Screening for endometrial cancer

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ABSTRACT

- Routine screening for endometrial carcinoma is currently not justified.
- Postmenopausal women need to be educated about the importance of seeking attention if any vaginal bleeding occurs. All postmenopausal bleeding requires review and appropriate investigation.
- Women taking tamoxifen have a higher risk of endometrial cancer and should report any bleeding or spotting; however, ultrasound screening is not recommended for asymptomatic women taking tamoxifen.
- Families with hereditary non-polyposis colon cancer have a higher risk of endometrial cancer and require counselling about this risk.
- A Pap test is not a screening test for endometrial cancer, but the incidental finding of endometrial cells on a Pap smear in a postmenopausal woman requires investigation.

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ENDOMETRIAL CARCINOMA is the most common gynaecological carcinoma, with one in 80 women in Australia developing the disease by the age of 75 years.[1]

Risk factors

The risk factors for endometrial carcinoma are well known; they include obesity, type 2 diabetes mellitus and hypertension. Anovulation is highly associated with endometrial carcinoma, particularly in the presence of polycystic ovarian syndrome, which is linked with the development of premenopausal endometrial cancer. Long-term use of unopposed oestrogens for hormone replacement therapy also increases the risk of endometrial cancer. Although prescribing oestrogens alone is now uncommon, women with an intact uterus can still be prescribed unopposed oestrogens, increasing their risk of developing endometrial cancer sixfold. Taking tamoxifen increases the risk of endometrial carcinoma by two to three times, and this risk is higher as the duration of use increases, particularly after 5 years. However, most cancers associated with tamoxifen use are Stage I (confined to the uterus), with either Grade 1 or 2 morphology, and thus associated with a better outcome. Finally, genetic causes of endometrial cancer are uncommon, although there is an association with hereditary non-polyposis colon cancer (HNPCC) syndrome, in which the individual risk rises to a cumulative incidence of 40% by age 70 years.[2] This risk appears directly related to age, endometrial carcinoma usually occurring 15 years earlier than found typically, with the highest risk being between the ages of 55 and 65 years. In a group of 293 Finnish women with HNPCC syndrome, the risk rose from 3.7% at age 40 to 43% at age 80 years.

Presentation

Most endometrial carcinomas are diagnosed at an early stage and have a good prognosis. The most common presenting symptom is postmenopausal bleeding. As there is no evidence to support routine screening for endometrial cancer, effort should be directed towards making women and their carers aware that postmenopausal bleeding, however slight, is abnormal and deserves prompt investigation. Because most patients with endometrial carcinomas present early, it is unlikely, based on current technology, that a population screening program would be of any value. Gerber et al, in a retrospective analysis, compared 190 postmenopausal women with symptoms of bleeding with 123 women without symptoms but with a transvaginal ultrasound examination showing endometrial changes suggestive of carcinoma.[3] They found that the asymptomatic women had no prognostic advantage over the symptomatic women, if bleeding had occurred for fewer than 8 weeks. They correlated the duration of postmenopausal bleeding with increasing tumour stage and reduced survival time.[3] Importantly, they also found that women at high risk of endometrial carcinoma were less likely to present with postmenopausal bleeding. While bleeding may be an early symptom, it was not always assessed as being important by the patient. Endometrial screening often resulted in unnecessary operations with increased morbidity and cost.[3]

Screening methods

Studies examining endometrial carcinoma screening methods for asymptomatic postmenopausal women have used ultrasound-determined endometrial thickness as an indication of risk. The thickest anteroposterior diameter of the endometrium is measured during ultrasound examination, and it is generally accepted that a normal endometrium is less than 5 mm thick. Healthy asymptomatic postmenopausal women, some using hormone replacement therapy, were screened with transvaginal ultrasound examination and concurrent endometrial biopsy. At an endometrial-thickness threshold value of 5 mm, transvaginal ultrasound had a positive predictive value of 9% for detecting any abnormal-

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ity. The sensitivity was 90%, the specificity was 48%, but the negative predictive value was 99%. Based on these values, over half of the women would require investigation, with a low yield (4%) of endometrial carcinomas.[4]

A report by Fleischer et al described 1926 women who underwent transvaginal ultrasound examination as part of entry into an osteoporosis prevention trial; 42 of 93 women with an endometrial thickness greater than 6 mm underwent endometrial aspiration, with abnormal findings in only one woman. A further 1750 of 1833 women with an endometrial thickness of 6 mm or less underwent sampling, yielding five abnormal results. The sensitivity was 17% for a threshold thickness of 6 mm, which was improved to 33% using a threshold thickness of 5 mm.[5]

Analysis of studies of women with abnormal bleeding has provided most information about the sensitivity of transvaginal ultrasound examination. In symptomatic postmenopausal women not taking hormone replacement therapy, an endometrial thickness of more than 4.0 mm was used as the cutoff point, based on two studies involving 930 and 1138 women, respectively. For detection of endometrial cancer, the sensitivity was 98%, with a specificity of 36%–68%.[6,7] An endometrial thickness of less than 5 mm in a symptomatic woman would indicate a 1% chance of endometrial cancer, compared with a 10% risk in the general population. However, in the context of screening, there is no evidence to support introducing routine transvaginal ultrasound examination in asymptomatic women.

The endometrium can be screened directly, with commercially available endometrial samplers. These techniques are simple, with generally good results, and have been used in an office setting to investigate postmenopausal bleeding. However, because of cervical stenosis and atrophy, endometrial sampling may be difficult in postmenopausal women. Recognised complications include patient intolerance, infection, bleeding and, occasionally, uterine perforation. This difficulty of access, combined with a recognised sampling error, makes direct endometrial sampling an uncertain screening tool. Even with formal hysteroscopy and endometrial curettage, only 65% of the endometrial cavity is sampled. There are no randomised studies showing a reduction in mortality associated with a sampling-based screening program.

Screening of high-risk women

There are cogent reasons for endometrial screening of high-risk women. These women include:

- those taking tamoxifen for chemoprophylaxis (to prevent or to treat breast cancer);
- those with a genetic disorder, such as HNPCC; and
- those carrying a proven DNA mismatch repair gene.

With tamoxifen use, the endometrial thickness becomes less reliable as an indicator of uterine disease, because of tamoxifen-induced subepithelial stromal hypertrophy. Over 40% of women taking tamoxifen will have an endometrial thickness of more than 5 mm. Several studies have reported a high false positive rate, even when the cutoff value for endometrial thickness was increased to 10 mm. Gerber et al identified 247 women taking tamoxifen matched to 98 controls. Of those taking tamoxifen, 52 asymptomatic patients with endometrial thickening underwent curettage. Four uterine perforations occurred in this group, and one endometrial carcinoma was diagnosed. Twenty women complained of bleeding and were investigated, and two endometrial carcinomas were diagnosed.[8] The Royal Australian College of Obstetricians and Gynaecologists produced a consensus statement suggesting screening was not required,[9] but prompt investigation of any bleeding was strongly recommended.

HNPCC carriers, although a small group, have a significant risk of developing endometrial cancer. No studies exist showing the benefit of screening in this group, although it would be appropriate to discuss with these women screening with annual transvaginal ultrasound examination, or, alternatively, prophylactic hysterectomy and salpingo-oophorectomy. As many of these cancers will arise after menopause, surgical intervention may be more attractive. Equally, education on the need to promptly present for investigation if any bleeding occurs is essential.

Opportunistic screening

Pap smears provide an opportunistic method of detecting occult endometrial carcinomas, but are unreliable as a true screening test. Detecting endometrial cells on Pap smear in asymptomatic postmenopausal women can herald a 6% risk of having underlying endometrial carcinoma, and about 13% will have endometrial hyperplasia.[10] While 50% of women with a proven endometrial carcinoma will have an abnormal Pap smear, this is not sufficient for it to be used as a screening test.[11]

Conclusion

Current levels of evidence do not support routine endometrial cancer screening in the general population. Perhaps the greatest screening tool available is education of patients and doctors about the significance of postmenopausal bleeding and the need for further appropriate investigations.

Competing interests

None identified.

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