

Pancreatic and biliary tract cancers appear to have a connection to LS (60). According to estimates, LS mutation carriers have a 2% lifetime chance of developing these cancers (32). Family members with LS are not typically advised to undergo pancreas or biliary tract cancer surveillance. Also, concerning the screening for small bowel cancer, it is not in the guidelines for clinic management of family members with LS (60).

According to Vasen et al., MSH2 mutation carriers are more likely to develop brain tumors than MLH1 mutation carriers. Additionally, it has been noted that LS brain tumors exhibit microsatellite stability (61).

Emerging Therapies

Emerging therapies, including immune checkpoint inhibitors, targeted therapies, and poly ADP-ribose polymerase (PARP) inhibitors, are being studied as potential treatments for Lynch syndrome-associated cancers. Critical for self-tolerance, immune checkpoints serve as vital regulators within the immune system, preventing in-discriminate attacks on cells. The immune checkpoints programmed death 1 (PD-1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA4) pathways are negative feedback systems repressing T-cell cytotoxic immune responses. Immune checkpoint inhibition with antibodies against CTLA4, PD-1, or its associated ligands has led to phenomenal clinical responses in patients with various types of cancer (62). Cancers with high MSI (as in LS), manifest high mutation rates resulting in the production of mutant immunogenic proteins associated with a lymphocytic infiltrate (63). MMR deficiency leads to the generation of a substantial number of neo-antigens, more than 20 times higher than in tumors lacking MMR deficiency, potentially resulting in increased immunogenicity and inducing a significant immune response. These malignant cells also overexpress immune-checkpoint proteins (PD-1 and CTLA-4) (64). Clinical trials have shown promising results with immune-checkpoint inhibitors in treating advanced high-MSI colorectal cancer (65). Recent evidence has indicated a sustained impact in patients with high-MSI pancreatic cancer (66). Such findings suggest the potential for analogous results across various extracolonic tumors associated with Lynch syndrome, including those of urologic origin.

Future Directions

The Lynch syndrome was originally recognized as a colorectal cancer, however, in fact, it encompasses a wide range of diseases due to the presence of multiple affected organs, each of which requires a unique treatment approach. Providing the best care for patients with this disease requires a multidisciplinary medical team, which can be challenging not only in terms of diagnosis but also in terms of treatment.

Espenschied et al. discovered that 27.3% of patients did not fit any of the existing LS testing criteria and that MSH6 and PMS2 mutation carriers were substantially more likely than MLH1 and MSH2 mutation carriers to only meet the BRCA1/2 testing requirements (and not LS criteria) (67). Additionally, 15.2% of the MSI and/or IHC data that were available for individuals with MSH6 or PMS2 mutations were inconsistent, which may have made it possible for the mutation to go undetected in the absence of MGPT. It could be observed that MSI and IHC do not have 100% sensitivity for LS, and many of the discordant MSH6 mutations may be explained by known issues with IHC for the MSH6 protein (68.69). Lynch syndrome is the most prevalent cancer predisposition syndrome and is significantly underdiagnosed despite being relatively uncommon in the majority of clinicians' practices. This could involve developing new screening methods and treatments that could help identify those at risk of Lynch Syndrome and prevent them from developing certain types of cancer. Another area of focus could be on further understanding the genetics of Lynch

Syndrome and its associated cancers. This could involve studying how specific genetic variations can affect the development of cancer and how genetic factors interact with environmental factors.

Conclusions

Overall, the future of Lynch Syndrome research is filled with possibilities. Advances in genetic screening have revolutionized identification strategies, allowing for more precise and comprehensive detection of individuals at risk. With further research and understanding of the condition, there is hope for better prevention and detection of Lynch Syndrome and its associated pathologies. These insights have also shed light on the unique molecular pathways underlying Lynch syndrome-related cancers, paving the way for targeted therapies and immuno-therapeutic approaches.

Moreover, heightened awareness and interdisciplinary collaboration have underscored the importance of holistic care, emphasizing not just treatment but also psychological support and genetic counseling. This collaborative approach is pivotal in delivering comprehensive care, from early detection to tailored treatment plans, and facilitating informed decision-making for patients and their families.

Author's Contributions

Conceptualization: C.V.E., C.A.B., R.I.P; methodology, investigation: I.A.V., C. D.E., M. A.M.; writing original draft: C.V.E., C.A.B., R. I.P., M.A.M.; writing - review & editing: D.E.G.; supervision: P.G., B.G.; All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Vasen HF, Mecklin JP, Khan PM, Lynch HT. The International Collaborative Group on hereditary non-polyposis colorectal cancer (ICG-HNPCC). Dis Colon Rectum. 1991;34(5):424-5.
2. Koornstra JJ, Mourits MJ, Sijmons RJ, Leliveld AJ, Hollema H, Kleibeuker JH. Management of extracolonic tumors in patients with Lynch syndrome. Lancet Oncol. 2009;10(4):400-8.
3. Pearlman R, Frankel WL, Swanson BJ, Jones D, Zhao W, Yilmaz A, et al. A prospective statewide study of universal screening for hereditary colorectal cancer: the Ohio colorectal cancer prevention initiative. JCO Precis Oncol. 2021;5:779–91.
4. NICE. Pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency, 2020. Available: https://www.nice.org.uk/guidance/ta709).
5. Yurgelun MB, Hampel H. Recent Advances in Lynch Syndrome: Diagnosis, Treatment, and Cancer Prevention. Am Soc Clin Oncol Educ Book. 2018; 38:101-109.
6. Zhu L, Huang Y, Fang X, Liu C, Deng W, Zhong C, et al. A novel and reliable method to detect microsatellite instability in colorectal cancer by next-generation sequencing. J Mol Diagn. 2018;20(2):225-231.
7. Nowak JA, Yurgelun MB, Bruce JL, Rojas-RudillaV, Hall DL, Shivdasani P, et al. Detection of mismatch repair deficiency and microsatellite instability in colorectal adenocarcinoma by targeted next-generation sequencing. J Mol Diagn. 2017;19(1):84-91.
8. Gallego CJ, Shirts BH, Bennetie CS, Guzauskas G, Amendola LM, Horike-Pyne M, et al. Next-generation sequencing panels for the diagnosis of colorectal cancer and polyposis syndromes: a cost-effectiveness analysis. J Clin Oncol. 2015;33(18):2084-91.
9. Kloth M, Ruesseler V, Engel C, Koenig K, Peifer M, Mariotti E, et al. Activating ERBB2/HER2 mutations indicate susceptibility to pan-HER inhibitors in Lynch and Lynch-like colorectal cancer. Gut. 2016;65(8): 1296-305.
10. Ahadova A, Gallon R, Gebert J, Ballhausen A, Endris V, Kirchner M, et al. Three molecular pathways model colorectal carcinogenesis in Lynch syndrome. Int J Cancer. 2018;143(1):139-150.
11. Mangold E, Pagenstecher C, Friedl W, Mathiak M, Buettner R, Engel C, et al. Spectrum and frequencies of mutations in MSH2 and MLH1 were identified in 1,721 German families suspected of hereditary nonpolyposis colorectal cancer. Int J Cancer. 2005;116(5):692-702.
12. Boland CR. Recent discoveries in the molecular genetics of Lynch syndrome. Fam Cancer. 2016;15(3):395-403.
13. Tiwari AK, Roy HK, Lynch HT. Lynch syndrome in the 21st century: Clinical perspectives. QJM. 2016;109(3):151-8.
14. Bridge G, Rashid S, Martin SA. DNA mismatch repair and oxidative DNA damage: Implications for cancer biology and treatment. Cancers (Basel). 2014;6(3):1597-614.
15. Chung DC, Rustgi AK. DNA mismatch repair and cancer. Gastroenterology. 1995;109(5):1685-99.
16. Joost P, Therkildsen C, Dominguez-Valentin M, Jönsson M, Nilbert M. Urinary tract cancer in Lynch syndrome; increased risk in carriers of MSH2 mutations. Urology. 2015;86(6):1212-7.
17. Pinto D, Pinto C, Guerra J, Pinheiro M, Santos R, Vedeld HM, et al. Contribution of MLH1 constitutional methylation for Lynch syndrome diagnosis in patients with tumor MLH1 downregulation. Cancer Med. 2018; 7(2):433-444.
18. Bonadona V, Bonaïti B, Olschwang S, Grandjouan S, Huiart L, Longy M, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. JAMA. 2011;305(22):2304-10.
19. Ten Broeke SW, van der Klift HM, Tops CMJ, Aretz S, Bernstein I, Buchanan DD, et al. Cancer Risks for PMS2-Associated Lynch Syndrome. J Clin Oncol. 2018;36(29):2961-2968.
20. Vilar E, Gruber SB. Microsatellite instability in colorectal cancer-the stable evidence. Nat Rev Clin Oncol. 2010;7(3):153-62.
21. Hoeijmakers JH. Genome maintenance mechanisms for preventing cancer. Nature. 2001;411(6835):366-74.
22. Sobocinska J, Kolenda T, Teresiak A, Badziag-Lesnia N, Kopczynska M, Guglas K, et al. Diagnostics of Mutations in MMR/EPCAM Genes and Their Role in the Treatment and Care of Patients with Lynch Syndrome. Diagnostics (Basel). 2020;10(10):786.

23. Wang T, Lee LH, Vyas M, Zhang L, Ganesh K, Firat C, et al. Colorectal carcinoma with double somatic mis-match repair gene inactivation: Clinical and pathological characteristics and response to immune checkpoint blockade. Mod Pathol. 2019;32(10):1551-1562.
24. Snowsill T, Huxley N, Hoyle M, Jones-Hughes T, Coelho H, Cooper C, et al: A systematic review and economic evaluation of diagnostic strategies for Lynch syndrome. Health Technol Assess. 2014;18(58):1-406.
25. Vasen HF, Watson P, Mecklin JP, Lynch HT. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. Gastroenterology. 1999;116(6):1453-6.
26. Boland CR, Thibodeau SN, Hamilton SR, Sidransky D, Eshleman JR, Burt RW, et al. A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. Cancer Res. 1998;58(22):5248-57.
27. Giardiello FM, Allen JI, Axilbund JE, Boland CR, Burke CA, Burt RW, et al. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-Society Task Force on colorectal cancer. Gastroenterology. 2014;147(2):502-26.
28. Roupret M, Babjuk M, Comperat E, Zigeuner R, Sylvester R, Burger M et al. European guidelines on upper tract urothelial carcinomas: 2013 update. Eur Urol. 2013;63(6):1059-71.
29. Umar A, Boland CR, Terdiman JP, Syngal S, de La Chapelle A, Rüschoff J, et al. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst. 2004;96(4):261-8.
30. Kievit W, de Bruin JHFM, Adang EMM, Severens JL, Kleibeuker JH, Sijmons RH, et al. Cost effectiveness of a new strategy to identify HNPCC patients. Gut. 2005;54(1):97-102.
31. Lynch HT, Smyrk T. Hereditary nonpolyposis colorectal cancer (Lynch syndrome). An updated review. Cancer.1996;78 (6):1149-1167.
32. Aarnio M, Sankila R, Pukkala E, Salovaara R, Aaltonen LA, de la Chappellee A, et al. Cancer risk in mutation carriers of DNA-mismatch-repair genes. Int J Cancer. 1999;81(2):214-8.-I.
33. Vasen HFA, Wijnen JF, Menko FH, Kleibeuker JH, Taal BG, Griffioen G, et al. Cancer risk in families with hereditary nonpolyposis colorectal cancer diagnosed by mutation analysis. Gastroenterology. 1996;110 (4):1020-1027.
34. Hendriks YMC, Wagner A, Morreau H, Menko F, Stormorken A, Quehenberger F, et al. Cancer risk in hereditary nonpolyposis colorectal cancer due to MSH6 mutations: impact on counseling and surveillance. Gastroenterology. 2004;127(1):17–25.
35. Järvinen HJ, Aarnio M, Mustonen H, Aktan-Collan K, Aaltonen LA, Peltomäki P, et al. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. Gastroenterology. 2000;118(5):829-34.
36. Al LA et. Molecular testing strategies for Lynch syndrome in people with colorectal cancer. NICE guidance (Internet). 2017. Available from: https://www.nice.org.uk/guidance/dg27/resources/molecular-testing-strategies-for-lynch-syndrome-inpeople-with-colorectal-cancer-pdf-1053695294917
37. Monahan KJ, Lincoln A, East JE, Benton S, Burn J, DeSouza B, et al. Management strategies for the colonoscopic surveillance of people with Lynch syndrome during the COVID-19 pandemic. Gut. 2021;70(3):624-626.
38. Deng G, Bell I, Crawley S, Gum J, Terdiman JP, Allen BA, et al. BRAF mutation is frequently present in sporadic colo-rectal cancer with methylated hMLH1, but not in hereditary nonpolyposis colorectal cancer. Clin Cancer Res. 2004; 10(1 Pt 1):191-5.
39. Adar T, Rodgers LH, Shannon KM, Yoshida M, Ma T, Mattia A, et al. A tailored approach to BRAF and MLH1 methylation testing in a universal screening program for Lynch syndrome. Mod Pathol. 2017;30(3):440-447.
40. Aarnio M, Mecklin JP, Aaltonen LA, Nyström-Lahti M, Järvinen HJ. Life-time risk of different cancers in hereditary non-polyposis colorectal cancer (HNPCC) syndrome. Int J Cancer. 1995;64(6):430-3.
41. Dunlop MG, Farrington SM, Carothers AD, Wyllie A, Sharp L, Burn J, et al. Cancer risk associated with germline DNA mismatch repair gene mutations. Hum Mol Genet. 1997;6(1):105-10.
42. Ryan N, Snowsill T, McKenzie E, Monahan KJ, Nebgen D. Should women with Lynch syndrome be offered gynecological cancer surveillance? BMJ 2021;374:n2020
43. Hampel H, Frankel W, Martin E, Arnold M, Khanduja K, Kuebler P, et al. Screening for Lynch syndrome (hereditary nonpolyposis colorectal cancer) among endometrial cancer patients. Cancer Res. 2006;66(15):7810-7.
44. Aarnio M, Salovaara R, Aaltonen LA, Mecklin JP, Järvinen HJ. Features of gastric cancers in hereditary non-polyposis colorectal cancer syndrome. Int J Cancer. 1997;74(5):551-5.
45. Renkonen-Sinisalo L, Sipponen P, Aarnio M, Julkunen R, Aaltonen LA, Sarna S, et al. No support for endoscopic surveillance for gastric cancer in hereditary non-polyposis colorectal cancer. Scand J Gastroenterol. 2002; 37(5):574-7.
46. Vasen HFA, Moslein G, Alonso A, Aretz S, Bernstein I, Bertario L, et al. Guidelines for the clinical management of Lynch syndrome (hereditary non-polyposis cancer). J Med Genet. 2007;44(6):353-62.
47. van der Post RS, Kiemeney LA, Ligtenberg MJL, Witjes JA, Hulsbergen-van de Kaa CA, Bodmer D, et al. Risk of urothelial bladder cancer in Lynch syndrome is increased, in particular among MSH2 mutation carriers. J Med Genet. 2010;47(7):464-70.
48. Watson P, Vasen HFA, Mecklin JP, Bernstein I, Aarnio M, Jarvinen HJ, et al. The risk of extracolonic, extraendometrial cancer in the Lynch syndrome. Int J Cancer. 2008;123(2):444-449.
49. Myrhøj T, Andersen MB, Bernstein I. Screening for urinary tract cancer with urine cytology in Lynch syndrome and familial colorectal cancer. Fam Cancer. 2008;7(4):303-7.
50. Siegel RL, Miller KD, Jemal A. Cancer statistics. CA Cancer J Clin. 2019; 69(1):7-34.
51. Levy-Lahad E, Friedman E. Cancer risks among BRCA1 and BRCA2 mutation carriers. Br J Cancer. 2007;96(1):11-5.
52. Ryan S, Jenkins MA, Win AK. Risk of prostate cancer in Lynch syndrome: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev. 2014;23(3):437-49.
53. Dominguez-Valentin M, Joost P, Therkildsen C, Jonsson M, Rambech E, Nilbert M. Frequent mismatch-repair defects link prostate cancer to Lynch syndrome. BMC Urology. 2016;16:15.
54. Venkitaraman AR. Cancer susceptibility and the functions of BRCA1 and BRCA2. Cell. 2002;108(2):171-82.
55. Barrow PJ, Ingham S, O'Hara C, Green K, McIntyre I, Lalloo F, et al. The spectrum of urological malignancy in Lynch syndrome. Fam Cancer. 2013;12(1):57-63.
56. Honecker F, Wermann H, Mayer F, Gillis JMA, Stoop H, van Gurp RJLM, et al. Microsatellite instability, mismatch repair deficiency, and BRAF mutation in treatment-resistant germ cell tumors. J Clin Oncol. 2009;27(13):2129-36.
57. Cárcano FM, Lengert AH, Vidal DO, Scapulatempo Neto C, Queiroz L, Marque H, et al. Absence of microsatellite instability and BRAF (V600E) mutation in testicular germ cell tumors. Andrology. 2016;4(5):866-72.
58. Velasco A, Riquelme E, Schultz M, Wistuba II, Villarroel L, Pizarro J, et al. Mismatch repair gene expression and genetic instability in testicular germ cell tumor. Cancer Biol Ther. 2004;3(10):977-82.
59. Grindedal EM, Renkonen-Sinisalo L, Vasen H, Evans G, Sala P, Blanco I, et al. Survival in women with MMR mutations and ovarian cancer: a multicentre study in Lynch syndrome kindreds. J Med Genet. 2010;47(2):99-102.
60. Mecklin JP, Järvinen HJ, Virolainen M. The association between cholangiocarcinoma and hereditary non-polyposis colorectal carcinoma. Cancer. 1992;69(5):1112-4.
61. Vasen HFA, Stormorken A, Menko FH, Nagengast FM, Kleibeuker JH, Griffioen G, et al. MSH2 mutation carriers are at higher risk of cancer than MLH1 mutation carriers: a study of hereditary nonpolyposis colorectal cancer families. J Clin Oncol. 2001;19(20):4074-80.
62. Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med. 2012;366(26):2455-65.
63. Buckowitz A, Knaebel HP, Benner A, Bläker H, Gebert J, Kienle P, et al. Microsatellite instability in colorectal cancer is associated with local lymphocyte infiltration and low frequency of distant metastases. Br J Cancer. 2005;92(9):1746-53.

64. Llosa NJ, Cruise M, Tam A, Wicks EC, Hechenbleikner EM, Taube JM, et al. The vigorous immune microenvironment of microsatellite instable colon cancer is balanced by multiple counter-inhibitory checkpoints. Cancer Discov. 2015;5(1):43-51.
65. Overman MJ, McDermott R, Leach JL, Lonardi S, Lenz HJ, Morse MA, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. Lancet Oncol. 2017;18(9): 1182-1191.
66. Abida W, Cheng ML, Armenia J, Middha S, Autio KA, Vargas HA, et al. Analysis of the prevalence of microsatellite instability in prostate cancer and response to immune checkpoint blockade. JAMA Oncol. 2019;5(4): 471-478.
67. Espenschied CR, LaDuca H, Li S, McFarland R, Gau CL, Hampel H. Multigene Panel Testing Provides a New Perspective on Lynch Syndrome. J Clin Oncol. 2017;35(22):2568-2575.
68. Palomaki GE, McClain MR, Melillo S, Hampel HL, Thibodeau SN. EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome. 2009;11(1):42-65.
69. Bao F, Panarelli NC, Rennert H, et al. Neoadjuvant therapy induces loss of MSH6 expression in colorectal carcinoma. Am J Surg Pathol. 2010;34(12): 1798-804.