Cancer Risks After Endometrial Cancer in Mismatch Repair Mutation Carriers

Patrick M. Lynch

Correspondence to: Patrick M. Lynch, JD, MD, Department of Gastroenterology, Hepatology, Nutrition, University of Texas MD Anderson Cancer Center (e-mail: plynch@mdanderson.org).

Recent years have seen increasing attention to the management of endometrial cancer risk in families with hereditary nonpolyposis colorectal cancer or Lynch syndrome (HNPCC/LS). Nevertheless, because endometrial cancer is less common and carries a lower mortality (1) than colorectal cancer in mismatch repair gene (MMR) mutation carriers, it may be an afterthought for many providers and patients.

Endometrial cancer can often be the sentinel event for a patient and family with HNPCC/LS. Because the prognosis for young women with endometrial cancer is good, such patients will live long enough to be at risk for other cancers. It is understood that most diagnoses of HNPCC/LS are made after a diagnosis of new colorectal cancers (2–4). However, clinicians are diagnosing MMR mutations in women through the same stepwise process that is followed in cases of colorectal cancer: initial microsatellite instability testing (by polymerase chain reaction–based assay or immunohistochemistry against MMR proteins), either triggered by early onset or family history (5) or performed on the basis of a more universal testing strategy (6,7). When informative, microsatellite instability testing is followed by germline mutation testing. Caveats are many, including that failure to detect a MMR mutation does not exclude a diagnosis of HNPCC/LS, such that in many cases clinically affected women continue to need to be treated as if HNPCC/LS is present. So, we can expect an increasing number of patients to begin cancer screening after an endometrial cancer diagnosis or to continue ongoing screening after a herald diagnosis of endometrial cancer.

In this issue of the journal, Win et al. (8) have added to our understanding of these matters. Investigators from the international Cooperative Colon Cancer Family Registries project evaluated a cohort of women who had a history of endometrial cancer and were known to have mutations in one of the MMR genes responsible for HNPCC/LS. The endpoint in the study was risk of colorectal and other cancers. The effort has been a hybrid of population-based and clinic-based programs. By design, these programs detected HNPCC/LS within a given family on the basis of a diagnosis of colorectal cancer; although the basic considerations would have been largely the same had index cases had endometrial cancer, as noted above. A given family found to carry an MMR mutation would have been, almost by definition, sensitized by the presence of at least one case of colorectal cancer, with a result, presumably, of greater interest in colon cancer screening among family members. The focus in this analysis was the 127 MMR mutation carriers with prior endometrial cancer. At 20 years of follow-up, the risks of colorectal, kidney or ureter, bladder, and breast cancers were 48%, 11%, 9%, and 11%, respectively, and the relative risks compared with the general population were significantly increased for each.

Strengths of the study include the substantial patient population, of relatively unbiased source, the comprehensive approach to genetic diagnosis and cohort follow-up, and the experience of the investigators. The data on cancer incidence after endometrial cancer diagnosis are helpful but require attention to the details of surveillance, not all of which were available. Frequency of colonoscopy or other screening was based on questionnaires. Interventions to communicate HNPCC/LS screening guidelines or to otherwise foster cancer surveillance were not identified and were presumably heterogeneous.

For these reasons, it is worth considering the aftermath of endometrial cancer diagnosis in the setting of HNPCC/LS. Unsurprisingly, a protective role for colonoscopy screening was seen. A linear reduction in freedom from colorectal cancer was found with increased interval of surveillance, from 44% in those having annual exam to 13% in those with exams at 4- to 5-year intervals. However, colorectal cancer did occur despite even annual surveillance. This phenomenon has been seen in more formal screening studies, underscoring the limitations of colonoscopy generally in assuring protection against colorectal cancer (9). More specifically, the subtlety of early lesions and their rapid growth to become interval cancer was very likely a factor, although unproven by the limited numbers.

Consistent with other data, colorectal cancer risk was lower in MSH6 mutation carriers (standardized incidence ratios of 4.46 vs 38.7 and 58.5 for MLH1 and MSH2 mutation carriers, respectively). Despite this, no changes in screening guidelines have yet been recommended for MSH6 mutation carriers. Colorectal cancer risk could not be assessed for PMS2 mutation carriers because data were not collected for them. This group has been considered to be at lower risk of colorectal cancer (10).

No data were available regarding screening for other at-risk organs. The modest increased risk of breast cancer was thought to have perhaps been an artifact of increased screening, but no actual screening data were brought to bear on this. Again, no enhancement of breast cancer screening has yet been recommended in HNPCC/LS.

The study by Win et al. (8) does not describe the circumstances in which the endometrial cancer itself was diagnosed—that is, whether on the basis of screening or, more likely, evaluation of symptoms.

Recommendations for endometrial screening in HNPCC/LS have not been particularly evidence based (11). Transvaginal...
ultrasound has been a part of the HNPCC/LS screening guidelines for years, but several studies have shown transvaginal ultrasound to be unhelpful for both endometrial and ovarian cancer early detection (12). Ovarian cancer screening remains problematic in all settings. However, we have been encouraged with results from a combined colon/endometrial screening program in which at-risk women underwent colonoscopy and, while under sedation from this examination, endometrial biopsy was performed (13). Although there were modest logistic considerations in coordinating schedules of endoscopists and gynecologists, the approach has been well-received by patients. It is too early to evaluate endometrial biopsy sensitivity and specificity, but some screening experience is being gained (14).

As clinicians from various fields become more familiar with HNPCC/LS, the opportunity to diagnose the condition based on a presentation of endometrial cancer will be possible. The study by Win et al. (8) was from a series of colorectal cancer patients worked up for evidence of MMR deficiency, but the same approach could have been taken with a series of endometrial cancer patients. Such efforts have been taken and largely parallel the experience when colorectal cancer is the starting point. Using the Bethesda Guidelines or modifications, a diagnostic algorithm can be followed (5,7,15). Selecting cases for microsatellite instability/immunohistochemistry according to various age cutoffs has been shown to have an acceptable sensitivity for detecting HNPCC/LS.

In conclusion, we have seen that patients whose sentinel HNPCC tumor is an endometrial cancer have a considerable risk of other cancer. The Win et al. study provides the most unbiased, and thus likely the most accurate, data to date on this issue. These data are highly consistent with other earlier reports and again support a modest increase in risk of breast cancer in HNPCC/LS. Consequently, it is time to redouble efforts to conduct reasonable screening trials to establish the screening benefit for those extra-colonic tumors that have been relatively neglected to date. Substantial challenges exist in considering such screening. Although the relative risk of small bowel cancer is an extraordinary 63-fold after endometrial cancer, its absolute rarity still leaves the potential uselessness of screening, such as by capsule endoscopy, an open question. The standardized incidence ratio for pancreatic cancer of nearly 9 suggests a possible role for screening, but the costs (high) and yields (probably low) of tools such as endoscopic ultrasound and magnetic resonance imaging leave this an area of controversy as well. But at least now we have better measures of the actual risks.

References

Notes

Affiliation of author: Department of Gastroenterology, Hepatology, Nutrition, University of Texas MD Anderson Cancer Center, Houston, TX (PML).