International Journal of Research in Medical Sciences
Modi BP. Int J Res Med Sci. 2025 Mar;13(3):1362-1368
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20250715

Review Article

The lynch syndrome - a tip of an iceberg: a review of articles

Birenkumar P. Modi*

Department of Surgical Oncopathology, Nirali Hospital, Navsari, Gujarat, India

Received: 17 January 2025
Revised: 12 February 2025
Accepted: 13 February 2025

***Correspondence:**
Dr. Birenkumar P. Modi,
E-mail: dr.birenmodi@yahoo.com

ABSTRACT

Lynch syndrome priorly was known as hereditary non-polyposis colorectal cancer (HNPCC), is an autosomal dominant hereditary disorder due to mutation in a mismatch repair (MMR) gene. Individuals with HNPCC are at increased risk for synchronous and metachronous colorectal cancer (CRC). Most common hereditary colorectal carcinoma syndrome (accounts for 2-5% of all colorectal carcinomas) along with 80% of patients develop colorectal carcinoma and also increased risk of endometrial carcinoma (60%), ovarian carcinoma (10-15%) and other cancers including gastric, ovarian, small bowel, urothelial (ureter, renal pelvis, and bladder), prostate, biliary tract, pancreatic, brain (glioblastoma), cutaneous sebaceous neoplasms. Most colorectal cancers are sporadic, but inherited syndromes cause 5% to 10% of cases. Patients with Lynch syndrome tend to develop carcinomas at an earlier age than the general population (average age: 44 years old). The lifetime risk for ovarian cancer in families with Lynch syndrome is ~8%, which is lower than colorectal and endometrial cancers. Molecular profiles at the genetic level indicate that ovarian cancer in Lynch syndrome has a more favorable prognosis than sporadic ovarian cancer. More than half of sporadic ovarian cancers are diagnosed in stage III or IV, but ≥80% of ovarian cancers in Lynch syndrome are diagnosed in stage I or II. This article provides a framework for understanding the etiology of Lynch syndrome, including how to diagnose patients effectively, differentiate somatic from germline causes and how to monitor based on molecular presentation.

Keywords: Lynch syndrome, HNPCC, MSI, MMR, NGS

INTRODUCTION

Patients with Lynch syndrome - an autosomal dominant disorder, have a monoallelic germline mutation in one of these genes - mainly MSH2 and MLH1 and less frequently MSH6 and PMS2.[1,2] When the other allele is somatically mutated, the two alleles are inactivated and normal expression of the MMR protein is lost. This causes a phenomenon referred to as microsatellite instability (MSI) which are multiple tandem repeats of 1–6 nucleotides in the genome that occur during DNA replication. In cells without MMR proteins or with an aberrant MMR protein, this repair is not usually performed and MSI develops due to an accumulation of abnormal microsatellite repeats leads to the development of various types of cancer, including colorectal, endometrial, small intestinal, gastric, ovarian, urothelial (ureter, renal pelvis, and bladder), prostate, biliary tract, pancreatic, brain (glioblastoma), cutaneous (sebaceous) neoplasms.[3-8]

Mutations in epithelial cellular adhesion molecule (EPCAM)/tumor associated calcium signal transducer 1 (TACSTD1) gene may result in MSH2 promoter hypermethylation and subsequent inactivation of MSH2. Rarely due to inactivation through germline promoter hypermethylation of MLH1; differs from the somatic MLH1 hypermethylation, which may be seen in sporadic colon cancers.[9]

Rarely the result of inactivation of cell cycle checkpoint kinase 2 (CHEK2).

Lynch syndrome confers a 70 to 80% lifetime risk of developing colorectal cancer (CRC). Compared to

sporadic forms of colon cancer, Lynch syndrome occurs at a younger age (mid 40s). Similar to familial adenomatous polyposis, numerous extracolonic manifestations occur. Nonmalignant disorders include café-au-lait spots, sebaceous gland tumors, low-grade skin cancer, kerato-acanthoma, can occur.

Ovarian cancer is a familial gynecological malignancy with a poor prognosis and epidemiological risk of development is 2-6 fold higher in females who have a first-degree relative with ovarian cancer, suggesting a strong link with their genetic background.[10] Only 30% of cases are diagnosed in stage I or II and the majority of ovarian cancer is diagnosed at an advanced stage. Hereditary ovarian cancer may be classified into hereditary breast-ovarian cancer syndrome (including site-specific ovarian cancer and breast/ovarian cancer predisposition) and Lynch syndrome, while other pathogenesis accounts for ≤2% of hereditary ovarian cancer. Lynch syndrome accounts for 10–15% of hereditary ovarian cancers.[11,12]

The lifetime cumulative risk of endometrial cancer for women with Lynch syndrome is 40% to 60%, which equals or exceeds their risk of colorectal cancer. A combination of family and personal medical history and tumor testing provides an efficient combination for diagnosing Lynch syndrome in women with endometrial cancer. Current gynecologic cancer screening guidelines for women with Lynch syndrome include annual endometrial sampling and transvaginal ultrasonography beginning at the age of 30 to 35 years.[13]

DIAGNOSIS, RESULTS, INTERPRETATION

A definite diagnosis of Lynch syndrome can be made on the fulfillment of Amsterdam criteria II, the Revised Bethesda Guidelines, high MSI, the abnormal immunostaining of MMR proteins and confirmation of a germline mutation of an MMR gene.

Laboratory

Histologic features of Lynch syndrome associated carcinoma

MSI-H etiology includes - tumor infiltrating lymphocytes and peritumoral lymphocytes, Crohn's-like lymphoid reaction, mucinous features, medullary features, tumoral heterogeneity and absence of dirty necrosis. Colonic lesions are more likely to be proximal to the splenic flexure. The precursor lesion is usually a single colonic adenoma, unlike the multiple adenomas present in patients with familial adenomatous polyposis, the other main hereditary form of CRC.

Ovarian cancers in Lynch syndrome mostly have non-serous histology and different properties from those of sporadic ovarian cancers.

Endometrial tumors are of endometrioid histotype and frequently arise in lower uterine segment. Associated with tumor infiltrating lymphocytes and peritumoral lymphocytes and association with dedifferentiated/undifferentiated histotypes. In the general population non-endometrioid endometrial carcinoma is typically diagnosed in older women, with a mean age of 65 to 68 years. Lynch syndrome patients mean age of endometrial cancer diagnosis in the Lynch syndrome group overall (46.8 years). Interestingly, the non-endometrioid tumors occurred in patients with hMSH2 mutations. Almost 25% of the patients with Lynch syndrome had pathologic findings for which adjuvant radiation or chemotherapy would be indicated.

Germline testing for mutations can be performed. Microsatellite Instability testing of tumor specimens via PCR is widely utilized; this typically consists of a panel of 5 mono / dinucleotide repeats which are analyzed, and a shift in PCR product size of tumor versus normal indicates instability; designation of MSI-H requires instability in at least 30% of examined loci.

Immunohistochemical testing panel for 4 MMR proteins (MLH1, MSH2, PMS2, MSH6) is widely utilized. BRAF V600E mutation analysis may be performed on cases with loss of MLH1 and PMS2 IHC staining: if mutation is present, then Lynch syndrome is virtually excluded. MLH1 gene promoter hypermethylation may be utilized to determine sporadic versus Lynch syndrome related colon cancers. Syndromic cancers have better survival than non-syndromic.

DISCUSSION

In the last 25 years since the discovery of microsatellite instability (MSI) and the first recognition of germline mismatch repair (MMR) gene variants as the etiologic basis of Lynch syndrome, there has been tremendous progress in the understanding of the spectrum of cancer risk associated with Lynch syndrome as well as in cancer prevention and risk-reduction strategies. The past few years, have brought transformative changes in the treatment of Lynch syndrome–associated cancers with immune checkpoint inhibitors. Advances in next-generation sequencing (NGS) technologies now allow rapid and scalable somatic and germline sequencing that promises to help identify Lynch syndrome in individuals who otherwise lack classic phenotypes. Last, real progress is being made to understand more sophisticated methods of precision cancer prevention, including chemotherapeutic prevention agents (e.g., aspirin) and strategies that leverage the immune system to facilitate primary cancer prevention in otherwise-healthy Lynch syndrome carriers.

Lynch syndrome tumor screening programs are available however protocols vary widely. The current algorithm of making the diagnosis of Lynch syndrome involves meeting the criteria laid out in the Bethesda guidelines.

Conversely others advocate the routine screening of CRC pathology specimens for MSI and immunohistochemical expression of MMR. This approach has been shown to have a better rate of identifying mutation carriers as compared to relying solely on the Bethesda guidelines. EGAPP working group have advocated Lynch syndrome screening on all newly diagnosed CRC patients for the benefit of identifying at-risk relatives. Recently, the revised guidelines for the clinical management of Lynch syndrome recommended that all CRC (<70 years) and all endometrial cancers (<70 years) should be tested by immunohistochemistry or MSI for the identification of patients potentially with Lynch syndrome. The phenomenon of MSI-H, which is a hallmark of Lynch-associated cancers, results in the accumulation of frame shift mutations at known microsatellite loci scattered throughout the coding and noncoding regions of the tumor genome. The predictable nature of such frameshift mutations and their associated neopeptides has led to great interest in the notion of leveraging immune-based methods, such as vaccines, for primary prevention of Lynch syndrome–associated cancers. Curiously, data have shown that healthy, cancer-free individuals with Lynch syndrome harbor circulating T cells that are reactive to such MSI-induced frame shift neopeptides, although they have never had detectable cancer; this strongly suggests that innate immunosurveillance mechanisms already play a role in suppressing MSI-induced carcinogenesis in such individuals. Non-neoplastic colonic crypts from healthy Lynch syndrome carriers have been shown to demonstrate MMR-D by IHC and MSI-H by PCR, which leads to the intriguing hypothesis that the healthy colon of patients with Lynch syndrome is itself a key source of immunogenic frameshift neopeptides that serve to autovaccinate such patients and suppress MSI-induced carcinogenesis. A more precise understanding of the mechanisms by which Lynch syndrome– associated carcinogenesis escapes immune surveillance will be key to help leverage such discoveries into immune-based cancer prevention.

Recommended management for at-risk members of families with Lynch syndrome.

Screening colonoscopy every 1–2 years beginning at age 20–25 years (age 30 years in MSH6 families), or 10 years younger than the youngest age at diagnosis in the family, whichever comes first. At colonoscopic screening, patients have a similar rate of adenomas as non-syndrome patients but much higher incidence of carcinoma. Endometrial sampling Every year beginning at age 30–35 years.

Transvaginal ultrasound for endometrial done every year beginning at age 30–35 years and ovarian cancer urinalysis with cytology every 1–2 years beginning at age 25–35 years history and examination with detailed review of systems, education, and counseling regarding Lynch syndrome every year beginning at age 21 years colorectal resection. For persons with a diagnosed cancer or polyp not resectable by colonoscopy, subtotal colectomy favored with preferences of well-informed patient activity elicited.

Hysterectomy or oophorectomy discuss as an option after childbearing.

Universal testing of all colorectal and endometrial cancers with MMR protein IHC (or PCR-based MSI analysis) is recommended as a screen for Lynch syndrome.

The use of NGS may revolutionize the diagnosis of Lynch syndrome, both by facilitating NGS-based assessment of tumor specimens to screen for MSI and through the growing availability of NGS-based multigene panels for direct germline testing.

Treatment of advanced/metastatic Lynch-associated cancers (and non-Lynch cancers with MSI) with anti–PD-1 monoclonal antibodies (pembrolizumab or nivolumab) yields 70% or greater disease control rates, many of which are quite durable.

Aspirin (600 mg/day) for 2 or more years reduces the risk of Lynch-associated colorectal cancer by greater than 50% and may reduce the risk of other Lynch associated cancers.

Individuals with Lynch syndrome may experience auto-vaccination against microsatellite instability–induced frame shift in peptides that serve as innate immunosurveillance, which suggests that immune based mechanisms for primary cancer prevention are promising as an avenue of future research.[14-21]

Guidelines to reduce the risk of malignancy, leading to a better prognosis for patients with HNPCC

Select recommended interventions based on the pathophysiology of Lynch syndrome.

Improve recognition of the various presentations of Lynch syndrome.

Identify both the prophylactic & post-diagnostic treatment options for Lynch syndrome.

Implement multidisciplinary care coordination using current practice guidelines for

Lynch syndrome to optimize patient outcomes.

Prospective data with long-term follow-up have demonstrated that frequent and early colonoscopic evaluation of healthy individuals with Lynch syndrome can significantly reduce colorectal cancer incidence, colorectal cancer–associated mortality, and overall mortality, thereby solidifying such screening as the core preventive intervention in Lynch syndrome.

The phenomenon of MSI-H, which is a hallmark of Lynch-associated cancers, results in the accumulation of

frameshift mutations at known microsatellite loci scattered throughout the coding and noncoding regions of the tumor genome. The predictable nature of such frameshift mutations and their associated neopeptides has led to leveraging immune-based methods, such as vaccines, for primary prevention of Lynch syndrome–associated cancers. Curiously, data have shown that healthy, cancer-free individuals with Lynch syndrome harbor circulating T cells that are reactive to such MSI-induced frameshift neopeptides, although they have never had a detectable cancer; this strongly suggests that innate immunosurveillance mechanisms already play a role in suppressing MSI-induced carcinogenesis in such individuals. Nonneoplastic colonic crypts from healthy Lynch syndrome carriers have been shown to demonstrate MMR-D by IHC and MSI-H by PCR, which leads to the intriguing hypothesis that the healthy colon of patients with Lynch syndrome is itself a key source of immunogenic frameshift neopeptides that serve to autovaccinate such patients and suppress MSI-induced carcinogenesis. A more precise understanding of the mechanisms by which Lynch syndrome–associated carcinogenesis escapes immune surveillance will be key to help leverage such discoveries into immune-based cancer prevention.

Guidelines for MLH1, MSH2, MSH6, PMS2 and EPCAM mutation carriers

Colon

Colonoscopy begins at age 20 to 25 and repeats every 1 to 2 years, or 5 years younger than the youngest person diagnosed (although the risk may vary depending on germline variant).

Colectomy if colon cancer is diagnosed or if an advanced adenoma is found that cannot be otherwise removed. The preferred treatment remains colectomy with ileorectal anastomosis. Segmental colectomy may be considered in older or select patients. Follow-up surveillance with colonoscopic examination is suggested every 1 to 2 years postoperatively.

Colectomy can be considered if surveillance measures cannot be followed.

Endometrium, uterus, and ovaries

A pelvic exam, transvaginal ultrasound, endometrial sampling, and CA-125 yearly from age 30.

Abnormal uterine or vaginal bleeding warrants immediate evaluation.

Hysterectomy with bilateral salpingo-oophorectomy following completion of childbearing (this recommendation may be variant-dependent).

Extracolonic Lynch-syndrome-associated cancers - NCCN has no screening guidelines for Lynch syndrome-associated malignancies.[22]

Recommendations depend on a family history of a specific cancers

Upper endoscopy (esophagogastroduodenoscopy) with extended duodenoscopy every 1 to 3 years beginning at age 30 to 35 years in select individuals or families or those of Asian descent. Consider testing and treating for *H. pylori*. Computed tomography (CT) enterography or capsule endoscopy every 2 to 3 years to assess for small bowel cancer.

Urinalysis at 30 to 35. The optimal age to begin screening for urinary tract cancers has not been determined, but the risk of developing such types of cancer before age 30 years is quite low. Smoking increases the risk.

Consider endoscopic retrograde cholangiopancrea-tography (ERCP), endoscopic ultrasound, or other diagnostics concerning pancreatic malignancy. Screening for prostate cancer in MSH2 and MSH6 variants. Screening for urothelial cancer in men, those with a family history of transitional cell. Urinary tract malignancies, and those with an MSH2 variant. Screening for breast cancer based on personal and family history and general recommendations.[23-25]

A list of differential diagnoses should be kept in mind or to be ruled out during the workup of malignancies associated with Lynch syndrome include Attenuated familial adenomatous polyposis, Cowden disease, Cronkite-Canada syndrome, familial adenomatous polyposis, familial clustering of late-onset colorectal neoplasms, hyperplastic polyps, juvenile polyposis syndrome, lymphomatous polyposis, Muir-Torre syndrome, nodular lymphoid hyperplasia, sporadic colon cancer, Turcot syndrome, and urothelial cancer (smoking-related).[26]

Patients with Lynch syndrome present at earlier ages than cohorts with somatic malignancies. The tissue of younger persons with colonic and extracolonic malignancies should be tested for heritable mutations. The discovery of high MSI and mismatch repair dysfunction should be followed by germline mutation testing and genetic counseling. Distinguishing between somatic and germline mutations is important. Generally, patients with heritable mutations are younger, whereas those with somatic mutations present at an older age. If, for example, testing reveals the absence of MLH1 and PMS2, think promoter methylation (especially with colorectal and endometrial cancers in women and older patients); rule out this cause before germline testing. However, some genetic mutations demonstrate an incomplete penetrance or variable presence in microsatellite analysis; if suspicion remains high, consider referral for DNA testing without PCR or IHC findings. The immunogenic properties of Lynch syndrome tumors are

used to devise target therapy to upregulate the immune response. Most metastatic cancers are tested for mutations to guide directed therapy.

Prognosis

The overall reduction in life expectancy in patients with Lynch syndrome is primarily due to the increased incidence of cancer, especially colon cancer, and its appearance at an earlier age.

The 10-year overall survival from colorectal cancer in patients with Lynch syndrome remains high at 70% for recto-sigmoid malignancies and 88% for colon cancer. Improved colorectal cancer surveillance increases survival further.

A more aggressive surgical approach to colonic resection (total colectomy vs hemicolectomy) is also associated with improved cancer-free survival. The estimated risk of a second colorectal cancer after a segmental colonic resection in patients with Lynch syndrome has been estimated at 16% over 10 years, 41% by 20 years, and 62% at 30 years.

Lynch syndrome was mainly caused by germline variants in the MSH6 and PMS2 genes. Patients with Lynch syndrome-associated endometrial carcinoma showed a trend towards better recurrence free survival and higher risk for second primary cancers compared with patients with endometrial carcinoma caused by MLH1 hypermethylation. Besides a prognostic impact, screening all incident endometrial carcinoma without an upper age limit to identify Lynch Syndrome using tumor-based triage may benefit counselling, affect treatment decisions, and facilitate prevention strategies for current and future patients and their families.[27-32]

CONCLUSION

Despite the imperfections of current genetic testing, clinical judgment should dictate management plans and at risk patients should be enrolled in regular CRC surveillance programs. Patients who have a confirmed MMR gene mutation should undergo colonoscopy every 1–2 years beginning at the age of 20–25, or 10 years before the earliest age of onset in the family. There has been a steady increase in Lynch syndrome tumor screening programs since 2000 and institutions are rapidly adopting a universal screening approach. It is time to standardize institutional high-risk/hereditary CRC clinics. International guidelines should determine the requirements and quality standards for establishing these clinics.

The identification and management of individuals and families with Lynch syndrome has evolved rapidly during the past decade or so. Advances in molecular testing and NGS technologies now allow all patients with colorectal and endometrial cancers to reliably receive screening for underlying Lynch syndrome, whereas innovations in immuno-oncology promise to continue revolutionizing the treatment of Lynch-associated cancers. To continue moving the needle forward, expanded efforts to diagnose Lynch syndrome in healthy, cancer-free individuals are needed, rather than relying on the identification of Lynch syndrome through a new cancer diagnosis. Identification of Lynch syndrome offers the potential to prevent cancer-related morbidity and mortality, and continued progress in understanding the immune system's ability to recognize, eradicate, and intercept Lynch-associated neoplasia offers many intriguing possibilities for immune based primary cancer prevention.

Ovarian cancer in Lynch syndrome has different properties from those of sporadic ovarian cancer and hereditary breast-ovarian cancer syndrome, which are other forms of hereditary ovarian cancer. The absence of p53 and KRAS/BRAF mutations in ovarian cancer in Lynch syndrome is similar to the hereditary features of colorectal cancer in Lynch syndrome. Anti-epidermal growth factor antibodies may have efficacy for this form of colorectal cancer and may also be useful for ovarian cancer in Lynch syndrome. Cases with PIK3CA mutations may be treated effectively using mTOR inhibitors. Further clinical studies and investigation of the genetics of ovarian cancer in Lynch syndrome are required to improve risk assessment, screening and development of novel drugs for this disease. Patients with Lynch syndrome and carriers require lifelong surveillance and genetic counseling. Professionals must remain engaged and updated on recommendations for screening and treatment as guidelines change to reflect current research and available targeted therapy.

Further research is needed to determine the efficacy of screening methods compared with prophylactic surgery for the reduction of endometrial cancer morbidity and mortality in women with Lynch syndrome, to identify possible chemoprevention strategies and to assess the effect of prophylactic surgery on survival and gynecologic cancer-related deaths. General recommendation that individuals diagnosed with Lynch syndrome be counseled by their health care providers to follow the current screening recommendations and be offered the choice of prophylactic surgery.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Jass JR. Hereditary Non-Polyposis Colorectal Cancer: the rise and fall of a confusing term. World J Gastroenterol. 2006;12(31):4943-50.
2. Watson P, Riley B. The tumor spectrum in the Lynch syndrome. Fam Cancer. 2005;4(3):245-8.
3. Sehgal R, Sheahan K, O'Connell PR, Hanly AM, Martin ST, Winter DC. Centre for Colorectal Disease, St. Vincent's University Hospital, Elm Park, Dublin

4, Ireland. Available at: https://www.stvincents.ie /research-and-education/our-research-groups/centre-colorectal-disease/. Accessed on 28 December 2024.
4. Lim A, Rao P, Matin SF. Lynch syndrome and urologic malignancies: a contemporary review. Curr Opin Urol. 2019;29(4):357-63.
5. Shih AR, Kradin RL. Malignant mesothelioma in Lynch syndrome: A report of two cases and a review of the literature. Am J Ind Med. 2019;62(5):448-52.
6. Kaur RJ, Pichurin PN, Hines JM, Singh RJ, Grebe SK, Bancos I. Adrenal Cortical Carcinoma Associated With Lynch Syndrome: A Case Report and Review of Literature. J Endocr Soc. 2019;3(4):784-90.
7. Dominguez-Valentin M, Sampson JR, Seppälä TT, Ten Broeke SW, Plazzer JP, Nakken S, et al. Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. Genet Med. 2020;22(1):15-25.
8. Hendriks YM, Jagmohan-Changur S, van der Klift HM, Morreau H, van Puijenbroek M, Tops C, et al. Heterozygous mutations in PMS2 cause hereditary nonpolyposis colorectal carcinoma (Lynch syndrome). Gastroenterology. 2006;130(2):312-22.
9. Hampel H, Frankel WL, Martin E, Arnold M, Khanduja K, Kuebler P, et al. Screening for the Lynch syndrome (hereditary nonpolyposis colorectal cancer). N Engl J Med. 2005;352(18):1851-60.
10. Neesham D. Ovarian Cancer Screening, Aust Fam Physician. 2007;36:126-8.
11. Lu KH. Hereditary Gynecologic Cancers: risk, prevention & management. Clinical relevence of hereditary endometrial cancer. 1st edition. Informer Healthcare; New York, NY. 2008;15-28.
12. Aarnio M, Sankila R, Pukkala E, Salovaara R, Aaltonen LA, de la Chapelle A, et al. Cancer risk in mutation carriers of DNA-mismatch-repair genes. Int J Cancer. 1999;81(2):214-8.
13. Parker WH, Broder MS, Liu Z, Shoupe D, Farquhar C, Berek JS. Ovarian conservation at the time of hysterectomy for benign disease. Obstet Gynecol. 2005;106(2):219-26.
14. Yurgelun MB, Hampel H. Recent Advances in Lynch Syndrome: Diagnosis, Treatment, and Cancer Prevention. Am Soc Clin Oncol Educ Book. 2018;38:101-9.
15. NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High-Risk Assessment: Colorectal, Version 3. 2017. Available at: http://www.nccn.org/ professionals/ physician_gls/pdf/ genetics_colon.pdf Accessed on 27 December 2024.
16. Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW; American College of Gastroenterology. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. 2015;110(2):223-62.
17. 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.
18. Møller P, Seppälä T, Bernstein I, Holinski-Feder E, Sala P, Evans DG, et al; Mallorca Group (http://mallorca-group.eu). Cancer incidence and survival in Lynch syndrome patients receiving colonoscopic and gynaecological surveillance: first report from the prospective Lynch syndrome database. Gut. 2017;66(3):464-72.
19. Ahadova A, von Knebel Doeberitz M, Bläker H, Kloor M. CTNNB1-mutant colorectal carcinomas with immediate invasive growth: a model of interval cancers in Lynch syndrome. Fam Cancer. 2016;15(4):579-86.
20. Balmaña J, Balaguer F, Cervantes A, Arnold D; ESMO Guidelines Working Group. Familial risk-colorectal cancer: ESMO Clinical Practice Guidelines. Ann Oncol. 2013;24(6):vi73-80.
21. Giardiello FM, Allen JI, Axilbund JE. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US multi - society task force on colorectal cancer. Gastroenterology. 2014;147:502-26.
22. Evans DG, Ingham SL. Reduced life expectancy seen in hereditary diseases which predispose to early-onset tumors. Appl Clin Genet. 2013;6:53-61.
23. Dominguez-Valentin M, Sampson JR, Seppälä TT, Ten Broeke SW, Plazzer JP, Nakken S, et al. Cancer risks by gene, age, and gender in 6350carriers of pathogenic mismatch repair variants: findings from the Prospective LynchSyndrome Database. Genet Med. 2020;22(1):15-25.
24. 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.
25. 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.
26. Bhattacharya P, Leslie SW, McHugh TW. Lynch Syndrome (Hereditary Nonpolyposis Colorectal Cancer). In: StatPearls. Treasure Island (FL): StatPearls Publishing. 2024.
27. Meyer LA, Broaddus RR, Lu KH. Departments of Gynecologic Oncology (LAM, KHL) and Pathology (RRB) at The University of Texas M. D. Anderson Cancer Center, Houston, Texas. Available at: https://faculty.mdanderson.org/profiles/larissa_meyer .html. Accessed on 27 December 2024.
28. Yurgelun MB, Hampel H. Recent Advances in Lynch Syndrome: Diagnosis, Treatment, and Cancer Prevention. Am Soc Clin Oncol Educ Book. 2018;38:101-9.
29. Domingo E, Laiho P, Ollikainen M, Pinto M, Wang L, French AJ, et al. BRAF screening as a low-cost effective strategy for simplifying HNPCC genetic testing. J Med Genet. 2004;41(9):664-8.
30. Nakamura K, Banno K, Yanokura M, Iida M, Adachi M, Masuda K, et al. Features of ovarian cancer in

Lynch syndrome (Review). Mol Clin Oncol. 2014;2(6):909-16.
31. Lindor NM, Petersen GM, Hadley DW, Kinney AY, Miesfeldt S, Lu KH, et al. Recommendations for the care of individuals with an inherited predisposition to Lynch syndrome: a systematic review. JAMA. 2006;296(12):1507-17.
32. Vasen HF, Möslein G, Alonso A, Bernstein I, Bertario L, Blanco I, et al. Guidelines for the clinical management of Lynch syndrome (hereditary non-polyposis cancer). J Med Genet. 2007;44(6):353-62.

Cite this article as: Modi BP. The lynch syndrome - a tip of an iceberg: a review of articles. Int J Res Med Sci 2025;13:1362-8.