

Management of extracolonic tumours in patients with Lynch syndrome

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Hereditary nonpolyposis colorectal cancer, or Lynch syndrome, is responsible for 2–3% of all colorectal cancers. Lynch syndrome is also associated with a high risk of extracolonic cancers, including endometrial, stomach, small bowel, pancreas, biliary tract, ovary, urinary tract, brain, and skin cancer. In this Review, we discuss the risks, surveillance tests, and guidelines for the management of extracolonic tumours associated with Lynch syndrome. For all types of extracolonic cancer, evidence supporting surveillance is scarce. A benefit of surveillance is evident only for endometrial cancer, where transvaginal ultrasound and endometrial sampling detect tumours in early stages. Surveillance is generally recommended for urinary tract and gastric cancer, especially in families with more than one member with these types of cancer. For the other types of cancer, surveillance is typically not recommended. Prophylactic hysterectomy and bilateral salpingo-oophorectomy should be considered for women with Lynch syndrome who are past childbearing age, especially during surgery for colorectal cancer. No data show efficacy of chemopreventive drugs in reducing the risk of extracolonic cancers for patients with Lynch syndrome.

Introduction

Lynch syndrome, or hereditary non-polyposis colorectal cancer, is the most common hereditary colon cancer and is characterised by a predisposition to early onset colorectal cancer and several extracolonic malignancies (figure 1). In the past, diagnosis was based on family history and clinical criteria, such as the Amsterdam criteria.¹ Identification of susceptibility genes for Lynch syndrome narrowed the diagnosis to families with pathogenic germline mutations in one allele of the mismatch repair genes *MLH1*, *MSH2*, *MSH6*, or *PMS2*. Mutations in mismatch repair genes on both alleles cause a rare form of childhood onset cancer that we do not discuss. Disrupted mismatch repair function leads to replication errors in repetitive DNA segments, known as microsatellites. Microsatellite instability also occurs in some sporadic cancers.

The most common malignancy in individuals with Lynch syndrome is colorectal cancer, with a cumulative lifetime risk of up to 70% at age 70 years.¹ People who are carriers of mutations in mismatch repair genes also have a risk of extracolonic cancers; these include cancer of the endometrium, ovary, stomach, urinary tract, biliary tract, pancreas, small bowel, brain, and skin (figures 1 and 2). Carcinogenesis and biological behaviour of colorectal tumours differ in individuals with and without Lynch syndrome.¹ Whether the same is true for other cancers associated with Lynch syndrome is unknown.

Surveillance is done in asymptomatic individuals to diagnose malignant or premalignant lesions at an early stage to improve survival. For people with Lynch syndrome, colorectal surveillance via colonoscopy is recommended every 1–2 years beginning at age 20–25 years. This strategy has reduced the incidence of and mortality from colorectal cancer.^{2,3} Surveillance of all other organs in which tumours might develop is not realistic with current methods. It is unclear for which extracolonic cancer types surveillance is beneficial, at what age to start, and how often. In this systematic Review, we outline the risks, surveillance tests, and guidelines for the management of extracolonic malignancies in Lynch syndrome.

Risk of extracolonic malignancies

Finding the best surveillance strategy for a tumour type first requires knowledge of the lifetime risk and age distribution at the time of diagnosis. Cancer risk is affected by external factors, such as diet and lifestyle, and by internal factors, such as genetic characteristics.

The risk of extracolonic tumours for people with Lynch syndrome depends on which mismatch-repair gene is mutated. Carriers of mutations in *MLH1*, *MSH2*, *MSH6*, and *PMS2* have different cancer risks. However, most individuals with Lynch syndrome have mutations in either *MLH1* or *MSH2*, and data on the risks associated

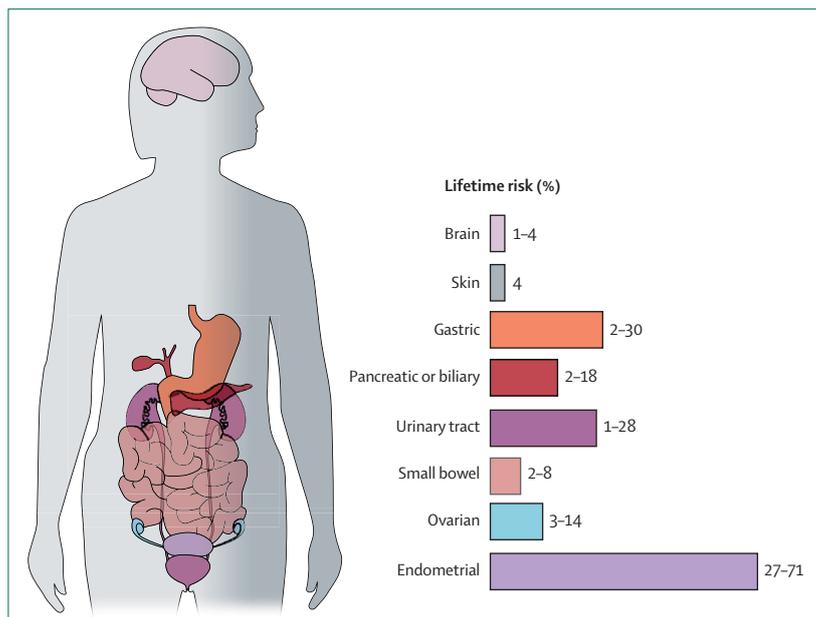


Figure 1: Lifetime risks of extracolonic tumours in people with Lynch syndrome

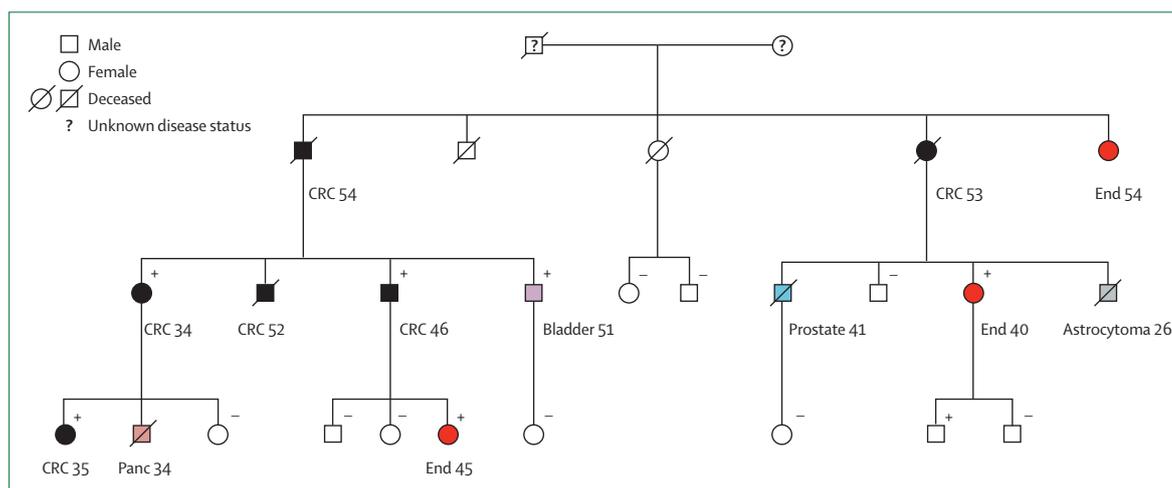


Figure 2: Pedigree of a family with Lynch syndrome (*MSH2* mutation)

+ = proven mutation carrier. - = non-mutation carrier. CRC = colorectal cancer. Bladder = bladder cancer. End = endometrial cancer. Panc = pancreatic cancer. Prostate = prostate cancer. Numbers after tumour type refer to age at diagnosis. Not all relatives chose to have genetic testing.

with the other mismatch repair genes are limited. Some studies report risks associated with particular genes and others present collective risks. Estimations of cancer risk in patients with Lynch syndrome are from both proven and assumed carriers of mutations. Men have a higher risk of (non-gynaecological) malignant diseases than do women.⁴⁻²⁸ Mutations in genes not involved in mismatch repair can affect cancer risk in families with Lynch syndrome; however, testing for these variants is not part of the clinical risk assessment for Lynch syndrome. Risks of malignancies in individuals with Lynch syndrome are often expressed as standardised-incidence ratios: observed incidence in people with Lynch syndrome relative to that in the general population. Estimated lifetime risks and standardised-incidence ratios for extracolonic cancers in Lynch syndrome are summarised in table 1.⁴⁻²⁸ The epidemiology and surveillance strategy for each type of cancer are discussed in the following sections. Treatments for each tumour type do not differ from treatment of the sporadic forms and are not addressed.

Gynaecological tumours

Epidemiology

For women with a genetic predisposition for Lynch syndrome, lifetime risk of endometrial cancer is higher than that of colorectal cancer. Women with Lynch syndrome have a 27–71% cumulative lifetime risk of endometrial cancer compared with 3% in the general population. Risk is between 27% and 60% for women with mutations in *MLH1* and *MSH2* and 60–71% for those with mutations in *MSH6*. Annual incidence of endometrial cancer in women with Lynch syndrome who are older than 40 years is 2.5%.²⁹ Mean age at diagnosis for carriers of mutations in *MLH1* and *MSH2* is 59 years and 54 years for *MSH6*,^{8,17-19} although Vasen

and colleagues³⁰ reported a younger age at onset. They studied 125 patients with endometrial cancer from families with Lynch syndrome and found a mean age at diagnosis of 48 years (range 27–72 years).³⁰ Of all endometrial cancers, 57% were diagnosed before age 55 years and 98% before the age of 60 years.³⁰ The lifetime risk of ovarian cancer in women with Lynch syndrome is around 7% (3–14%), compared with 1.4% in the general population. In 72 women with Lynch syndrome, twice as many with mutations in *MSH2* as with mutations in *MLH1* had ovarian cancer, and the highest risk was in those aged 40–55 years.¹⁶

Endometrial carcinomas have the same histopathology in patients with and without Lynch syndrome.^{31,32} Cancers in the lower uterine segment seem to be associated with Lynch syndrome. In 35 of 1009 patients with endometrial cancer, the tumour was in the lower uterine segment.³³ Ten of these patients (29%) were found to be from women confirmed to have, or strongly suspected to have, Lynch

	Lifetime risk (%)	SIR	Median age at diagnosis (years)
Endometrial cancer ⁴⁻²⁰	27-71	10-62	46-62
Ovarian cancer ^{4,7-20}	3-14	7-13	40-47
Gastric cancer ^{4,7-8,10-16,21-23}	2-30	3-14	47-56
Small bowel cancer ^{5,8,11,13-16,23-28}	2-8	6	39-53
Pancreatic or biliary cancer ^{4,7,11,14-16}	2-18	2-9	43-66
Urinary tract cancer ^{4,7,8,10-16}	1-28	3-52	49-60
Brain tumours ^{7,8,11,14-16}	1-4	2-4	33-52
Skin cancer ^{10,15}	4	4	51

SIR=standardised incidence ratio. Lifetime risks depend on the type of mismatch repair gene mutated and the sex of the mutation carrier.

Table 1: Reported estimates of lifetime risks of extracolonic malignancies in patients with Lynch syndrome

syndrome. In unselected series of endometrial cancers, around 1.8% of cases are associated with Lynch syndrome. Further studies are needed to confirm these data. Most endometrial cancers associated with Lynch syndrome are detected at an early stage and have a good prognosis.

Ovarian tumours in women with Lynch syndrome are often non-serous.³⁴ A recent meta-analysis found that ovarian tumours with mismatch-repair deficiency had earlier stage disease at presentation than did tumours without mismatch-repair deficiency.³⁴ Only one study systematically investigated ovarian cancer survival in patients with Lynch syndrome compared with a registry-based control group; survival rates did not substantially differ.³⁵

Strategies to lower the risks of endometrial and ovarian cancer in women with Lynch syndrome include surveillance, chemoprevention, and prophylactic surgery.

Surveillance

A high risk of endometrial cancer in women with Lynch syndrome and an easily-detectable premalignant stage are factors that support surveillance for endometrial cancer. These women are less aware of their risk for endometrial versus colorectal cancer and undergo endometrial cancer surveillance less often than colonoscopy.³⁶ Generally, endometrial cancer diagnosed with transvaginal ultrasound in asymptomatic patients is associated with a better prognosis than when it is diagnosed at a symptomatic stage.³⁷

A few studies have investigated the efficacy of gynaecological surveillance in women with suspected Lynch syndrome.^{38–40} Dove-Edwin and co-workers³⁸ retrospectively assessed 269 women with suspected or proven Lynch syndrome undergoing annual or biennial transvaginal ultrasound. The median age at the first investigation was 42 years. No cases of endometrial cancer were detected by surveillance during 826 patient-years. However, two early-stage interval cancers did develop. Both cases were detected after a previous normal ultrasound, suggesting that annual or biennial ultrasound alone might not effectively detect early endometrial carcinoma.³⁸ A retrospective study³⁹ of 41 women with known or suspected Lynch syndrome who had an annual transvaginal ultrasound included 197 patient-years, and ultrasonographic abnormalities were found in 17 of 179 visits. Subsequently, three premalignant lesions with complex atypical hyperplasia were found but no cases of endometrial cancer.³⁹ One symptomatic interval cancer was found at an early stage 8 months after an ultrasound that detected no abnormalities.³⁹ Renkonen-Sinisalo and colleagues⁴⁰ assessed gynaecological surveillance that consisted of transvaginal ultrasound and intrauterine biopsies of the endometrium. In 175 women with Lynch syndrome studied for 759 patient-years, 14 endometrial cancers were diagnosed, 11 as a result of surveillance. Only four

endometrial cancers were detected by transvaginal ultrasound. Intrauterine sampling detected nine endometrial cancers and 14 premalignant hyperplasias. For patients with endometrial cancer, stage distribution and survival were more favourable in the surveilled than in the unsurveilled group.

In the study by Renkonen-Sinisalo and colleagues,⁴⁰ four patients were diagnosed with ovarian cancer that was previously undetected by transvaginal ultrasonography.⁴⁰ Surveillance for ovarian cancer is not effective in women with mutations in *BRCA1* or *BRCA2*, which confer the highest risk for inherited ovarian cancer.⁴¹ Evidence does not support surveillance for ovarian cancer in patients with Lynch syndrome; however, data are scarce and studies on gynaecological surveillance have mainly focused on endometrial cancer.

Surveillance for endometrial carcinoma and premalignant abnormalities is probably more effective with combined transvaginal ultrasound and endometrial biopsy than with ultrasound alone. Endometrial microsampling is a very accurate procedure that can be done in an office setting without anaesthesia.⁴² Further studies are needed to make recommendations on surveillance for ovarian cancer in women with Lynch syndrome.

Chemoprevention

Women who take a combined oral contraceptive pill have a lower risk of endometrial and ovarian cancer than those who do not.^{43,44} Furthermore, risk of these cancers decreases with increasing duration of oral contraceptive use. The protective effect on the ovaries is permanent whereas the protective effect on the endometrium seems to persist for at least 5 years after stopping of oral contraceptive use. Although evidence is insufficient to recommend oral contraceptives for the prevention of endometrial or ovarian cancer in women with Lynch syndrome, use is not contraindicated and might reduce risk of endometrial and ovarian cancers.

Prophylactic surgery

Women with Lynch syndrome, especially those who need surgery for colon cancer, should be given the choice of prophylactic hysterectomy and bilateral salpingo-oophorectomy to eliminate the risk of endometrial and ovarian cancer. Schmeler and co-workers⁴⁵ did a case-control study of 315 women with Lynch syndrome, one-third of whom had prophylactic hysterectomy and bilateral salpingo-oophorectomy. After a 10-year follow-up, endometrial cancer was detected in 33% and ovarian cancer in 5% of women in the control group, whereas no gynaecological cancers were diagnosed in the women who had prophylactic surgery. Chen and colleagues⁴⁶ confirmed the efficacy of prophylactic surgery for women with Lynch syndrome. They found that one diagnosis of endometrial cancer was prevented for every six surgeries and one diagnosis

of ovarian cancer for every 28. Surgeons should be aware that undetected endometrial cancer can be present at the time of hysterectomy. Therefore, endometrial sampling before prophylactic surgery is recommended.⁴⁷ If an occult endometrial cancer is found on preoperative investigations, surgeons should assess disease stage accordingly.

No prospective studies have been done on symptoms, side-effects, and quality of life after prophylactic surgery in women with Lynch syndrome. In premenopausal women, prophylactic bilateral salpingo-oophorectomy results in premature menopause, and symptoms of hot flushes, decreased sexual interest, vaginal dryness, and disturbed sleep, but treatment of these symptoms with hormone replacement therapy is not contraindicated.

Although evidence of effectiveness of gynaecological surveillance in women with Lynch syndrome is limited, current guidelines include annual transvaginal ultrasound and endometrial sampling starting at age 30–35 years.^{48,49} Given the age distribution for development of endometrial cancer, we recommend surveillance from the age of 35–40 years. Women should be instructed to contact their physician in case of unusual signs or symptoms, such as unexpected vaginal bleeding. Prophylactic hysterectomy and bilateral salpingo-oophorectomy should be offered to women with Lynch syndrome who are past childbearing age, especially if surgery for colorectal cancer is needed. Hormone replacement therapy until the age of 50 years should be prescribed to all women with Lynch syndrome with premature surgical menopause.

Stomach cancer

Epidemiology

The lifetime risk of gastric cancer in people with Lynch syndrome varies substantially between populations (table 1).^{4–28} Lifetime risk is 2·1% in the Netherlands⁸ and around 30% in Korea.²² Clearly, risk is higher in areas that have high risk of gastric cancer in the general population, such as in Asia.²² Many patients with Lynch syndrome who develop gastric cancer are diagnosed before the age of 50 years, whereas 90% of sporadic gastric cancers are found after the age of 55 years.²² Gastric cancer seems to affect equal proportions of individuals with mutations in *MLH1* and *MSH2*,^{16,50} although in Finland the risk was higher in carriers of mutations in *MLH1* than *MSH2*.⁷ However, *MLH1* mutations are the more common of the two in Finland.

Gastric cancer in individuals with Lynch syndrome is usually of the intestinal type and has a high degree of microsatellite instability.⁵¹ Intestinal-type gastric cancer is thought to develop through *Helicobacter pylori* infection (the most common proven risk factor),⁵² chronic atrophic gastritis, and intestinal metaplasia to dysplasia. Eradication of *H pylori* before any preneoplastic lesions are present, such as atrophy or intestinal metaplasia, could reduce the risk of gastric cancer.

Surveillance

Currently, there is an increasing trend to recommend surveillance of the stomach by upper gastrointestinal endoscopy, although no consensus exists. Surveillance of the stomach by upper gastrointestinal endoscopy is recommended if more than one family member has gastric cancer.⁴⁹ Clustering of gastric cancer within families, especially those with mutations in *MSH2*, has been suggested¹³ but not confirmed.⁵⁰ Another proposal is to screen in countries with a high incidence of gastric cancer.⁴⁹ Gastric surveillance was not recommended, but could be offered periodically, in guidelines set out by Lindor and co-workers.⁴⁸ A German group has proposed regular gastric surveillance in patients with Lynch syndrome beginning at age 35 years, although no age-specific rates were given to justify this recommendation.⁵⁰ No neoplastic lesions were found with gastroduodenoscopy in 73 patients with Lynch syndrome and a median age of 49 years.⁵³

Although some investigators suggest regular gastroduodenoscopy for all individuals at risk, we think evidence is insufficient to justify such an approach. Surveillance should be considered in families with clustering of gastric cancer and in countries with a high prevalence. Additionally, we suggest *H pylori* detection and subsequent eradication in patients with Lynch syndrome.

Small-bowel cancer

Epidemiology

For people with Lynch syndrome, the lifetime risk of small bowel cancer is around 4%: over 100 times the risk in the general population.⁵⁴ A review of available case series reported a median age at diagnosis of between 39 years and 53 years.⁵⁴ Compared with the general population, patients with Lynch syndrome who develop small-bowel cancer usually present 10–20 years earlier, and the risk is slightly higher in men than in women.⁵⁴ Tumours are usually in the duodenum or the jejunum, with a small proportion in the ileum. The incidence of small-bowel cancer is similar in carriers of *MLH1* and *MSH2* mutations and somewhat rare in those with mutations in *MSH6* and *PMS2*. At the molecular level, most adenocarcinomas show high levels of microsatellite instability.⁵⁵

Surveillance

Surveillance for small-bowel cancer is not in the guidelines for clinical management of families with Lynch syndrome because, until recently, visualisation of the small bowel was limited. Capsule endoscopy and double balloon enteroscopy has substantially improved accessibility of the small bowel. Small-bowel capsule endoscopy, in which patients swallow an optical capture device,⁵⁶ is a safe, patient-friendly, minimally invasive technique for visualisation of the small bowel. Although helpful in the diagnosis of small-bowel cancer,⁵⁷ the technique is limited by the inability to obtain tissue for histological diagnosis

or to provide endoscopic interventions. Double balloon enteroscopy is a reliable approach to detect lesions in the small bowel and allows direct access to the area.⁵⁸

With capsule endoscopy as the most acceptable and potentially sensitive surveillance test for small bowel cancer, the usefulness and cost-effectiveness of surveillance with this technique warrants investigation. Until results are available from an ongoing study in the Netherlands, physicians should discuss the risks and benefits of such a strategy with individual patients.

Pancreatic and biliary cancer

Epidemiology

Early single-family studies reported an association between Lynch syndrome and pancreatic or biliary cancer.^{59–61} The first larger series, done by Mecklin and co-workers,⁶² assessed 18 patients with pancreatic or biliary cancer from families with suspected Lynch syndrome. 15 patients had carcinoma of the biliary tract or papilla of Vater. Mean age at the time of diagnosis was 56 years.⁶² Geary and colleagues¹³ recently reported an incidence of pancreatic cancer seven times higher than in the general population in 319 individuals with Lynch syndrome. Most individuals with pancreatic cancer were diagnosed before the age of 60 years and there was evidence of family clustering. Cancer of the biliary tract was rare.¹³ No data indicate a high risk of hepatocellular cancer in people with Lynch syndrome.

Surveillance

Endoscopic ultrasound is the most sensitive technique for the detection of early pancreatic cancers⁶³ and studies of surveillance in individuals with Lynch syndrome are ongoing. So far, no surveillance approaches are successful in detecting pancreatic cancer at an early, possibly curable stage—not even in high risk groups, such as people with familial atypical multiple mole melanoma (FAMM) syndrome.⁶⁴ Early detection of cancer of the biliary tract is even more difficult than pancreatic cancer. Surveillance for pancreatic or biliary cancer is not recommended for people with Lynch syndrome.

Urinary-tract cancer

Epidemiology

In patients with Lynch syndrome, the risk of urinary tract cancer, in particular cancer of the renal pelvis and ureter, is up to 12%.^{4,7,8,10–16,65} Watson and colleagues¹⁶ assessed 2683 proven or probable carriers of pathogenic *MLH1* or *MSH2* mutations and reported cumulative risks to the age of 70 years of: 6% (8% including bladder cancer risk) for the total group, 0.4% (1%) for women with *MLH1* mutations, 2% (4%) for men with *MLH1* mutations, 9% (12%) for women with *MSH2* mutations, and 20% (28%) for men with *MSH2* mutations.¹⁶ The highest risks were seen between the ages of 50 and 70 years. No data are available on the risk of urinary tract cancer in people with *PMS2* and *MSH6* mutations.

Surveillance

Ideally, upper urinary-tract cancer is detected in asymptomatic patients at an early stage when kidney-sparing therapy is possible. Detection of early stage bladder cancer would be an additional benefit. Very little is known about surveillance for urinary tract cancer in people with Lynch syndrome. The only report on urinary tract surveillance with urine cytology indicated a sensitivity of only 29%.⁶⁶ probably a result of the low number of cancer cells discarded in the urine. Immunocytochemical testing,⁶⁷ or β -glucuronidase activity testing,⁶⁸ improves the sensitivity of detection of upper urinary tract cancer, although sensitivity remains low. The fluorescence in-situ hybridisation assay⁶⁹ might be highly sensitive but requires selective washing of the upper tract and is therefore classified as invasive. Testing for microsatellite instability in urine⁷⁰ to identify tumour DNA seems promising; however, data on its use in a surveillance setting are scarce. Of the possible imaging methods, abdominal ultrasound is not very sensitive for the detection of urinary-tract cancer.⁷¹ Urography with CT is more sensitive than ultrasound⁷ but is not recommended because of the expense and repeated exposure to radiation. We believe that testing for haematuria with a simple and inexpensive urine dipstick is the most attractive approach to surveillance for urinary-tract cancer.^{72,73}

Recommendations differ for the surveillance of urinary-tract cancer in individuals with Lynch syndrome. Lindor and co-workers⁴⁸ advocate annual urinalysis with cytology, because of the low cost and non-invasiveness, without stratification of risk groups. Vasen and colleagues⁴⁹ recommend urinalysis with cytology and abdominal ultrasound, at an annual to biannual interval, beginning at the age of 30–35 years in families with a history of urinary tract cancer. Watson and colleagues¹⁶ propose surveillance from age 50 years, especially for families that carry mutations in *MSH2*. Watson's group also recommend that preventive measures should not be limited to families with a history of urinary-tract cancer.¹⁶

We recommend annual surveillance for haematuria by urine dipstick. If haematuria is confirmed by urine microscopy, patients should have cystoscopy and abdominal ultrasonography—with a contrast study of the upper urinary tract in case of negative ultrasonography. We believe that surveillance should begin at age 45–50 years. In families with a history of urinary-tract cancer before age 45 years, surveillance should begin 5 years before the earliest age at diagnosis.

Skin cancer

Epidemiology

Sebaceous tumours (adenoma, epithelioma, or carcinoma) and keratoacanthomas are prevalent in people with Lynch syndrome: an association known as Muir-Torre syndrome. South and colleagues⁷⁴ report Muir-Torre syndrome in 14 of 50 families and 14 of 152 individuals with Lynch

syndrome. Although predominantly associated with *MSH2* mutations, Muir-Torre syndrome can also occur in families with mutations in *MLH1* or *MSH6*.^{74,75} Skin tumours associated with Lynch syndrome often appear on the face, but can develop anywhere on the body. Most patients who develop skin lesions do so after diagnosis of another malignant disease associated with Lynch syndrome, but in some cases, skin cancer is the first sign of the syndrome. In a recent population-based study, patients with sebaceous carcinoma had a 43% increased risk of a second malignancy, especially in the colon, pancreas, and endometrium, compared with the general population.⁷⁶ Individuals diagnosed with sebaceous carcinoma before the age of 50 years had a higher risk for subsequent cancers compared with individuals diagnosed over the age of 50 years.⁷⁶

Surveillance

No recommendations on surveillance for skin lesions among patients with Lynch syndrome are available. Given the high rate of skin lesions, regular dermatological examination is a reasonable strategy for detection, especially in families with clustering of Muir-Torre syndrome. However, the age at which to start surveillance and the optimum interval are unclear. Patients who are at risk should be counselled to be alert for skin abnormalities and seek early medical attention.

Brain tumours

Epidemiology

Lynch syndrome is associated with an increased risk of brain tumours.^{7,8,11,14–16,77} In 6041 proven or probable carriers of pathogenic *MLH1* or *MSH2* mutations, or their first-degree relatives, cumulative risk of brain tumours to the age of 70 years was 2% for the total group, 1.7% for carriers of *MLH1* mutations, and 2.5% for carriers of *MSH2* mutations.¹⁶ Risks might have been underestimated because individuals who developed brain tumours as children were less likely to be identified. Median age at the time of brain tumour diagnosis is lower in those with Lynch syndrome than in the general population; 26% of the diagnoses were made before the age of 25 years.¹⁶ The most common tumour types are glioblastoma multiforme and astrocytoma, but oligodendrogliomas and ependymomas have also been reported. Brain tumours in individuals with Lynch syndrome are rarely associated with microsatellite instability.⁷⁸ Despite a low incidence, brain tumours were the third highest cancer-related cause of death in a large Dutch cohort of patients with Lynch syndrome.³

Surveillance

No studies have investigated surveillance for brain tumours in Lynch syndrome. Given the low risk of brain tumours associated with this syndrome and the absence of surveillance methods known to decrease morbidity and mortality, surveillance has not been recommended.

Other tumours

Other tumour types that have been reported in patients with Lynch syndrome include breast, prostate, larynx, lung, thyroid, and testicular cancers, and melanoma, lymphoma, leukaemia, and soft tissue sarcomas.^{16,79–83} Molecular findings showed that mismatch repair deficiency contributed to the development of those tumours.^{79–83} Evidence does not show an increased risk of breast or prostate cancer for individuals with Lynch syndrome, although breast cancer risk is somewhat controversial and might differ between populations.^{84,85} The absolute risk for the other cancer types listed is probably too low to justify surveillance, even if effective methods are available. Ponti and co-workers⁷⁹ suggest surveillance for melanomas already identified in families with Lynch syndrome but the effectiveness of this strategy is unknown. In families suspected to have Lynch syndrome but without the more typical colorectal or endometrial cancers, a practical approach might be to study molecular signs of mismatch repair deficiency in selected rare tumour types in the diagnostic work-up.

Conclusion

In this Review, we discussed management of extracolonic malignancies in Lynch syndrome with an emphasis on surveillance. For individuals with Lynch syndrome, the colorectum is the only organ in which surveillance reduces the risk of cancer and mortality. We advocate discussing with the patient the risks and surveillance strategies for other types of tumours associated with Lynch syndrome. Nilbert and colleagues⁸⁶ confirmed the need to start surveillance at a young age by showing genetic anticipation—earlier age at onset of cancer in successive generations.

Table 2^{48,49} summarises guidelines for surveillance of extracolonic malignancies in people with Lynch syndrome. None of these recommendations, however, are supported by solid evidence. Although the risk of extracolonic tumours might be higher in individuals with

	Beginning age (years)	Interval (years)	Examination
Generally recommended^{48,49}			
Endometrial and ovarian cancer	30–35	1	Transvaginal ultrasound, intrauterine sampling, gynaecological examination
Upper urinary-tract cancer*	25–35	1–2	Urinalysis and cytology
Stomach cancer†	30–35	1–2	Gastroduodenoscopy
Generally not recommended but can be considered for individual cases or families			
Skin cancer	Dermatological inspection
Small-bowel cancer	Capsule endoscopy
Pancreaticobiliary tumours	Endoscopic ultrasound

*Some recommend limiting surveillance to families with more than one case of urinary-tract cancer;⁴⁹ others do not propose any restrictions.^{16,48} †Recommended in families with more than one case of stomach cancer or in populations with a high incidence.⁴⁹

Table 2: Guidelines for surveillance for extracolonic malignancies in patients with Lynch syndrome

Search strategy and selection criteria

A literature search of PubMed was done by use of the terms "Lynch syndrome" or "hereditary non-polyposis colorectal cancer" and each of the following: "endometrial", "endometrium", "ovarian", "small bowel", "small intestine", "gastric", "stomach", "urinary", "ureter", "renal pelvis", "kidney", "bladder", "pancreas", "pancreatic", "biliary", "hepatocellular", "brain", "skin", "cancer", "tumour", and "neoplasm". Reference lists of identified articles were reviewed. Only full-text articles published in English between January, 1990, and December, 2008, were included.

mutations in *MSH2* compared with *MLH1*,^{5,8,12} and the risks in *MSH6* and *PMS2* mutation carriers are not well known, no evidence indicates that surveillance strategies should differ. We endorse the guidelines in table 2 but suggest a different approach to surveillance for urinary tract cancer. We recommend that surveillance starts at age 40–45 years with annual urinalysis dipstick test and that surveillance is not limited to families with a history of urinary-tract tumours. For gastric cancer, we propose once only serological *H pylori* determination and eradication. The outcome of each surveillance strategy for patients with Lynch syndrome should be systematically collected and analysed.

Data are limited with respect to chemoprevention to reduce cancer risk in Lynch syndrome. A recent randomised placebo-controlled trial studied the efficacy of aspirin and resistant starch on reducing the risk of colorectal neoplasia in Lynch syndrome.⁸⁷ The use of either treatment, alone or in combination, for up to 4 years, had no effect on the incidence of colorectal neoplasia. No data show efficacy of chemopreventive agents in reducing the risk of extra-colonic neoplasia.

We have focused on management of patients who are proven carriers of mutations associated with Lynch syndrome. In practice, these recommendations are also applied to first-degree relatives of known mutation carriers who decline genetic testing, and patients and their first-degree relatives from families suspected to have Lynch syndrome but with unknown mutations. Surveillance should be preceded by genetic counselling about the natural history of the syndrome and the need for long-term follow-up. Counselling should acknowledge that the recommendations are generally based on expert opinions rather than evidence from clinical trials.

Contributors

JJK is responsible for conception of the paper. JJK, MJEM, RHS, and AML contributed to writing the article. All authors participated in the article design, critical revision, and final approval. JJK and JHK are guarantors of the paper.

Conflicts of interest

The authors declared no conflicts of interest.

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