Ovarian cancer

Ovarian cancer is notoriously difficult to diagnose and is frequently diagnosed late. However, it is not a silent killer. How best can we work out when to suspect it and what investigations to do?

Ovarian cancer statistics (from BMJ 2009;339:b4650)
- Overall 5-year survival for ovarian cancer is 30–40%.
- However, if diagnosed at an early stage, 5-year survival is around 70%.

Usually when discussing a topic for which NICE have just issued new guidance I present the new NICE guidance and then discuss the evidence behind the guidance. However, for ovarian cancer I want to look at the evidence first, as it is very important you read the guidance in the light of the evidence.

The key things we need to bear in mind are:
- Ovarian cancer is NOT a silent killer. It does cause symptoms, even at a relatively early stage. Recent research has identified which symptoms are most predictive of ovarian cancer.
- However, for the symptoms suggestive of ovarian cancer, the positive predictive values of each symptom (and even combination of symptoms) is still very low – that is, even if you have some of these symptoms, the chance of having cancer is still low. And many, many people with these symptoms will not have ovarian cancer.
- Having said that, we don’t have anything better at present, so we must use what we have.
- So, we need to be aware that early presentation is often vague, with much overlap with other common diseases such as IBS. The NICE guidance helps by summarising the key symptoms and giving us a relatively cheap and easy combination of investigations we can do on what will be quite large numbers of women, to help sift the wheat from the chaff, and to try to detect disease at an earlier and more treatable stage.

The research on symptoms of ovarian cancer

Do note the difference between intermittent abdominal distension (today I can’t do my jeans up but tomorrow they will fit just fine) and permanent abdominal distension (I used to fit size 10 jeans but now I need size 12 and fairly soon I might need to get some in size 14…) – patients call both bloating so always ask what exactly they mean when they talk about ‘bloating’!

Three important studies have tried to identify what symptoms/symptom complexes might help us identify women with ovarian cancer, and it is on these that the NICE guidance is based.

Systematic review of presenting symptoms (BJOG 2005;112:1)
This paper was a systematic review of presenting symptoms of ovarian cancer.
- Only 7.2% with ovarian cancer were asymptomatic: so not a ‘silent killer’ in most.
- When women with ovarian cancer were compared with women without, the symptoms most predictive of ovarian cancer were (no odds ratios; this was a systematic review):
  - Bloating
  - Lack of appetite
  - Abdominal/low back pain.
- Combinations of symptoms increased the chance of having more advanced disease.

Qualitative review of symptoms (BJOG 2008;115:1008)
This paper is from the authors of the BJOG paper above and tries to eliminate some of the biases that came through the sort of analysis done above.

In this study they interviewed 124 women referred to hospital with suspected ovarian cancer.
- 44 were diagnosed with ovarian cancer. Of these, 25 had stage 3 or more.
- 59 had benign pathology
- 21 were considered normal (no pathology identified).
• All women with cancer experienced some symptoms – ovarian cancer is not a ‘silent killer’. The problem was that these symptoms were often considered normal for their age, which caused delay in seeking medical advice.

• The symptoms which were significant were:
  - Post-menopausal bleeding
  - Persistent abdominal distension
  - Loss of appetite
  - Early satiety
  - Progression of symptoms

• In this study, intermittent distension was not associated with ovarian cancer.

Case control study of symptoms presenting to the GP (BMJ 2009;339:b2998)
Importantly this research looked specifically at symptoms presented to UK GPs – ideal for us!
212 women with ovarian cancer were matched to over 1000 controls. They matched for age and for registered GP practice (which should rule out variations in practice).

• Seven symptoms were associated with ovarian cancer:
  - Permanent abdominal distension
  - Post-menopausal bleeding
  - Loss of appetite
  - Increased urinary frequency
  - Abdominal pain
  - Rectal bleeding
  - Intermittent abdominal distension

However, the positive predictive values (PPVs) were low for all these symptoms: 2.5% for permanent abdominal distension and <1% for the other symptoms. Unsurprisingly, combinations of symptoms were more predictive, but PPVs were still low, so even in a cohort of people with several of these symptoms the chance of actually having ovarian cancer remains low.

• 85% of cases presented at least one of these symptoms to the GP before diagnosis, but so did 15% of the controls!

• For symptoms presented within 180 days of diagnosis the most predictive symptoms of cancer were distension, pain and urinary frequency. These were independently associated with cancer.

So what do these studies tell us?

Ovarian cancer is difficult to diagnose, but symptom patterns are emerging to help us. It is not a silent disease in the vast majority!

Research suggests we should be particularly aware of the following symptoms:
  - Persistent abdominal distension & possibly bloating (intermittent distension)
  - Post-menopausal bleeding
  - Early satiety
  - Loss of appetite
  - Pain
  - Increasing urinary frequency Progression of symptoms

Now let’s look at the NICE guidance designed to help us identify and investigate those possible ovarian cancer.
NICE on diagnosis and initial investigations of ovarian cancer

NICE issued new guidance on recognising and investigating suspected ovarian cancer in April 2011. Here I will focus on the issues that relate to primary care.

### NICE on recognition and initial management of ovarian cancer  NICE CG122, 2011

#### Presenting symptoms

NICE want us to consider the possibility of ovarian cancer in the following situations:
- **Women presenting with the following symptoms, if persistent or frequent (especially if more than 12x/month) and especially if the woman is over 50y:**
  - Persistent abdominal distension
  - Early satiety and/or loss of appetite
  - Pelvic or abdominal pain
  - Increased urinary urgency and/or frequency
  - OR
  - **Any of the following symptoms:**
    - Unexplained weight loss
    - Fatigue
    - Changes in bowel habit
  - OR
  - **New onset of IBS symptoms in the last 12m in women aged 50 or over (IBS rarely presents for the first time at this age)**
  - OR
  - **Physical examination suggests ascites and/or pelvic or abdominal mass.**

#### Investigations

If we suspect ovarian cancer:
- **Measure CA125** (unless mass/ascites when urgent referral is indicated without delay).

If **CA125 is ≥35 IU/ml**: Do abdominal and pelvic ultrasound.
  - If ultrasound abnormal, refer urgently.
  - If ultrasound normal, reassess symptoms: are there other explanations for her symptoms? Investigate these appropriately.

If **CA125 is <35 IU/ml**: re-assess carefully: are there other explanations for her symptoms? Investigate these appropriately.

- **In secondary care a Risk of Malignancy Index (RMI) score should be calculated.**
  
  RMI score is based on ultrasound status (U score), menopause status (M score), and CA125 level.
  
  \[
  \text{RMI} = \text{U score} \times \text{M score} \times \text{CA125 (in IU/ml)}
  \]

  **M score is calculated:**
  - M=1 if premenopausal
  - M=3 if postmenopausal (>12m since last period OR any woman over 50y who has had a hysterectomy)

  \[
  \text{U score is calculated in the following way:}
  \]

  Score 1 point for each of the following and then see below:
  - 1 point for each of the following features:
    - multilocular cysts
    - solid areas
    - ascites
    - bilateral lesion
    - metastases.

  \[
  \text{U= 0 if no points for the ultrasound}
  \]

  \[
  \text{U= 1 if 1 point on ultrasound}
  \]

  \[
  \text{U=3 if score of 2-5 on ultrasound}
  \]
Whilst thinking about ovarian cancer, just a few other things to consider...

**The BRCA gene and ovarian cancer**

The Department of Health issued some guidance in 2009 on ovarian cancer (DH, Key messages on ovarian cancer for health professionals, 2009, http://tinyurl.com/DH-ovarian-cancer ). This guidance reminds us that in some cases breast and ovarian cancer are related to the BRCA genes. Women who carry the BRCA 1 or 2 genes are at increased risk of both breast and ovarian cancer. So women with 2 or more cases of ovarian or breast cancer diagnosed at an early age in first degree relatives may be at increased risk of ovarian (and breast) cancer. Ashkenazi Jews and women of Polish descent are also at increased risk of carrying the BRCA genes. This is discussed in more detail in the online Handbook available at www.gp-handbook.co.uk. All these women should be offered referral for genetic counselling and consideration for prophylactic surgery.

**Ovarian cancer and the COCP**


This is an important epidemiological study of links between the combined oral contraceptive pill (COCP) and ovarian cancer.

It has been known for some years that the combined oral contraceptive pill (COCP) can reduce the risk of ovarian cancer in women. However, ovarian cancer is rare, and the risk increases with age. What hasn’t been clear is how long this protection lasts after stopping the COCP and whether there would be any public health benefits as a result of any reduction in cancers.

By pooling data from 45 epidemiological studies the authors were able to include over 100 000 women – 23 000 with ovarian cancer and 78 000 controls.

A few cautions –

- The researchers were not always able to tell who used the COCP and who used the POP, but they can say that over 95% of women in the study were using the COCP.
- Some of the data go back to the days when the COCP contained 50mcg or even 100mcg of oestrogen rather than 30mcg. However, from 1980 onwards most women used the 30mcg pill. Most of the studies were done in the late 90s or later, when women would have been on the lower dose pills for at least 15 years, if not more. Any benefits gained from the higher dose pills would be minimal.

The findings showed:

- **The longer women used the OCP, the lower their ovarian cancer risk (p<0.0001).**
  
<table>
<thead>
<tr>
<th>Duration of use</th>
<th>Relative risk of ovarian cancer (&lt;1 = reduced risk of cancer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>1</td>
</tr>
<tr>
<td>1-4y</td>
<td>0.78</td>
</tr>
<tr>
<td>5-9yrs</td>
<td>0.64</td>
</tr>
<tr>
<td>10-14y</td>
<td>0.56</td>
</tr>
<tr>
<td>15 yrs or more</td>
<td>0.42</td>
</tr>
</tbody>
</table>

- **Reduced risk persisted for at least 30y, although benefit declined during this time.**
  
  Risk reduction for every 5 years of use was:

<table>
<thead>
<tr>
<th>Duration</th>
<th>Benefit Declined During This Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>29% 10 years</td>
<td>(CI 23–34%)</td>
</tr>
<tr>
<td>19% 10–19 years</td>
<td>(CI 14–24%)</td>
</tr>
<tr>
<td>15% 20–29 years</td>
<td>(CI 9–21%)</td>
</tr>
</tbody>
</table>

- **Neither age at first and last use, or use before or after the birth of a child, had any effect on ovarian cancer risk.**
- **Modelling from these data suggests that if current contraceptive use continues as it is, 30 000 cases of ovarian cancer would be prevented every year worldwide.**

**What does this mean in practice?**

COCP use reduces the risk of ovarian cancer and the benefits are greater the longer you take it for.
This data is really important and, as the accompanying editorial highlights, is powerful evidence of a beneficial effect even after fairly modest use, for a disease that is often fatal. What is more, the benefits persist for many years after stopping.

While we are thinking about the COCP and ovarian cancer, here is a quick summary of the impact of the COCP on other cancers.

**COCP and cervical cancer**

A systematic review and meta-analysis looked at data from 16 000 women with cervical cancer or CIN 3 and 35 000 women without. It assessed whether the COCP really is a risk (Lancet 2007;370:1609–21). Importantly they stratified risk by age, number of sexual partners, age at first intercourse, parity, smoking and cervical screening attendance. This review uses about 85% of all published worldwide data on cervical cancer and pill use so is probably the best analysis we will have for some time!

Once again, sometimes it was impossible to separate out those taking the POP from those on the COCP and the two were analysed as if they were all on the COCP. In the studies where POP use could be identified separately, an analysis of the effect of the POP on cervical cancer could not be done because there were insufficient numbers.

The MHRA summarised the findings of this trial neatly, and I find this useful when talking to patients (Drug Safety Update 2008, Volume 1, Issue 9):

- The COCP increases the risk of cervical cancer but the absolute risk increase is small and the disease is rare. Risks fall after stopping the pill.

- If 10 000 women from age 20:
  - never took the pill there would be 38 cases of cervical cancer by age 50 (total 38/10 0000 women).
  - took the pill for 5 years there would be an extra 2 cases of cervical cancer by age 50 (total 40 cases/10 0000 women).
  - took the pill for 10 years there would be an extra 7 cases of cervical cancer by age 50 (total 45 cases/10 0000 women).

- Your risk of cervical cancer is low, even if you’ve been using the COCP for some years.

- Other factors (age at first intercourse, number of partners, HPV status, screening, parity, smoking) did not seem to have any effect on these figures. Screening didn’t seem to have an effect, but this may be because screening data were patchy.

**Other cancers and the COCP**

A paper in the BMJ summarised the data on just this question from the RCGP Oral Contraceptive Study. This is an inception cohort study of over 46 000 women, half of whom were never users. This study showed a relative risk for ever use of the COCP for the following cancers (with RR and CI given afterwards). All are less than 1, showing a reduced risk of cancer with ever use:

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Relative risk (&lt;1 = reduced risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>0.72 (CI 0.58–0.9)</td>
</tr>
<tr>
<td>Uterine</td>
<td>0.58 (CI 0.42–0.79)</td>
</tr>
<tr>
<td>Ovary</td>
<td>0.54 (CI 0.4–0.71)</td>
</tr>
<tr>
<td>Any cancer</td>
<td>0.88 (CI 0.83–0.94)</td>
</tr>
</tbody>
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- The risk of colon, uterine, ovarian and any cancers are reduced by ever COCP use.

- In the RCGP Oral Contraceptive Study statistical significance was not reached for either breast or cervical cancer, although a larger study (detailed above) suggests a slightly increased risk of cervical cancer with COCP use.
Drawing all this together, what does it all mean in practice?

Ovarian cancer, particularly in the early stages, presents with vague symptoms that are commonly seen in general practice. This research has led NICE to recommend particular vigilance with the following symptoms:

- Frequent or persistent (especially if >12x/month) and especially if the woman is over 50y:
  - Persistent abdominal distension
  - Early satiety and/or loss of appetite
  - Pelvic or abdominal pain
  - Increased urinary urgency and/or frequency

Or any of the following symptoms:

- Unexplained weight loss
- Fatigue
- Changes in bowel habit (including new onset IBS in a woman aged ≥50y)

We should be alert to these symptoms and be willing to investigate women presenting with any of these symptoms appropriately, whilst acknowledging that even in those with several symptoms, there will still be very few cancers actually diagnosed.

We should also be alert to the link between the breast cancer BRCA genes and ovarian cancer.

COCP use, even for relatively short periods, reduces ovarian cancer risk.

How can we remember these symptoms?

How do we remember the key symptoms that should trigger us to consider ovarian cancer more seriously? For those who like mnemonics, how about this: Ask yourself:

**Have you PAUSeD to think: in this Women's Football Club player could these symptoms be ovarian cancer?**

**PAUSeD**

1. **P** pain
2. **A** appetite loss
3. **U** urinary symptoms
4. **Se** satiety (early)
5. **D** distension
6. **W** weight loss
7. **F** fatigue
8. **C** change in bowel habit

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### Ovarian cancer

- Ovarian cancer is difficult to diagnose but it is not a silent killer.
- New NICE guidelines highlight the key symptoms that should make us suspicious of ovarian cancer. Be particularly aware of pelvic or abdominal Pain, loss of Appetite, Urinary urgency or frequency, early Satiety, persistent Distension, Weight loss, Fatigue or Change in bowel habit. **Mnemonic: PAUSeD-WFC.**
- Consider ovarian cancer before diagnosing new onset IBS in women over 50.
- First line investigation is a CA125. An ultrasound should be requested if the CA125 is ≥35 IU/ml.
- Remember the link between the BRCA gene & ovarian cancer; refer at risk women for genetic counselling.
- **The COCP and ovarian cancer:** COCP use reduces the risk of ovarian cancer. The longer you take the COCP the greater the protection. Benefits persist for up to 30yrs after stopping the pill.
- **The COCP and cervical cancer:** the COCP increases the risk of cervical cancer but the absolute risk increase is small (an extra 7 cases by age 50 after 10 000 women take the pill from age 20 to 30). The increased risk declines on stopping the pill.
- **The COCP and other cancers:** Research for the RCGP cohort study confirms that the COCP reduces the risk of colon, uterine and any cancer risk. The RCGP study does not show an increased risk of breast cancer with ever use of the COCP.
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- London - Saturday October 15
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