A recent study suggests that expanded testing for Lynch syndrome in women with endometrial cancer may be indicated and beneficial (J Clin Oncol [published online ahead of print May 2, 2011] doi: 10.1200/JCO.2010.32.9979).

Janice Kwon, MD, MPH, assistant professor in the department of obstetrics and gynecology at the University of British Columbia in Vancouver, Canada and colleagues developed a model to evaluate different strategies to screen women with endometrial cancer for Lynch syndrome. They found that immunohistochemical (IHC) triage (when IHC staining of the cancer indicates the absence of one or more of the mismatch repair proteins) of women at any age with at least one first-degree relative (FDR) with a Lynch-associated cancer (endometrial, colorectal, gastric, small bowel, ureter, and renal pelvis) would identify more women with Lynch syndrome and be cost-effective compared with Amsterdam II criteria.

“The MD Anderson Cancer Center has adopted the testing guideline from this paper. In my institution, we have not adopted this yet but we will be revisiting our existing guidelines in the near future,” says lead author Dr. Kwon.

Rationale and Model Criteria
The risk of endometrial cancer in women with Lynch syndrome may be as high as 60%, which equals or exceeds their lifetime risk of colorectal cancer. Currently, genetic testing is encouraged in women with endometrial cancer if their history fulfills the Amsterdam II criteria: at least 2 other relatives with a Lynch-associated cancer (endometrial, colorectal, gastric, small bowel, ureter, and renal pelvis) would identify more women with Lynch syndrome and be cost-effective compared with Amsterdam II criteria.

Henry Lynch, MD, chair of preventive medicine and public health, professor of medicine, and director of the Creighton Hereditary Cancer Center in Omaha, Nebraska, says women are not being tested as frequently as they should be based on the criteria currently recommended in most guidelines. “Unfortunately, the Amsterdam II criteria and Bethesda guidelines are often overlooked in patients with endometrial cancer,” he adds.

To estimate the costs and benefits of 6 approaches to selecting women with endometrial cancer who should undergo Lynch syndrome testing (by sequencing of 4 mismatch repair genes), the researchers developed a Markov Monte Carlo simulation model for a hypothetical cohort of women diagnosed with endometrial cancer. The model compares 6 criteria:

- Fulfilling Amsterdam II criteria
- Younger than 50 years with at least one FDR having a Lynch-associated cancer at any age
- IHC triage if younger than 50 years
- IHC triage if younger than 60 years
- IHC triage at any age if one FDR has a Lynch-associated cancer
- IHC triage of all endometrial cancers

The team determined the incremental cost-effectiveness ratios (ICERs), defined as the additional cost of a specific strategy divided by its additional health benefit, as compared with the next least costly alternate strategy. The numerator of the ICER was the difference in average
lifetime cost in US dollars and the denominator was the average life expectancy gain in years. A strategy was considered cost-effective if the ICER was below $50,000 per year of life gained, which is a commonly used cutoff.

Model assumptions regarding health care costs, colorectal cancer risks, and mortality rates were estimated from published literature. The proportion of patients diagnosed before age 50 years or 60 years was estimated from the Surveillance, Epidemiology, and End Results (SEER) database. It was also assumed that abnormal IHC results would prompt genetic testing and those individuals identified as carriers would be properly screened for colorectal cancer.

The authors noted that testing for microsatellite instability (MSI) and IHC testing have similar sensitivities, but IHC was chosen because it can be done in any pathology laboratory whereas MSI requires more sophisticated testing. “I was surprised that MSI was not included, but IHC can identify the loss of a protein, which MSI cannot do, and its lesser cost makes it more practical,” Dr. Lynch says.

Results

IHC triage of all cases of endometrial cancer provided the highest life expectancy, but the ICER was very high at $648,494 per year of life gained. Selecting patients for testing according to Amsterdam II criteria, IHC triage at age younger than 50 years, and IHC triage at age younger than 60 years were all found to be less effective and more costly than IHC triage at any age with at least one FDR with a Lynch-associated cancer. The ICER of IHC triage at any age with at least one affected FDR was $9126.

According to the authors, the findings remained consistent even when compliance with genetic testing and colorectal cancer screening were estimated to be as low as 50%. Based on an annual incidence of approximately 45,000 cases of endometrial cancer in the United States, this model predicted that 827 women (1.8%) would be found to have Lynch syndrome if all cases were triaged with IHC. Using the criteria of testing those at any age younger than 50 years, and IHC triage at age younger than 60 years were all found to be less effective and more costly than IHC triage at any age with at least one FDR with a Lynch-associated cancer. The ICER of IHC triage at any age with at least one affected FDR was $9126.

Study Strengths and Limitations

While this study has the strength of allowing an estimation of the costs and benefits associated with Lynch syndrome testing options in a large cohort of women that would be difficult to achieve with a clinical trial, the authors note several limitations.

First, there is some uncertainty regarding parameters, including the prevalence of Lynch syndrome within specific age groups, their colorectal cancer risk and mortality rate, and costs of care for colorectal cancer. Also, it was assumed that the women put in each strategy were comparable with regard to other risk factors such as smoking, body mass index, and comorbidities. Furthermore, it was assumed that they had comparable risks of other Lynch-associated cancers. Lastly, 100% compliance with colorectal cancer screening was assumed, although lower rates have been observed.

Despite these limitations, the authors point out in their article that the proportion of women with endometrial cancer and Lynch syndrome who fulfill Amsterdam II criteria may be as low as 30%, while those with endometrial cancer and Lynch syndrome who have at least one FDR with a Lynch-associated cancer may be as high as 80% to 100%, based on the literature. Testing these women with IHC and referring those with abnormal IHC results to genetic counseling and mismatch repair gene sequencing would identify more women who need closer colorectal cancer screening in a cost-effective manner. Furthermore, their FDRs without cancer may then be tested and have appropriate screening strategies employed.

Dr. Kwon says the main point of the study is that clinicians should rethink Amsterdam II criteria for Lynch syndrome testing in women with endometrial cancer. “Our study has demonstrated that by casting a broader net, we can identify more women with Lynch syndrome than by selecting patients according to Amsterdam II criteria, and at lower cost,” she says.

According to Dr. Lynch, a carefully taken history remains an important strategy in identifying at-risk patients. “A well-orchestrated family history, inclusive of cancer of all sites, including the age of onset and patterns of multiple primary combinations in an individual, remains extremely important,” he says.

Murray Joseph Casey, MD, professor in the department of gynecology and obstetrics at Creighton University in Omaha, Nebraska, says the model used in the study should increase the clinician’s alertness to discussing the possibility of hereditary cancers with patients with endometrial cancer having any FDRs with a Lynch-associated cancer. “However, when family histories are unknown or incomplete or there are other reasons to suspect that individual patients may be at risk, the physician is obligated to thoroughly discuss these concerns with their patients and offer strategies that may benefit and not rely completely on hypothetical models for management decisions in their personal care of individuals,” he says.

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Note: The name of this section has been changed from “News & Views” to “Perspectives: Research in Context.” It continues to provide the context for major developments in cancer prevention, detection, and treatment.