Gynaecological cancer surveillance for women with Lynch syndrome: systematic review and cost-effectiveness evaluation

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Scientific summary

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Scientific summary

Background

Lynch syndrome is an inherited cancer predisposition syndrome, which leads to an increased lifetime risk for colorectal, endometrial and ovarian cancers. These cancers are typically observed at younger ages in people with Lynch syndrome than in the general population. Cancer risks depend somewhat on which deoxyribonucleic acid (DNA) mismatch repair gene is affected in the patient, with *path_MLH1* and *path_MSH2* genotypes generally having the highest penetrance, *path_MSH6* having high penetrance for endometrial cancer but lower penetrance for colorectal and ovarian cancer, and *path_PMS2* having lower penetrance still. Survival from colorectal and ovarian cancer among patients with Lynch syndrome tends to be better than survival among unselected patients, and this may also be true for endometrial cancer, but survival from endometrial cancer is already more favourable.

When Lynch syndrome is diagnosed, measures are put in place to manage cancer risks. These measures typically include biennial colonoscopic surveillance from 25 years of age and the offer of risk-reducing gynaecological surgery (hysterectomy with bilateral salpingo-oophorectomy) after completion of childbearing and before the individual faces a significant risk of gynaecological cancer (surgery is generally recommended from 35 years). In addition, some patients may use aspirin as chemoprophylaxis and may have surveillance of other organs besides the colon.

Gynaecological cancer surveillance is contentious. It is perceived that there is a lack of evidence to support widespread adoption of colonoscopic surveillance but also that there is insufficient evidence that it is ineffective so should not be offered to patients. Many women with Lynch syndrome do want gynaecological surveillance, and some resort to private healthcare if it is not provided by their local NHS hospital. Some women may wish to receive colonoscopic surveillance for a time before opting for risk-reducing surgery when they are older; some women may not ever want to undergo risk-reducing surgery, and some may be unsuitable for surgery.

Research aims

We aimed to determine whether gynaecological surveillance was effective and/or cost-effective in Lynch syndrome. Our objectives were to conduct systematic reviews of clinical effectiveness and cost-effectiveness evidence, as well as a systematic review of health state utility values, and to develop a whole-disease economic model for Lynch syndrome and use it to conduct a cost-effectiveness analysis.

Systematic review of clinical effectiveness evidence

Methods

We conducted a systematic review in line with a preregistered protocol (PROSPERO CRD42020171098). Our study identification methods included bibliographical database searches, citation chasing and hand screening of conference proceedings and clinical trials registries. Searches were updated to 3 August 2021. Study selection was conducted independently by two reviewers. A broad range of outcomes were determined a priori and a broad range of study designs were considered eligible for inclusion, including non-comparative observational studies (e.g. cross-sectional studies and case series). Risk of bias was assessed using one or more of three checklists, according to the study design. Narrative synthesis was performed, supported by cross-tabulation. Studies were too methodologically heterogeneous and insufficiently numerous to justify quantitative synthesis (i.e. meta-analysis).

Results

A total of 30 studies were included in the review, of which 20 were single-arm studies. Five studies compared colonoscopic surveillance with risk-reducing surgery, three compared time periods with different surveillance approaches and two compared surveillance with no intervention. There was a high likelihood of overlap between some studies.

No studies provided high-quality evidence that is precise and at low risk of bias. The most significant contribution to the risk of bias in studies was failure to adequately consider and address confounding factors. Some studies adopted a diagnostic accuracy evaluation design and were generally reported too poorly to enable good assessment of the risk of bias or were found to be at high risk of bias.

Mortality and survival

Some evidence suggests that all-cause mortality rates are lower with surgery than with surveillance, and lower with surveillance than with no intervention. Some evidence suggests that endometrial cancer-specific mortality is lower with surveillance than with no intervention, but lower still with risk-reducing surgery. Endometrial cancer survival for cancers detected by surveillance was not significantly different from survival for occult cancers diagnosed upon risk-reducing surgery. A similar but even weaker pattern was observed for ovarian cancer.

Stage at diagnosis

Data were generally too sparse to be meaningful, but there was some evidence of ovarian cancers being diagnosed in earlier stages with surveillance than without surveillance.

Fertility

One study found that 5 of 41 participants in a surveillance programme gave birth over a 10-year period. Another study found that participants had concerns that hysteroscopy could lead to fertility issues (due to infection risk).

Cancer detection

Detection rates of endometrial cancer, ovarian cancer and premalignancies were low, with zero events in some studies. This and the lower number of comparative studies make it difficult to draw conclusions about the effect of surveillance on cancer detection rates.

Symptomatic and asymptomatic cancers

The proportion of cancers that were symptomatic detected during surveillance was extremely heterogeneous across the studies, with some studies reporting that all cancers were asymptomatic and others reporting that all were symptomatic. Only two studies had a mixture of symptomatic and asymptomatic cancers. It is clear that some cancers judged to be asymptomatic (at least by clinical researchers) can be detected by surveillance, albeit in small numbers.

Interval and missed cancers

Cancers detected due to symptoms soon after a negative surveillance visit (interval cancers) and occult cancers detected following risk-reducing surgery soon after a negative surveillance visit (missed cancers) were reported in a number of studies. Although numbers were generally low, it is clear that surveillance does not detect all cancers and that cancers can arise very soon after a negative surveillance visit.

Test accuracy and test failures

Five studies attempted to evaluate the accuracy of surveillance tests. False positive results were recorded for pelvic ultrasound and false negative results were recorded for hysteroscopy. Test failure rates were rarely reported, but did reach as high as 24% and 26% for endometrial biopsy and hysteroscopy in one study, while the failure rate was 4% for transvaginal ultrasound.

Harms of surveillance

One study found no uterine perforations among 69 hysteroscopies with endometrial sampling. Numerous studies measured pain and some also measured use of pain relief. On average, endometrial biopsy was reported as moderately painful, although some individuals experienced no pain and others experienced severe pain. One study found that transvaginal ultrasound was less painful than endometrial biopsy or hysteroscopy. Use of non-steroidal anti-inflammatories for pain relief was common. Around one in seven women in one survey had undergone general anaesthetic for surveillance (rising to around one in four when restricted to those receiving hysteroscopy).

Factors that may affect adverse events

Some evidence suggested that endometrial biopsy is more painful in postmenopausal women, but one study did not find this to be the case. Pain ratings for endometrial biopsy were higher for nulliparous participants compared with parous participants.

Systematic review of cost-effectiveness evidence

Methods

Our study identification methods included bibliographical database searches and citation chasing. Study selection was conducted independently by two reviewers. Data extraction and quality appraisal were conducted and included the use of a set of bespoke quality appraisal questions. Narrative synthesis was conducted, supported by cross-tabulation.

Results

Three cost-effectiveness analyses were identified. All three studies were based on relatively simple decision analytical models. All studies included at least one surveillance arm and one risk-reducing surgery arm. Two studies included a 'no intervention' arm. Risk-reducing surgery was economically dominant (less costly and more effective than alternatives) in two studies and was highly cost-effective in the other. Surveillance was dominated by risk-reducing surgery in all analyses. If risk-reducing surgery strategies were removed, one study would find surveillance cost-effective versus no intervention, while the other study would find it not cost-effective (producing health benefits but at too great a cost).

Systematic review of utility values

Methods

We sought utility values relating to endometrial cancer, ovarian cancer, gynaecological cancer surveillance and risk-reducing gynaecological surgery. We did not restrict the population to people with Lynch syndrome. In expectation that there would be insufficient data on risk-reducing gynaecological surgery, we also sought utility values relating to gynaecological surgery for benign gynaecological conditions.

Our study identification methods included bibliographical database searches and citation chasing. Study selection was conducted independently by two reviewers. Data extraction and quality appraisal were conducted. Narrative synthesis was conducted, supported by cross-tabulation.

Results

Fifty-eight studies were identified, with more than half relating to ovarian cancer. Only four studies related to gynaecological surveillance and only two studies related to risk-reducing surgery for Lynch syndrome. The studies relating to surveillance and risk-reducing surgery asked participants to value hypothetical disease states, while most of the other studies asked patients to describe or value their own health.

Utility values tended to be lower for more advanced endometrial or ovarian cancer.

The studies reporting utility values for gynaecological surveillance were either methodologically flawed or reported minimal detail of their methods.

The studies reporting utility values for risk-reducing surgery in Lynch syndrome were similarly methodologically flawed.

For benign gynaecological conditions, utility generally drops sharply following surgery for a recovery period, and eventually reaches a level higher than preoperative utility. This finding is not expected to be replicated in risk-reducing surgery, but some studies may be a useful proxy for the utility of risk-reducing surgery, particularly if they include premenopausal bilateral oophorectomy.

Model-based economic evaluation

Methods

We developed a whole-disease model using a discrete event simulation methodology. The model included natural history components for colorectal, endometrial and ovarian cancers that were calibrated to aggregate data from published studies, including the Prospective Lynch Syndrome Database. Clinical parameters (e.g. cancer survival) were estimated, where possible, from studies of Lynch syndrome populations.

We used the model to conduct a cost–utility analysis of risk-reducing strategies for gynaecological cancer, including surveillance and risk-reducing surgery, and comparing these with a no intervention strategy. The economic evaluation was generally conducted in line with the National Institute for Health and Care Excellence (NICE) reference case and quality-adjusted life-years (QALYs) were the measure of health benefit.

Results

Risk reduction strategies are predicted to be cost-effective compared with no intervention, except for *path_PMS2* Lynch syndrome. For other genotypes, surveillance (alone or with risk-reducing surgery also offered) is expected to lead to more QALYs (and greater costs) than only offering risk-reducing surgery and to be cost-effective. For *path_PMS2*, risk-reducing surgery and surveillance led to significant cost increases, since there were minimal changes to cancer outcomes to offset these costs.

Value of information calculations suggest that further research to obtain more precise parameter estimates would be very valuable. Further value of information analyses may help to prioritise research.

Conclusions

Clinical effectiveness evidence for gynaecological cancer surveillance in Lynch syndrome is sparse and methodologically limited. There is some evidence that surveillance can prevent some deaths compared with no intervention, but there is also evidence that risk-reducing surgery prevents more deaths. Some asymptomatic cancers are detected by surveillance, but some cancers are also missed. Recipients of surveillance have a wide range of pain experiences.

While existing publications have concluded that risk-reducing surgery is clearly cost-effective (generally leading to a substantial gain in QALYs while lowering or only slightly increasing costs) and that surveillance alone is not cost-effective if risk-reducing surgery is an option, we have found that surveillance can be a cost-effective way to manage the risk of gynaecological cancer. Further research is

needed to reduce the uncertainty in model parameters, both to determine cost-effectiveness and to provide context to patients about the potential clinical value of risk-reducing strategies.

Implications for health care

People with Lynch syndrome should be informed that gynaecological cancer surveillance is not expected to reduce the risk of gynaecological cancer and cancer death to the same extent as risk-reducing surgery. There is some evidence that surveillance could be beneficial compared with no risk reduction (e.g. some asymptomatic cancers detected), but there is also evidence that some cancers are missed and that some individuals find surveillance severely painful. The prognosis from endometrial and ovarian cancer appears to be better for people with Lynch syndrome than for unselected patients.

Gynaecological cancer surveillance is estimated to cost the NHS over £300 per year per patient, while risk-reducing surgery is estimated to cost over £6000.

Recommendations for research

1. Researchers should consult with biostatisticians or epidemiologists or other methodological experts before conducting trials and publishing further in this area – the quality of current research falls below the level needed to inform decision-making.
2. More in-depth value of information analyses should be conducted to identify which parameters or groups of parameters are most critical to research further.
3. Health utilities should be directly elicited from individuals with Lynch syndrome to identify the potential effects of surveillance and risk-reducing surgery on health-related quality of life and QALYs; relatedly, it may be beneficial to consider whether willingness to pay is a better indication of the value of undergoing or avoiding surveillance.

Study registration

This study is registered as PROSPERO CRD42020171098.

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