Ovarian cancer

Ovarian cancer is the leading cause of death from gynaecological cancers. Most cases are diagnosed at an advanced stage. In this article, we consider how we can increase our chances of making an earlier diagnosis of ovarian cancer in primary care; how to use the tests we have available to best effect; and the role of screening now and in the future.

This article was updated in November 2022.

Ovarian cancer headlines

- **Ovarian cancer is difficult to diagnose, but it is not a 'silent killer'**. Most women DO have symptoms, but they are nonspecific and often overlap with other cancers and more benign conditions such as IBS. Symptoms only have modest positive predictive values. We need a high index of suspicion.
- **Population screening doesn't impact mortality**. There had been hope that screening may help to improve early detection and survival, but disappointing results of the UKCTOCS trial (see below) mean that a valid screening strategy is still at least a decade away (Lancet 2021;397:2182).
- **Earlier diagnosis *may* help improve survival.** Most cases (58%) are diagnosed at advanced stage (III or IV), and this impacts survival (CRUK Ovarian cancer survival in England accessed November 2022):

Stage at diagnosis	5-year survival
I	95%
II	70%
III	27%
IV	13%

- **Referral is often delayed:** one-third of women diagnosed with ovarian cancer in the UK present 3 or more times before specialist referral; one-quarter take ≥160 days to be diagnosed following initial presentation (BJGP 2022; 72(720):312).
- The current NICE guideline referral pathway (CG122 (2011) and NG12 (2015)) may not make optimal use of the tests we have available, and does not yet reflect subsequent primary care research (BJGP 2022;72(720):312).
- **Women aged ≥50y with a CA125 ≥35U/ml who are not found to have an ovarian cancer should be investigated for non-ovarian cancers,** including lung, gastrointestinal, uterine and pancreas – we may need to use a Rapid Diagnostic Centre approach.

Presentation, investigation and referral

NICE guidelines (2011 & 2015) differ from the Scottish referral guidelines for suspected cancer (2019) in their use of CA125 and transvaginal ultrasound:

For those working in England (NICE NG12 2015 and NICE CG122 2011)	
Symptoms	**Action**
Physical examination suggests ascites and/or pelvic or abdominal mass not obviously a fibroid.	Refer using suspected cancer (2ww) pathway.
Women presenting with any of the following if persistent or frequent (particularly if >12x per month) and especially if age >50y: • Persistent abdominal distension. • Early satiety/loss of appetite. • Pelvic/abdominal pain. • Increased urinary urgency or frequency. OR Any of the following symptoms: • Unexplained weight loss. • Fatigue. • Change in bowel habit.	**Consider the possibility of ovarian cancer and perform primary care tests (CA125 initially then possibly USS if CA125 raised – see below).** **If CA125 is ≥35U/ml, refer for urgent USS of abdomen and pelvis.** **If CA125 is <35U/ml or is raised but USS normal, safety-net carefully and review if symptoms persist or become more frequent (*see below for sensitivity of CA125).***

OR • New-onset IBS symptoms in the past 12m in women aged 50y or over.	
For those working in Scotland (2019 guidance)	
Symptoms	**Action**
• Any woman aged >50y with new symptoms in the past 12 months that suggest IBS. OR • Women (especially those over 50y) with one or more unexplained and recurrent symptoms (most days) of: o Abdominal distension or persistent bloating. o Feeling full quickly or difficulty eating. o Loss of appetite. o Pelvic or abdominal pain. o Increased urinary urgency and/or frequency. o Change in bowel habit.	Abdominal palpation, CA125 and urgent pelvic ultrasound scan.

NICE does not include postmenopausal or abnormal bleeding in this list even though these can be symptoms of ovarian cancer. It is expected that women with these symptoms would be investigated after referral through the appropriate 2ww guidance for these symptoms.

Remember that for many of these symptoms, we would also offer a FBC and FIT test as part of our work-up.

Investigating symptomatic women: CA125 then scan, or CA125 and scan at the same time?

- NICE recommends a **sequential approach** using CA125 as an initial test and ONLY referring on for transvaginal ultrasound if the level is ≥35U/ml. This potentially introduces delay and is open to false negative CA125 results.
- Scottish cancer guidelines recommend a **parallel approach** where CA125 AND transvaginal ultrasound are done at the same time.

We don't know the best approach, but many academics suspect that current NICE guidance needs to change. This was considered as part of an interesting editorial in the BJGP (BJGP 2022;72(720):312).

These two strategies have not yet been compared head-to-head. When the NICE pathways were designed, they were based on data extrapolated from secondary care. Evidence about primary care use of CA125 has now been published.

How well does CA125 perform in detecting ovarian and non-ovarian cancers in primary care?

A well-designed UK CPRD cohort study explored the diagnostic performance of CA125 in primary care in the time period straight after the NICE pathway was introduced (PLOS Med 2020 17(10):e1003295). Between 2011 and 2014, more than 50 000 women underwent CA125 testing in primary care.

- The higher the CA125, the greater the chance a cancer would be diagnosed.
- More non-ovarian cancers were diagnosed than ovarian cancers. Overall, in women with a raised CA125 ≥35U/ml:
  - 10% were diagnosed with ovarian cancer.
  - 12% were diagnosed with another cancer (most commonly lung, pancreas, gastrointestinal, breast or uterus).
- CA125 performed 'better' in women aged ≥50y, reflecting the greater prevalence of disease in this age group, which peaked at age 70y. Of those women aged ≥50y with a raised CA125:
  - 15% were diagnosed with ovarian cancer.
  - 20% were diagnosed with non-ovarian cancer.

What is really striking here is the risk of a non-ovarian cancer in women aged ≥50y with a raised CA125!

The properties of CA125 reached the 'magic' PPV 3% at different cut-offs for different ages, for example:

Age (in years)	CA125 level (in U/ml) with a PPV ≥3%
40	104
70	32

These are best appreciated in the graphs in the original paper, which is free to access (PLOS Med 2020 17(10):e1003295). The authors propose that this information might enable a more nuanced approach where women with a very high CA125 go straight for specialist investigation and imaging on a 2ww pathway, while those with a low-but-not-no-risk PPV have an ultrasound.

What does this mean in practice?

We will miss nearly a quarter of cases of ovarian cancer initially if we rely on CA125 alone. In this study, CA125 with a cut-off ≥35U/ml has an overall sensitivity of 77% for ovarian cancer (85% for invasive subtypes) – so, while useful, a significant proportion of women with ovarian cancer will have a CA125 in the normal range and will experience delayed diagnosis (usually roughly twice as long) if the NICE strategy is adopted. We need to safety-net carefully and, if our clinical suspicion is high, investigate further.

A poll of the Red Whale team showed that, in real life (despite all working in England and Wales and following NICE), many of us request CA125 and ultrasound in parallel, particularly for women over 50y, if we have a strong clinical suspicion.

We should consider non-ovarian cancers in women with raised CA125 levels. The high rate of non-ovarian cancers in women ≥50y with a raised CA125 means that Rapid Diagnostic Centres may be useful to identify other underlying causes if initial ultrasound is normal (pancreas, lung, GI and uterine cancer were most common). There is a large UK study ongoing evaluating the efficacy of CT imaging as the next test for women with raised CA125.

We might use a more 'nuanced' risk-based triage in the future**,** looking at CA125 in the context of age (a bit like how we interpret PSA levels). This still needs some more work, including economic evaluation, but we may see this in the next iteration of the NICE guideline.

The NICE guideline needs an overhaul. The 2011 guideline was based on an estimate that 0.81% of symptomatic primary care women with a CA125 ≥35U/ml would have ovarian cancer, and all economic modelling, and the sequential test regimen, was based on this. This primary care-based study shows that, in fact, the PPV is more than 12 times higher than this estimate.

The authors of this study, and the subsequent BJGP editorial, argue that the NICE guidance is now outdated and should be reviewed as soon as possible. They suggest that, in the meantime, performing the two tests (CA125 and USS) in parallel *could* improve sensitivity and facilitate earlier diagnosis. Clearly, there are cost and capacity issues to consider here, particularly in the post-COVID environment (BJGP 2022;72(720):312).

Now, a reminder of some background information…

Risk factors

The risk of developing ovarian cancer is directly proportional to the number of ovulatory cycles. Some risk factors are modifiable and others are not (CRUK accessed 2022).

Protective factors:

- Pregnancy.
- Combined hormonal or anovulatory contraception.

Risk factors:

- Older age.
- Overweight and obesity.
- Nulliparity.
- Postmenopausal status (75% of cases are diagnosed in women over 55y).
- Personal history of breast cancer.
- Family history of breast or ovarian cancer.
- Small increased risk with HRT.
- Genetics, particularly *BRCA* genes and Lynch syndrome.

Types of ovarian cancer

There are multiple histological types of ovarian cancer. A simple understanding of these may help in interpreting discharge letters. For simplicity, they can be grouped as follows (CRUK 2022):

-	**Low-grade ovarian cancer (type 1)**	**High-grade ovarian cancer (type 2)**
Proportion	20–30%.	70–80%.
Characteristics	Slow growing. Respond poorly to chemotherapy (so can be more difficult to treat).	Fast growing. Spread early. Most commonly originate in the distal fallopian tube. Primary peritoneal cancers are related and treated similarly. More sensitive to chemotherapy.
Genetics	–	18% of women will have the *BRCA* gene – testing should be offered as it may impact on treatment.

Screening for ovarian cancer

Screening is not the magic bullet: population screening is not currently recommended for ovarian cancer. The tests we have available for screening have been shown to increase early-stage diagnosis of ovarian cancer but have no significant impact on ovarian cancer deaths or all-cause mortality.

For details of the trial, read on:

UKCTOCS was a large UK-based RCT screening trial that enrolled more than 200 000 postmenopausal women aged 50–74y across the UK (Lancet 2021;397:2182). Participants were randomised to three possible screening strategies:

- Multimodal screening (CA125 + transvaginal ultrasound scan (TVUSS) if indicated).
- Annual TVUSS.
- No screening.

Follow-up was for a median 16.3y.

The trial showed that:

- Ovarian cancer can be detected earlier by screening: more stage I disease was detected in the multimodal group.
- Earlier detection did not translate into fewer ovarian or tubal cancer deaths, nor reduce all-cause mortality.
- Women with screen-detected cancers did not have 'high-alert' symptoms.
- Harms and financial costs need to be considered but were not part of this trial.

The authors concluded that:

"*Given that screening did not significantly reduce mortality from ovarian or tubal cancer, population screening cannot be recommended*".

They went on to state that achieving a mortality reduction will require a different screening strategy that can detect disease even earlier and in a larger proportion of women – and that this is likely to be at least a decade away (Lancet 2021;397:2182).

Women with higher-than-population risk

It is important to note that this trial did not include women with *BRCA* mutations, and it is unlikely that RCTs would ever get ethical approval in these groups. Women with known *BRCA* mutations will be offered bespoke screening and management options (see *Breast cancer: genetic risk*).

Is earlier detection of symptomatic disease effective?

In the UKCTOCS trial, women with early screen-detected disease had no high-alert symptoms and, surprisingly, despite finding the disease at this early, asymptomatic stage, there was no impact on ovarian cancer mortality or all-cause mortality.

The authors comment that this means that earlier diagnosis in the ***symptomatic*** population is unlikely to translate into mortality benefits.

Does this mean we shouldn't bother? No. Treatment of advanced disease has improved substantially since the UKCTOCS trial began. The authors speculate that rapid diagnosis *is* likely to offer morbidity, quality of life and psycho-social benefits to women and their families (Lancet 2021;397:2182).

Management of ovarian cysts spotted on ultrasound

The ultrasound you requested comes back with the following report:

"Simple 6.8cm cyst, follow-up as appropriate."

What would you do? See the article on *Ovarian cysts* for more details and a helpful table summarising the RCOG guidance.

Management of ovarian cancer

Treatment is a combination of surgery and then, if the tumour is determined to be platinum sensitive, chemotherapy:

- Surgery can either be curative or palliative (to debulk and improve symptoms).
- Where the tumour is large, neo-adjuvant (pre-op) chemotherapy may be offered.

A study compared outcomes in women offered surgery then chemotherapy or chemotherapy then surgery (Lancet 2015;386:249); it found that neo-adjuvant chemotherapy was non-inferior to immediate surgery. This can buy time for women to receive their surgery at specialist centres where outcomes are known to be better.

Relapse

Relapse occurs in 70% of patients.

Management is with chemotherapy. This should be considered palliative even though long periods of further remission can be achieved.

How does relapse present?

Patients with relapse of ovarian cancer often present with acute or subacute bowel obstruction. This may be after a considerable period of remission, and clinicians need to be wary if patients with a previous history of ovarian cancer develop abdominal symptoms.

In addition, some of the modern targeted treatments increase the risk of intestinal perforation and fistula formation. These patients are complex to manage, and surgery is not always the best option.

<table>
<tr><td>  </td><td>Ovarian cancer
• Ovarian cancer is difficult to diagnose, but it is not a silent killer.
• Evidence suggests population screening using current tests would not be beneficial.
• Consider ovarian (and colorectal!) cancer before diagnosing new-onset IBS in women over 50y.
• NICE guidelines need review.
• Women aged ≥50y with a CA125 ≥35U/ml have an increased risk of ovarian AND non-ovarian cancers. If investigations for ovarian cancer are normal, a Rapid Diagnostic Centre approach may be beneficial. Pancreatic, gastrointestinal, uterine and lung cancers were most common.</td></tr>
<tr><td>  </td><td>Run a search for women aged ≥50y with a raised CA125 >35U/ml in the past 6–12 months who have not received a diagnosis of ovarian cancer. Have they been reviewed/appropriately safety-netted? Do they have ongoing symptoms that would benefit from referral to a Rapid Diagnostic Centre?</td></tr>
<tr><td>  </td><td>Useful resources:
<u>Websites</u> (all resources are hyperlinked for ease of use in Red Whale Knowledge)
• <u>Target Ovarian Cancer</u> (includes patient information leaflets about CA125 and pelvic ultrasound scans)</td></tr>
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