Research Report

Systematic Review: An Update on the Spectrum of Urological Malignancies in Lynch Syndrome

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Abstract.

Background: Lynch syndrome is an autosomal dominant disorder that predisposes individuals affected to certain malignancies. Colon and endometrial cancers are the malignancies most highly associated with Lynch syndrome. However, growing body of evidence links Lynch syndrome to urological cancers.

Objective: This review aims to clarify the type of urological malignancies that fall under the Lynch-associated cancer spectrum.

Methods: Using PRISMA guidelines, a systematic search between January 1990 to February 2018, was conducted using the MEDLINE database with the application of the following MESH terms: colorectal neoplasms, hereditary nonpolyposis; DNA mismatch repair; urologic neoplasms; kidney pelvis; ureteral neoplasms; urinary bladder; carcinoma, transitional cell; prostatic neoplasms; testicular neoplasms.

Results: Upper tract urothelial cancers are well established under the Lynch spectrum. Increasing evidence supports its association with prostate cancer. However, there is, inconclusive and limited evidence for an association with bladder and testicular cancer.

Conclusions: The evidence underpinning certain urological malignancies associated with Lynch syndrome has expanded in recent years. Our review may assist in providing a summary of the current standing in literature. However, we recommend further investigations to better clarify associations, particularly with prostate, bladder and testicular cancer.

Keywords: Colorectal neoplasms, hereditary nonpolyposis, DNA mismatch repair, urologic neoplasms, kidney pelvis, ureteral neoplasms, urinary bladder, carcinoma, transitional cell, prostatic neoplasms, -testicular neoplasms

INTRODUCTION

Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer (HNPCC), is an inherited autosomal dominant disorder that predisposes individuals to a spectrum of malignancies.

Although early-onset colorectal and endometrial cancer remain the predominant clinical manifestations of Lynch syndrome [1–4], the risk of other extracolonic malignancies is notable. Potential extracolonic malignancies described in the literature include cancers of the ovary, urinary tract, small bowel, stomach, hepato-biliary tract, skin and brain [5–7].

The evidence pertaining to urological malignancies in Lynch syndrome has expanded in recent

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years. Currently the increased risk and the underlying genetic mechanism of upper tract urothelial carcinoma (UTUC) in patients with Lynch syndrome is well described in the literature [7–11]. Whilst there is a strong association with UTUC, it is controversial whether there is a link between Lynch syndrome and other urological malignancies, especially those of the bladder, prostate and testis. Previous reviews have suggested a weak association, if any, between these cancers [12]. The question as to whether these should be considered part of the malignant spectrum of Lynch syndrome is explored in this review. We detail recent and seminal studies to explore the types of urological tumors that should be considered Lynch-associated cancers.

EVIDENCE ACQUISITION

A systematic search was conducted using the MEDLINE database using PRISMA guidelines. Papers were selected using the time period from January 1990 to February 2018. The following MESH terms were applied: colorectal neoplasms, hereditary nonpolyposis; DNA mismatch repair; urologic neoplasms; kidney pelvis; ureteral neoplasms; urinary bladder; carcinoma, transitional cell; prostatic neoplasms; testicular neoplasms. No language restrictions were imposed. Hand-searching references from articles was used to identify additional relevant studies. Initially, articles were selected using title and abstract. The full manuscript of these articles were then obtained and considered for eligibility. Overall, 18 articles were selected for upper tract urothelial cancer, 14 for bladder cancer, seven for prostate cancer and 11 for testicular cancer.

EVIDENCE SYNTHESIS

Mechanism of carcinogenesis

Genetics

Lynch syndrome is an autosomal dominant disorder. It is associated with a cancer susceptibility caused by a germline mutation(s) in one or more of the DNA mismatch repair (MMR) genes mutS homlog 2 (MSH2) [13], mutL homolog 1 (MLH1) [14], mutS homolog 6 (MSH6) [15] and postmeiotic segregation increased 2 (PMS2) [16]. It is also associated with the loss of expression of MSH2 due to deletions in the epithelial cell adhesion molecule (EpCAM) gene [17]. Urological tumors in Lynch syndrome are particularly associated with MSH2 mutation and MSH6 [11, 18].

Mismatch repair system

Normally, MMR proteins maintain genomic integrity by detecting and excising DNA mismatches that occur during DNA synthesis. MMR function requires the coordination of multiple MMR gene products, thus mutation of any of the four MMR genes results in the disruption of the overall repair system. MMR dysfunction results from the inactivation of both alleles in any one of the four MMR genes. The first allele inactivation in patients with Lynch syndrome originates from the inherited germline mutation; the second allele is inactivated by another mechanism (somatic mutation, loss of heterozygosity or epigenetic silencing).

Microsatellite instability

The loss of gene repair functioning results in the accumulation of errors due to MMR dysfunction, which usually occurs in the microsatellite regions of DNA. This is referred to as microsatellite instability (MSI). MSI is characteristic of Lynch-associated colorectal cancers [19], and also occurs in approximately 15% of sporadic cancers due to other faulty DNA repair mechanisms [20]. Unstable microsatellite regions are thought to affect cell growth, cell apoptosis and some DNA MMR genes.

MSI in recent years has been studied in regard to its association with colorectal tumor prognosis and management. For unclear reasons, MSI-high colorectal tumors are associated with a more favourable prognosis in both Lynch syndrome and sporadic cases [21]. Furthermore, the presence of MSI appears to be unlikely to derive significant benefit from adjuvant fluoropyrimidine-based therapy [22].

Although MSI is well recognised in colorectal cancer as a prognostic marker and aids in management, the microsatellites that are used for identification of MSI have not been fully validated in other Lynch-associated cancers [23]. Outside of the colon, the link between MSI and IHC becomes weaker, suggesting that microsatellites may be organ-specific [24]. The utility of MSI in directing management is yet to be investigated in extra-colonic cancers associated with Lynch syndrome. The link between MSI and IHC in UTUC has not been well investigated though recent data suggest that a proportion of Lynch syndrome-associated UTUC may be

MSI-stable [11] and sporadic tumours may be MSI-high [25, 26].

Identification of individuals at risk of Lynch Syndrome

Several clinicopathologic criteria, such as the Amsterdam criteria [27] (Table 1) and revised Bethesda criteria [28] (Table 2), can be used to identify individuals at risk of Lynch syndrome. As these studies have limited sensitivity, further clinical testing is advised for those who meet criteria. Excised tumors may initially be tested for microsatellite instability and immunohistochemistry as described above. However, the definitive diagnosis of Lynch syndrome requires a referral to a genetic counselor to perform genetic testing (prove a germline gene defect), as well as assessing personal history and outlining a comprehensive family pedigree.

Lynch-associated urological tumors

An updated understanding of the urological cancers involved in this syndrome is important to improve disease and family classification, risk estimates, and screening and surveillance recommendations in known carriers.

Upper tract urothelial cancer

Upper urinary tract urothelial carcinomas (UTUC) refer to malignancies that arise from the pyelocaliceal cavities and ureter. UTUC is a relatively uncommon, constituting five to ten percent of all urothelial cancers [29, 30]. However, it is well recognised as a Lynch-associated malignancy, especially in individuals with MSH2 and MSH6 gene mutation [18, 31–34]. MMR deficiency is detected in 5–11.3% of UTUC via immunohistochemistry, particularly the loss of expression in MSH6 +/– MSH2 (Table 3) [11, 33, 34]. Universal point of care testing using AMS II and IHC criteria in patients with UTUC identified 13.9% having potential Lynch syndrome and confirmed 5.2% had Lynch syndrome [11]. Histopathology may play a role in identifying tumours for MSI testing. Patterns of inverted growth, intra-tumoral lymphocytes, presence of pushing borders tumour grade and pleomorphism, may be suggestive of Lynch associated UTUC [33, 34]. However, the evidence is still lacking in this area. In patients with Lynch syndrome, the reported lifetime risk of developing UTUC is between 0.4 and 20 percent, which confers up to a 22 times greater risk than that of the general population [9, 12, 32, 35–38].

The median age of onset of UTUC in patients with Lynch syndrome is 56 years of age [37]. Furthermore, UTUC is almost twice as common in men compared with women in the normal population [39]. However, in Lynch syndrome, the rates between sexes appear to be similar [18]. This was detailed in a recent national retrospective cohort study of the Danish HNPCC registry of 288 Lynch syndrome families and included 64 individuals who developed UTUC. Analysis of tumor distribution amongst sex showed a cumulative risk of approximately four percent in males and five percent in females [18]. Overall, consistent evidence continues to support UTUC as a part of the Lynch-tumor spectrum.

There are several areas of unmet need for Lynch syndrome patients in regard to screening for UTUC [40]. Recent review and consensus opinion publications suggest frequent urinalyses in these patients, using the AUA criteria of microhematuria (and any gross hematuria) as triggers for screening [25, 40]. Mork et al acknowledged the high rates of microhematuria in the general public which could lead to a high negative workup, however suggested potential justification in this at-risk population [25]. Urinary cytology alone may miss low-grade tumors and is a poor screening test. Retrograde cystoscopy may be useful, however cystoscopy alone is not recommended as a means for screening [40]. Lynch syndrome patients also frequently have CT scans for follow up of colorectal or endometrial cancer, and thus a coordinated effort to modify these scans to contain a urographic phase may help minimize costs as well as radiation exposure. Pradere et al have recently summarised recommendations for post-radical nephroureterectomy surveillance regime involving cystoscopy, urinary cytology and CT urogram, depending on depth of tumour invasion [40]. It is also suggested that Lynch syndrome-related UTUC may be more sensitive to chemotherapy [41], as has been seen in colorectal cancer. While experience of the authors is consistent, there are no studies that have conclusively demonstrated this finding.

Bladder cancer

Bladder cancer is the most common urinary malignancy in the general population, with environmental exposures accounting for majority of cases. However, studies looking at heredity in bladder cancer suggest a small increase in risk in those with a positive family history [42]. A number of genes have been identified to play a role in its pathogenesis, most prominently the p53 and retinoblastoma genes [43, 44].

Table 1
Amsterdam II criteria for Lynch syndrome

For identifying individuals at risk of being MMR mutation carriers, where all criteria must be met:
Amsterdam II
• 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 criteria

Tumors from individuals should be tested for MSI in the following situations:
Revised Bethesda criteria
• Colorectal cancer diagnosed at less than 50 years of age.
• Presence of synchronous or metachronous colorectal, or other Lynch syndrome-associated tumor (endometrial, ovarian, pancreas, stomach, ureter, renal pelvis, biliary tract, brain, sebaceous gland adenomas, keratoacanthomas and small bowel)
• Colorectal cancer with high microsatellite instability histology (tumor-infiltrating lymphocytes, Crohn's like lymphocytic reaction, mucinous/signet ring differentiation or medullary growth pattern) diagnosed before the age of 60 years.
• Patient diagnosed with colorectal cancer with at least one first –degree relative with Lynch-related tumor diagnosed younger than the age of 50 years.
• Patient diagnosed with colorectal cancer with two or more first or second-degree relatives with Lynch-related tumors at any age.

Table 3
Loss of mismatch repair proteins in patients with UTUC at universal point of care testing

Author, year (reference)	Loss of mismatch repair protein	MSH2 + MSH6	MLH 1+PMS2	MSH 6	MSH2	MLH1
Metcalfe et al. [11]	11.3%	5.2%	0%	6.0%	0.0%	0.0%
Harper et al. [33]	7.0%	5.6%	0%	1.0%	0.0%	0.0%
Urakami et al. [34]	5.0%	3.5%	0.7%	0.7%	0.0%	0.0%

There is limited, but growing evidence, describing the relationship between Lynch syndrome and bladder cancer. As such, the inclusion of urothelial bladder cancer within the Lynch-associated tumor spectrum remains controversial. It was previously thought that bladder cancer did not have any relationship to Lynch syndrome due to the lack of reported incidence and differences in its mechanisms of carcinogenesis [12]. This notion was supported by studies that reported a low frequency of MSI in bladder tumors and/or no significant risk association between Lynch syndrome and bladder cancer [7, 45–47].

However, recently published literature supports a relationship [6, 18, 31, 38, 46, 48–50], with an estimated increased risk of bladder cancer in Lynch syndrome between 1–20%, especially amongst males and MSH2 carriers. In particular, Skeldon et al examined the risk of bladder cancer in Canadian cohort of 321 patients with MMR gene mutations. Of those with MSH2 mutations ($n = 177$), 6.21% of patients had bladder cancer ($n = 11$). When this was compared with the general Canadian population, the relative risk of bladder cancer in MSH2 carriers was significantly higher ($p < 0.001$) with earlier age of onset (59.6 years vs >70 years) [49]. Furthermore, a recent study reviewed records of 288 Lynch syndrome families with total of 3235 mutation carriers and first-degree relatives [18]. 54 patients with bladder cancer were identified, with 86% having a MSH2 mutation. This study estimated the increased risks for bladder cancer in this population at 3.3% for men and 2.6% for women for bladder cancer. Moller et al estimate survival rates of those with Lynch associated bladder cancer to be 93% at 5 years and 81% at 10 years [51].

Although a significant increase in risk of bladder cancer in Lynch syndrome has been reported, there are several factors that may undermine these observations. The association of Lynch syndrome with bladder cancer may be confounded by studies not accounting for sporadic cases of bladder cancer and those with higher environmental risk factors. Additionally, patients with prior or concurrent UTUC may confound results, as a result of seeding in the bladder. Furthermore, as previously discussed by Roupret et al. [12], the low rates of MSI reported in bladder cancer specimens may undermine its association with

Lynch syndrome [18], however the utility of MSI in extracolonic cancer, as aforementioned, requires further investigation. Phelan et al. [50] explore the difficulty in truly differentiation the role of inheritance or genetic association and environmental risk factor clustering in families.

Overall, we have identified several studies that suggest a potential association between bladder cancer and Lynch syndrome. Despite these reports, it remains difficult to suggest whether bladder cancer is a Lynch-associated cancer, and if it is, the penetrance is much less than UTUC. We recommend further investigation with larger cohort studies taking into account potential confounders to help further clarify the contention in the literature.

Prostate cancer

Prostate cancer is the most common malignancy in men and the second leading cause of cancer related deaths [30]. Most adenocarcinomas of the prostate are sporadic, however a small proportion are attributable to genetic factors, most notably the BRCA2 gene [52]. Although the molecular genetic mechanisms involved in prostate cancer are not well understood, recent epidemiological evidence supports a link between prostate cancer and Lynch syndrome.

The argument for the inclusion of prostate cancer in the Lynch syndrome spectrum has been underpinned by the 2014 systematic review and meta-analysis by Ryan et al. [53]. It identified 23 studies (six molecular studies, 18 risk studies) that analysed data on prostate cancer in MMR gene mutation carriers. It found that 74 percent (95%CI, range 57–85%) of prostate cancers in mutation carriers were MMR-deficient (especially MSH2 mutations). There was a relative risk of 3.67 for prostate cancer developing in those with the gene mutations (95%CI, 2.32–6.67). The authors also reported the epidemiologic risk of prostate cancer was significantly increased by two to three-fold in Lynch syndrome patients. This association was reinforced in a recent study of 188 males diagnosed with Lynch syndrome that had an almost five fold increase in prostate cancer incidence over a ten-year period [54]. These results are in accordance with the 2016 study of 288 Danish Lynch syndrome families, where almost 10% of the cohort developed prostate cancer. MMR–deficiency was identified in 69% of cases [55]. Also of note, current evidence suggests no increased risk of early of tumor onset [53] or advanced staging at diagnosis [54]. However higher-grade tumors (Gleason 8–10) have been reported [55].

The known susceptibility of BRCA mutation carriers to prostate cancer provides another interesting twist to this narrative, since the protein products of BRCA1 and BRCA2 are involved with DNA repair and other associated functions to stabilize DNA, similar to MMR proteins [56]. Given the state of evidence in the literature, we believe that there is a strong argument for the inclusion of prostate cancer in the Lynch syndrome tumor spectrum. However, the clinical implications for screening and surveillance remain unclear. Barrow et al recommended a trial of PSA testing in MSH2 mutation carriers from 40–50 years [47]. Ryan and colleagues suggest a more relevant role once there is clarification in the mutation specific risks [53]. There may also be therapeutic implications for Lynch syndrome patients diagnosed with prostate cancer in regard to therapies such as radiation which may potentiate a mutagenic phenotype.

Testicular cancer

Testicular germ cell tumors are the most frequent malignant neoplasm found in young males (25–35 years of age) [57]. Although familial aggregation of testicular cancer is well recognised [58], there have been no published reports of its occurrence in Lynch syndrome families. Notably, while MMR gene mutations and microsatellite instability in testicular cancer have been examined in contemporary literature, the existing evidence remains conflicting.

The studies that support the association are primarily those that investigate refractory testicular germ cell tumors [59–61]. Mayer et al found 33% of refractory specimens had MSI [59]. Another study proposed the distinct prognostic value of MSI [62]. It showed that MMR deficient tumors (MSH2) with MSI-high phenotype were significantly associated with faster clinical relapse and death following chemotherapy than germ cell tumors with an intact MMR system. The same authors published a later study that correlated MSI with increased tumor recurrence [63].

Conversely, Carcano et al found no microsatellite instability and normal MLH1 and MSH2 expression in all 133 specimens primary testicular germ cell tumors [64]. These results were consistent with several previously published studies [65–67].

This discrepancy in the literature may be explained by differences in methodology, demographics and the subgroup of tumor analysed. The lack of microsatellite instability is more often observed in studies pertaining to primary testicular cancers, whereas, its presence may play a role in refractory or recurrent

tumors. Given the uncertain nature of the data, it would be reasonable to systematically explore the association of Lynch syndrome with refractory or recurrent testicular germ cell tumors, keeping in mind the potential for discordant IHC and MSI findings and the potential for tissue-specific microsatellites.

CONCLUSIONS

Determining the urological malignancies that may be Lynch-associated is pertinent to refining the management course for families with Lynch syndrome. Patients with Lynch syndrome would benefit from informed measures for early detection and screening of susceptible urologic cancers. Unfortunately, there is insufficient evidence currently to direct such clinical decision-making. Although UTUC is well supported in the literature as a Lynch-associated cancer, a lack of awareness of this association may exist amongst clinicians, leading to a proportion of UTUC misclassified as sporadic [68]. The opportunity to appropriately screen and manage patients earlier in their disease progression is missed, as well as the missed opportunity to diagnose an inheritable syndrome that would impact family members. There is an emerging role of universal point of care testing for possible Lynch syndrome in those with UTUC [11]. Further studies investigating the utility of screening for prostate cancer in males with Lynch syndrome are required. Similarly, the paucity of consistent evidence for the development of bladder cancer in this syndrome and the inconsistent evidence for testicular cancer means that further evidence is needed to help clarify the potential association and relative importance in the Lynch syndrome spectrum.

DISCLOSURES

None.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

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