Evidence tables:

Author(s): Bankhead *et al.* (2005)

Design: Systematic review
Country: United Kingdom

Included population: Women with all stages of ovarian cancer.

Included studies:

Papers investigating the symptoms experienced by women before having been diagnosed with ovarian cancer and ranging in design from retrospective case-control studies, longitudinal studies, questionnaires and surveys. One prospective study was identified and included.

Excluded studies:

Papers describing treatment or palliative care, screening, prevention or risk factors; Papers describing women with other conditions; Diagnostic or prognostic studies; Case studies, non-research articles, conference proceedings, letters, abstracts and others.

Population: N~2,800. Ages ranged between 15 and 90 years. Early and late stage disease.

Intervention(s) and comparator(s): N/A

Outcomes:

To identify the percentage of women who were asymptomatic before the time of diagnosis of ovarian cancer and to determine the prevalence of symptoms reported from quantitative studies.

Results:

- **Outcome:** Proportion of women with ovarian cancer without symptoms before diagnosis (using quantitative data directly from patients; N=8 studies (see below)) = 0.07 (95% C.I: 0.06-0.08). Between studies heterogeneity was not significant: X^2 (Q) = 11.3; df = 7; P=0.013 (Q statistic equivalent, I^2 = 38%).

    - Flam *et al.* (1988): Retrospective questioning. 362 cancers (172 stages IA or IB & 190 stages IIB-IV). Patients recently diagnosed and questioned before treatment.

    - Olson *et al.* (2001): Retrospective case-control study. Interviewer-led symptom checklist. 37 stages I/II and 118 stages II/IV. Patients diagnosed within a median of 4.7 months.

    - Vine *et al.* (2001): Case-control study. Standardised interview with symptoms checklist. 767 ovarian cancer cases comprising 616 invasive and 151 borderline cancers.

    - Vine *et al.* (2003): Case-control study. Interviewer-led symptom checklist. 267 ovarian cancer cases comprising 200 invasive and 67 borderline cancers.

    - Chan *et al.* (2003): Open ended questionnaire study. 87 patients (43 stages I/II and 37 stages II/IV). Newly diagnosed cancer patients.

    - Koldjeski *et al.* (2003): Retrospective symptom checklist, part of a longitudinal study on the impact of ovarian cancer. 20 patients (6 stages I/II and 13 stages III/IV).

Cancer diagnosed within previous 2-3 weeks.

- Webb *et al.* (2004): Part of a case-control study. Open-ended questions regarding up to four symptoms later categorised into 8 broader groups. 811 cancers (218 stages I/II and 447 stages III/IV and 146 borderline cancers. Newly diagnosed cases.

- Goff *et al.* (2004): Case-control study. Prospective symptom checklist of experiences in the previous year. 44 cancers (11 stages I/II and 33 stages II/IV). Women going through diagnosis.

- **Outcome:** Proportion of women with ovarian cancer without symptoms before diagnosis (using data collected from hospital records; N=3 studies (see below)) = 0.23 (95% C.I: 0.18-0.27). Between studies heterogeneity was not significant: X^2 (Q) = 1.76; df = 2; P=0.42 (Q statistic equivalent, I^2 = 0%).

  Petignat *et al.* (1997): Retrospective cancer registry data. Symptoms were recorded from all available sources. 119 cancers diagnosed from 1989-1995; stages IA-IB and 92 stages IC-IV.

  Eltabbakh *et al.* (1999): Retrospective case note review. Symptoms recorded at the time of presentation. 72 cancers diagnosed from 1984-1999; 50 stage I/II and 22 borderline.

  Nelson *et al.* (1999): Retrospective data from hospital notes. Symptoms recorded at the time of presentation. 72 cancers diagnosed from 1989-1991; 91 stages I/II and 59 stages III/IV.

- **Outcome:** Frequencies of symptoms reported from quantitative studies when comparing cases with controls. Data from symptom checklists according to Goff *et al.* (2004) Olson *et al.* (2001) or Vine *et al.* (2003).

  - Bloating (including fullness and pressure in the abdomen/pelvis OR = 25.3 (95% C.I:15.6-40.9)
  - Bloating or feeling of fullness OR = 14.6 (95% C.I: 9.4-22.8)
  - Bloating OR = 3.6 (95% C.I: 1.8-7.0) with clinic controls
  - Bloating OR = 3.5 (95% C.I: 1.5-8.2) with clinic controls
  - Distended/hard abdomen OR = 29.2 (95% C.I: 16.5-51.8)
  - Increased abdominal size OR = 7.4 (95% C.I: 3.8-14.2) with clinic controls

  - Abdominal/lower back pain OR = 6.2 (95% C.I: 4.0-9.6)
  - Pelvic/abdominal discomfort or pain OR = 16.4 (95% C.I: 10.3-25.3)

  - Abdominal mass OR = 5.4 (95% C.I: 2.4-12.0) with clinic controls
  - Urinary urgency OR = 3.5 (95% C.I: 1.6-8.2) with benign tumour controls
  - Constipation OR = 3.5 (95% C.I: 1.5-8.1) with benign tumour controls
  - Lack of appetite OR =8.8 (95% C.I: 4.3-18.2)

Follow-up: N/A

Notes:

This high quality systematic review combined data from 24 papers on the symptoms of ovarian cancer. Selection was made after searching for studies (including those in a non-English language) dated between 1984 and 2004 from Medline, EMBASE and CINAHL databases as well as hand searches of several other (named) journals. The search strategy was described and resulted in the identification of 220 potentially relevant papers. After the titles and abstracts were read and papers selected, data were extracted independently by two of the review authors. During this process two papers were excluded because the source of data was unclear and one because the study did not distinguish between symptoms of women with malignant or benign conditions.

Data were pooled to identify the percentage of women who were asymptomatic at the time of diagnosis. The methodology followed the methodology of inverse variance and the results were shown as a forest plot. Separate analyses were conducted according to whether data were collected from study participants or were taken from hospital notes. Where practicable, data were also combined across studies to try and identify those symptoms which had a significantly higher prevalence in women with ovarian cancer compared with matched controls.

Points to consider from these results:

1. The results from the meta-analysis showed that the overall proportion of asymptomatic women with ovarian cancer was 7.2%.
2. The results also showed that women with late stage cancer were more symptomatic than women with early or borderline cancer.
3. The authors have concluded that salient predictive symptoms have not been identified because of the retrospective nature of the study, recall bias, inherent patient bias, long duration between interview and diagnosis, under-estimation of patient experiences in medical records.
4. The systematic review was well conducted with the available data and is of high quality.

References used in the meta-analyses:

Chan YM., Ng TY., Lee PW., Ngan HY and Wong LC (2003) Symptoms, coping strategies, and timing of presentations in patients with newly diagnosed ovarian cancer. *Gynecol Oncol* **90:** 651-656.

Eltabbakh GH., Yadav PR and Morgan A (1999) Clinical picture of women with early stage ovarian cancer. *Gynecol Oncol* **75:** 476-479.

Flam F., Einhorn N and Sjovall K (1988) Symptomatology of ovarian cancer. *Eur J Obstet Gynecol Reprod Biol* **27:** 53-57.

Goff BA., Mandel LS., Melancon CH and Muntz HG (2004) Frequency of symptoms of ovarian cancer in women presenting to primary care clinics. *JAMA* **291:** 2705-2712.

Koldjeski D., Kirkpatrick MK., Swanson M., Everett L and Brown S (2003) Ovarian cancer: early symptom patterns. *Oncol Nurs Forum* **30:** 927-933.

Nelson L., Ekbom A and Gerdin E (1999) Ovarian cancer in young women in Sweden, 1989-1991. *Gynecol Oncol* **74:** 472-476.

Olson SH., Mignone L., Nakraseive C., Caputo TA., Barakat RR and Harlap S (2001) Symptoms of ovarian cancer. *Obstet Gynecol* **98:** 212-217.

Petignat P., Gaudin G., Vajda D., Joris F and Obrist R (1997) [Ovarian cancer: the symptoms and pathology. The cases of the Cantonal Cancer Registry (1989-1995)]. *Schweiz Med Wochenschr* **127:** 1993-1999.

Vine MF., Ness RB., Calingaert B., Schildkraut JM and Berchuck A (2001) Types and duration of symptoms prior to diagnosis of invasive or borderline ovarian tumor. *Gynecol Oncol* **83:** 466-471.

Vine MF., Calingaert B., Berchuck A and Schildkraut JM (2003) Characterization of prediagnostic symptoms among primary epithelial ovarian cancer cases and controls. *Gynecol Oncol* **90:** 75-82.

Webb PM., Purdie DM., Grover S., Jordan S., Dick ML and Green AC (2004) Symptoms and diagnosis of borderline, early and advanced epithelial ovarian cancer. *Gynecol Oncol* **92:** 232-239.

Author(s): Attanucci *et al.* (2004).

Design: Retrospective case-control study
Country: United States of America.

Inclusion criteria:

Cases: Women with invasive and borderline ovarian cancer.

Controls: Women with an adnexal mass subsequently found to have a benign ovarian neoplasm.

Exclusion criteria:

Cases: Women whose tumours had been incompletely surgically staged (N=35).

Controls: Women without a pathology report confirming an adnexal mass (N=77), women who already had cancer (N=6), women who had not been treated within the study period (N=11) and women with a germ cell tumour (N=2).

Population:
Cases: N=147. Mean age of women with invasive disease: 62 years (range: 21-85); mean age of women with borderline tumours: 50 years (range: 20-86).
Controls: N=76. Mean age: 49 years (range: 15-81).

Intervention(s) and comparator(s): N/A

Outcomes:

To compare the symptoms experienced by women with early stage ovarian cancer with women having late stage, borderline and benign ovarian neoplasms.

Results:

33/147 women were diagnosed with early stage disease (I and II), 81 women were diagnosed with late stage disease (III and IV) and 33 women had borderline disease. All women in the control group had a benign ovarian neoplasm.

- **Outcome: comparison of symptoms:**

  Early stage cancer patients were significantly more likely to report symptoms of mass effect (frequency, constipation, palpable mass, pelvic pressure) compared to patients having benign, borderline or invasive cancers:

  Early stage vs. benign cancers: 67% vs. 15% (P<0.001)
  Early stage vs. invasive cancers: 67% vs. 40% (P=0.008)
  Early stage vs. borderline cancers: 67% vs. 33% (P=0.007)

  There was no significant difference in the reporting of pain, gastrointestinal or gynaecological symptoms between women with early stage ovarian cancer and women with benign and borderline cancers.

  Compared to women having late stage disease, women with early stage ovarian cancer were less likely to report gastrointestinal symptoms (30% vs. 63%, P=0.002) and more likely to report gynaecological symptoms i.e. irregular vaginal bleeding, vaginal discharge, dyspareunia, post-coital bleeding or changes in the menstrual cycle (46% vs. 24%, P=0.02). However, there were no significant between group differences

in the reporting of pain or constitutional symptoms i.e. fever, fatigue, weight loss or weight gain.

Follow-up: N/A

Notes:

This paper described the results of a retrospective case-control study conducted in the United States of America. All women were diagnosed between January 1st 1999 and 31st December 2001 and identified by tumour board registry and International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9) codes. Medical, operative and pathology records were reviewed to identify symptoms, verify diagnoses and stage tumours.

The authors concluded that mass effect symptoms such as frequency, constipation, palpable mass and pelvic pressure were more prevalent in women with early stage ovarian cancer. They hypothesised that early stage tumours, whilst large and symptomatic, may be less likely to metastasise but tumours of late stage disease may metastasise when relatively small and hence not cause symptoms associated with their mass. Conversely, women with more advanced cancer reported more gastrointestinal symptoms than women with early stage disease.

Points to be considered from these results:

1. There is an inherent bias from retrospective studies.
2. The data were retrieved from medical records reporting the patient's initial consultation, before receiving a cancer diagnosis, which might have minimised recall bias.
3. During an initial consultation, patients may have denied having symptoms, failed to report them or the symptoms may not have been recorded by the physician.
4. Women in the control group were referred to the senior author with an adnexal mass - they were not selected from a larger general population.
5. Comparing data from early stage disease with benign, borderline and late stage cancer showed consistent results.

Author(s): Smith *et al.*(2005)

Design: Population based, retrospective case-control study
Country: United States of America

Inclusion criteria:

Cases: Women diagnosed with ovarian cancer (stages IC and above) between 1994 and 1999.

Controls: [1] Women with early (stages 0 or I) breast cancer and [2] women without cancer, age matched to the cases and randomly selected.

All study participants had to be eligible for (if not necessarily claiming) Medicare, a national health insurance scheme, open only to people ≥65 years, those with a chronic disability or having various other (named) conditions.

Exclusion criteria:

Women not entitled to Medicare A and B (insurance cover for in-patient hospital and convalescent expenses) or who had not been enrolled continuously in the 36 months prior to the date of cancer diagnosis; women in managed care plans; women with ovarian or breast cancer for whom this was not their first primary tumour; data only available from an autopsy or death certificate.

Population:

Cases: N=1,985; median age = 77 years (range: 68-101).

Controls: [1] N=6,024; median age = 75 years (range: 68-102) [2] N=10,941; median age = 78 years (range: 68-101).

Intervention(s) and comparator(s): N/A

Outcomes:

To evaluate the pattern of symptoms and the associated diagnostic tests documented in women with ovarian cancer over 36 months prior to the date of diagnosis. Each Medicare claim included at least one diagnostic code (ICD-9-CM) which could be grouped into the following categories: GI symptoms, abdominal pain, pelvic pain and abdominal swelling. Frequencies were then compared between the cases and each of the control groups and were reported as odds ratios (OR).

Results:

Of 1,985 women, 73.2% were classed as having stage III or IV disease (12.3% were unassigned) and 89.2% of tumours were identified as being epithelial (7% were unassigned).

The frequency and adjusted OR for each symptom type (claim code) experienced by women with ovarian cancer (cases) versus women with breast cancer or age-matched women without cancer are shown in the Table 1 (see Appendix A). Please note that due to the large amount of relevant data reported over three years, the results table has been reproduced directly from the original paper but will not appear in the published ovarian cancer guideline – instead the table will be substituted by a reference to the appropriate page number in the publication.

The proportion of women with ovarian cancer experiencing abdominal pain was highest in months 1-3 (30.6%), similarly abdominal swelling (16.5%) pelvic pain (5.4%) and GI symptoms (8.4%). In addition, the symptoms during this time period were also significantly more prevalent in women with ovarian cancer compared with either women with breast cancer or women with no cancer: abdominal pain (OR: 6.0 and 6.2 respectively) abdominal swelling (OR: 30.9 and 39.2 respectively) pelvic pain (OR 4.3 and 4.2 respectively) and GI symptoms (OR: 2.3 and 2.0 respectively). The increased frequency of cancer symptoms, comparative to controls, continued to be significant 7-9 months before diagnosis and one year before diagnosis, 7.4% of women with ovarian cancer reported at least one target symptom.

Follow-up: N/A

Notes:

This paper described the results of a large retrospective case control study conducted in the United States of America using data from women diagnosed with ovarian cancer (stages IC and above) between 1994 and 1999. Data were extracted from the SEER database and linked by a patient unique identifier to claims submitted to the United States health insurance program, Medicare by healthcare providers. Details for each patient also included a Common Procedure Terminology (CPT) code identifying the service rendered by the practitioner to the patient. Controls were also selected through Medicare records.

The authors concluded from their study that ovarian cancer could potentially have been diagnosed earlier in some patients, currently delayed by up to four months because health care providers ordered tests that would were not appropriate to make a definitive cancer diagnosis. They suggested that the use of tumour markers or pelvic imaging at an earlier point in the treatment pathway could have reduced this delay.

Points to consider from these results:

1. This is a retrospective study which has an inherent risk of bias since patient records were selected for inclusion.
2. The linking of patient data to health claim records may reduce the incidence of recall bias since, although symptoms were recorded up the three years before diagnosis, they were being reported at the time, not being recalled later as happens in some retrospective studies.
3. The authors made clear that the data were limited because they were extracted from databases that were designed for other purposes.
4. Since the majority of women had stage III/IV cancer, the authors excluded data from women with stages IA and IB disease.
5. All the women in this study were aged 68 years or over and hence younger women, possibly with earlier disease stages, were unrepresented.
6. There may be a bias in only including women who were eligible for Medicare.
7. Having two independent control groups, against which the cases were compared with reasonably consistent results, may have strengthened the validity of the findings.

Author(s): Yawn *et al.* (2004).

Design: Population based retrospective cohort study
Country: United States of America

Inclusion criteria: Women with a diagnosis of primary ovarian cancer.

Exclusion criteria: None stated.

Population: N=107. Mean age: 64.7 years (range: 30.5-98.1).

Intervention or comparators: N/A

Outcomes: To investigate the presenting signs, symptoms and stages of ovarian cancer in a community cohort of women.

Results:

98/107 (92%) women had epithelial ovarian cancer. 60% of tumours were stage III or IV and 60% were grade 3 or 4.

The initial symptoms reported varied with the tumour stage. Patients with early disease (stages I and II) were likely to present with crampy, abdominal pain and urinary symptoms. Alternatively, these tumours were found on routine examination. Women with late stage disease (stages III and IV) generally presented with abdominal bloating and weight loss.

- **Outcome: Symptoms prior to diagnosis:**
    - Abdominal pain: 22% in early disease vs. 35% in advanced disease (no P value)
    - Increased abdominal girth: 19% in early disease vs. 10% in advanced disease, P≥0.05 (NSD)
    - Weight loss: 0% in early disease vs. 8% in advanced disease, P≥0.05 (NSD)
    - Bowel changes: 2% in early disease vs. 10% in advanced disease, P≥0.05 (NSD)
    - Asymptomatic: 28% in early disease vs. 6% in advanced disease, P<0.01

- **Outcome: The time of onset of symptoms:**
    - <2 months: 55% of patients.
    - 2-6 months: 31% of patients
    - >6 months: 13% of patients.

Follow-up: N/A

Notes:

This paper presented findings from a small community cohort study conducted in Minnesota, USA from 1985 to 1997. Data on symptoms experienced up to two years before receiving a cancer diagnosis and on the duration of those symptoms were collected from medical records using the Rochester Epidemiology Project (REP) and SEER databases. In addition, the data abstractors, nurses who were familiar with the topic of ovarian cancer, constructed a short summary of each woman's course of symptoms and care before diagnosis**.**

Patients were divided into two groups according to time from the first documentation of signs or symptoms that were later associated with a positive diagnosis: group (1) <2 months or group (2) ≥2 months. A team of one physician and three nurses helped the authors to develop themes or domains and developed six categories to describe factors associated with the diagnostic course.

The authors concluded that the majority of symptoms were entirely abdominal and not specific to the pelvis, making diagnosis difficult. However recurrent, unresolved, or unexplained symptoms required exclusion of ovarian cancer as aetiology.

Points to be considered from these results:

1. This is a cohort study conducted with data from white, non-Hispanic women and hence the results may not be generalisable to other women with ovarian cancer.
2. The data were obtained from medical records which may have reduced recall bias
3. Women may not have described all their symptoms or the physician may not have recorded all the symptoms described by patients.

Author(s): Wynn *et al.*(2007)

Design: Population based, retrospective case-control study
Country: United States of America

Inclusion criteria:

Cases: Women diagnosed with ovarian cancer and having made at least two medical claims between 1998 and 2002. To rule-out remissions, cases had to have had surgery consistent with diagnosis or treatment of ovarian cancer within fourteen days of diagnosis.

Controls: Women with at least one medical claim and without cancer were matched to the cases for age, geographic location, Medicare eligibility and health plan. Participants were then randomly selected from this population.

All study participants had to be eligible for Medicare, a national health insurance scheme, or private employer based health insurance.

Exclusion criteria:

Cases: Women who'd had ovarian cancer diagnostic codes recorded in the year previous to the current diagnosis within the study.

All: Women who had not been continuously enrolled in a health plan for nine months preceding, and one month after, confirming surgery. Women who were pregnant in the ten-month study period.

Population:

Cases: N=920. Median age: 59 years.
Controls: [1] N=2,760 Median age: 59 years.

Intervention(s) and comparator(s): N/A

Outcomes:

To compare the pattern of symptoms, conditions and procedures documented in Medicare claims in women with ovarian cancer over nine months prior to the date of diagnosis. A predetermined list of fifteen symptoms was identified for each patient through the ICD-9-CM coding of their claims records. Frequencies were then compared between the cases and control groups and the trend pattern for each of the symptoms was plotted over the nine month study period.

Results:

- **Outcome: Frequency of symptoms (cases vs. controls):**
    - Abdominal (36.2% vs. 7.5%) P<0.0001
    - Urethra/urinary tract (12.7%vs. 6.4%) P<0.0001
    - Menopausal (12.4% vs. 7.5%) P<0.0001
    - Female genital (9.8% vs. 2.7%) P<0.0001
    - Gastrointestinal symptoms (7.7% vs. 5%) P<0.0001

The increased frequency of cancer symptoms, compared to controls, was also significant in the sixty to ninety days prior to diagnosis but diverged thereafter.

Follow-up: N/A

Notes:

This paper described the results of a large retrospective case control study conducted in the United States of America using data from women diagnosed with ovarian cancer between 1998 and 2002. Data were extracted from the Medstat's MarketScan Commercial Claims and Encounters and Medicare Supplemental database. Details for each patient also included a Common Procedure Terminology (CPT) code identifying the service rendered by the practitioner to the patient. The Charleson Comorbidity Index (CCI) was calculated using claims accumulated during the 9-month period to assess general health status. Controls were also selected through these records.

The authors concluded from their study that there were quantitative differences in symptoms in women with ovarian cancer from two to three months prior to their diagnoses.

Points to consider from these results:

1. This was a retrospective study, which has an inherent risk of bias since patient claim records were selected for inclusion.
2. As the data were not from the cancer registry they may not be representative of all women diagnosed with ovarian cancer.

3. The authors made clear that the data were limited because they were extracted from databases that were designed for other purposes.
4. Since the study excluded patients who had not had surgery within fourteen days of diagnosis, data from some women e.g. the elderly or those in ill health were not considered.
5. The linking of patient data to health claims may have reduced recall bias since, although symptoms were recorded up the three years before diagnosis, they were being recorded at the time of reporting.
6. Only women who were eligible for insurance were included in this study.
7. Claims records do not show tumour staging or histological data and these data were not otherwise available, a point noted by the authors as a major limitation.
8. The results from the study were consistent with other studies but, nonetheless, this is limited, poor quality evidence.

Author(s): Friedman *et al.* (2005).

Design: Retrospective case-control study
Country: United States of America

Inclusion criteria:

All women were in the Kaiser Permanente Medical care program, an integrated health care system.

Cases: Women diagnosed with ovarian cancer in 2001 – approximately half to have early stage disease (IA or IB) and the remainder to have advanced disease (IC-IV).

Controls: Randomly selected female subscribers matched for age, length of scheme membership and medical facility attended.

Exclusion criteria:

Cases: Incomplete follow-up; second primary cancer.

Controls: None stated.

Population: N=102. Age range: 29-87 years.

Intervention(s) and comparator(s): NA

Outcomes:

To identify the early symptoms of ovarian cancer from pre-diagnostic medical records and to compare symptoms in women with and without ovarian cancer.

Results:

Thirty-three patients had stage IA or IB disease; sixty-nine patients had stages IC-IV disease. 95/102 (93%) epithelial ovarian tumours.

One hundred and four symptoms were identified from medical records and these were compared between cases and controls. Of these, sixteen symptoms were equally reported by case and controls and were considered to be possibly unrelated to ovarian cancer. Data analyses were restricted to the remaining eighty-eight symptoms which showed case-control differences.

- **Outcome: Symptoms experienced >50% more often in cases than controls:**

    - Overall: 67/88 (76% 95% C.I: 67%-85%)
    - In the 6 months before diagnosis: 78% (95% C.I: 68%-88%)
    - In the 6 months to 1 year before diagnosis: 69% (95% C.I: 58%-80%)
    - In the 1 year to 2 years before diagnosis: 58% (95% C.I: 47%-69%)

In early cancers none of the symptoms exceeded chance expectation when compared to the incidence in controls although obesity was prominent and what the authors described as notably excessive was the occurrence of abdominal pain up to six months before diagnosis.

In advanced disease (IC-IV), the highest percentage of excess reported was 87% (95% C.I: 79%-95%) in the six months before diagnosis. For details of specific symptoms please see Table 2 (Appendix A). Please note that due to the large amount of relevant data reported, the results table has been reproduced directly from the original paper but will not appear in the published ovarian cancer guideline – instead the table will be substituted by a reference to the appropriate page number in the publication. Note that in this study, statistical significance was regarded as being $P<0.10$, which is non-standard, and was adopted because of the relatively low population number.

Over the entire study period, the predominant symptoms experienced by women with advanced ovarian cancer when compared with controls, were abdominal and gastrointestinal and also included pelvic, rectal and flank pain, dysuria, unintentional weight loss, headache, fatigue, shortness of breath and menopausal symptoms. Likelihood ratios ranged from 1.73 (shortness of breath) to 13.0 (pain in the side of trunk or flank).

Follow-up: N/A

Notes:

This paper provides only low quality evidence and describes the results of a small retrospective study conducted in California, USA using data from women diagnosed with ovarian cancer in 2001. Data were extracted from patient notes by two medical record analysts.

The authors concluded that it was not clear whether or not symptoms would be present whilst ovarian cancer was still localised and since hundreds of women would have to be investigated in order to detect one positive case, the clinical utility of symptoms was uncertain. However, they asserted that health care providers should keep ovarian cancer in mind when women presented with abdominal pain and bloating.

Points to be considered from these results:

1. There is an inherent weakness with retrospective studies and medical record analyses although recall bias may have been reduced.
2. The authors made clear that one limitation of the study was the lack of blinding of data analysts to the case-control status of each patient.
3. The study recruited a very low number of women with early stage (IA and IB) disease which may well explain the non-significant results, even with the significance cut-off set at $P<0.10$.

Author(s): Goff *et al.* (2007).

Design: Case-control study
Country: United States of America

Inclusion criteria:

Cases: Women undergoing surgery for a pelvic mass

Controls: [1] women who presented for ultrasound (USS) and [2] healthy, high-risk women enrolled in the Ovarian Cancer Early Detection study (OCEDS). None of the controls developed ovarian cancer in the six months after the study.

Exclusion criteria: None stated.

Population:

Cases: 149 with ovarian cancer (55 patients with ovarian cancer were added from another study).

Controls: 233 from the USS group and 255 from OCEDS.

All women were randomly assigned into exploratory or confirmatory groups, with the exception that all 55 patients with ovarian cancer from one author's previous study went into the exploratory group.

Intervention(s) and comparator(s): N/A

Outcomes: To evaluate symptoms in women with ovarian cancer who were surveyed prior to surgery and women at risk of having or developing cancer.

Results:

55/149 women had early stage disease, 88 women had late stage disease, 6 had unknown stage. Women with ovarian cancer were significantly older than the USS and OCEDS groups (56 years vs. 46 years and 51 years respectively, P<0.001)

Based on a correlation coefficient of ≥0.70 the following pairs of symptoms were combined into four variables: pelvic and abdominal pain, urinary frequency and urgency, increased abdominal size and bloating, difficulty eating and feeling full quickly.

- **Outcome: symptoms (cases vs. controls) occurring >12 days in each month for <6 months and <12 months (odds ratio):**
    - Pelvic/abdominal pain: OR: 19.1(95% C.I: 2.2-163.1) and OR: 23.3 (95% C.I: 3.9-163.9).
    - Urinary frequency/urgency: OR: 5.3 (95% C.I: 0.9-30.7) and OR: 5.2 (95% C.I: 1.0-25.1).
    - Increased abdominal size/bloating: OR: 11.2 (95% C.I: 2.2-58.3) and OR: 5.5 (95% C.I: 1.4-23.9).
    - Difficulty eating/feeling full quickly: OR: 1.0 (95% C.I: 0.1-9.9) and OR: 0.9 (95% C.I: 0.1-6.3).

When tested in the confirmatory group, the most sensitive model was considered to be the presence of six symptoms (the above named pairs but excluding urinary frequency/urgency) if present for >12 times per month for <1 year. This model showed a sensitivity of 56.7% for early stage disease and 79.1% for advanced stage disease with specificity of 90% for women >50 years and 86.7% for women < 50 years.

Follow-up: N/A

Notes:

This paper presented the results from a case-control study in which symptoms reported by women

with ovarian cancer were compared to those of women at high-risk of developing ovarian cancer. Study participants completed a survey on the occurrence, severity, frequency and duration of twenty-three symptoms and were surveyed either before ultrasound or histological diagnosis in order to minimise recall bias.

The exploratory group was used to determine the odds ratios of various self-reported symptoms. Those variables that were identified as significant formed a symptom index using regression modelling. The symptom index was then used with participants in the confirmatory group to test sensitivity and specificity.

The authors concluded that women who complained of pelvic and abdominal pain, urinary frequency and urgency, increased abdominal size and bloating, difficulty eating and feeling full quickly, symptoms of less than 12 month duration and occurring more than 12 times a month should be evaluated for potential ovarian cancer.

Points to be considered from these results:

1. This was a well-conducted case-control study in which the symptoms were first determined from an exploratory group and then resulting index checked with a confirmatory group.
2. One of the limitations of the study might be that the author added fifty-five ovarian cancer patients into the exploratory group whilst the other patients had been randomly selected. This may introduce a selection bias.

Author(s): Lurie *et al.* (2009)

Design: Population based case-control study.
Country: United States of America

Inclusion criteria:

Cases: Women with histologically confirmed invasive ovarian cancer.

Controls: Women of 18 years and older with no prior history of ovarian cancer and having at least one intact ovary.

Exclusion criteria: None stated.

Population:

Cases: N= 432. Controls: N=491. Age range: 19-88 years.

Intervention(s) and comparator(s): N/A

Outcomes:
To develop a symptom index that might help to diagnose ovarian cancer at an early stage and to evaluate whether there were histologically specific symptoms.

Results:

Of the 432 cases, 30% of women had local disease (stages IA-IB), 26% had regional disease (stages IC-II), 42% had distant spread (stages III-IV) and 2% were of unknown stage.

Abdominal pain was the most common symptom noted in localised ovarian cancer (sensitivity: 49%, specificity: 82%)

The following symptoms had the best predictive value for localised ovarian cancer with ROC (receiver operating curve) data in brackets:
Abdominal pain (0.81), Distended abdomen and hard abdomen (0.83), palpable abdominal mass (0.88), vaginal bleeding not associated with periods(0.88)

Women with ovarian cancer were more likely than controls to report a higher number of symptoms (Mean: 3.6 ± 0.1 vs. 2.6 ± 0.1 P<0.0001).

The authors wished to compare the various symptom indices by combining symptoms into groups. The best predictive ability was observed for a 4-symptom index that included abdominal pain, distended and hard abdomen, abdominal mass and abnormal vaginal bleeding. This index showed a sensitivity of 74% and a specificity of 77% specificity (ROC: 0.90).

When the authors compared the symptoms experienced alongside final histological diagnosis they found no statistical significance in any comparisons. The largest variation was noted in abdominal mass and distended, hard abdomen in mucinous compared with other tumours.

Follow-up: N/A

Notes:

This paper reported the results from a retrospective case-control study in which the symptom data were collected from an interview-based preset symptom questionnaire. The interviews were conducted in each participant's home by staff trained and supervised to standardise interviewing and coding techniques. All women were asked whether they had experienced any of the following 10 symptoms within 12 months prior to their diagnosis or the time of interview (controls). The duration of the symptoms were recorded:

- Persistent abdominal or pelvic pain or discomfort
- Unusual bowel irregularities such as diarrhoea or constipation, flatulence, or bloating
- Urinary frequency, difficulty emptying the bladder, or dysuria
- Persistent distended and hard abdomen
- Persistent fatigue, or loss of appetite
- Persistent flank or back pain with or without exertion
- Vaginal bleeding not associated with periods
- A palpable abdominal mass that the woman herself had noticed
- Weight gain and swelling of lower extremities
- Nausea, vomiting or heartburn.

The authors conclude that greater awareness of such symptoms, potentially related to ovarian cancer, might lead to an earlier diagnosis which might improve survival.

Points to be considered from these results:

1. There was a risk of recall bias as the interviews were conducted within a year after diagnosis.

2. Although of reasonable evidential quality, this study has all the usual disadvantages of a retrospective design.

Author(s): Lataifeh *et al.* (2005)

Design: Retrospective cohort study
Country: Australia

Inclusion criteria:

[1] Women early stage epithelial, ovarian cancer (stages IA and IB) [2] women with advanced stage epithelial, ovarian cancer (stage IIIC). Ten patients with early stage and 10 patients with advanced stage disease were selected consecutively for each of 10 years of study.

Exclusion criteria: Women with borderline and primary peritoneal cancers.

Population: N=200 (100 in groups [1] and [2])

Intervention(s) and comparator(s): N/A

Outcomes:

To determine the nature and duration of ovarian cancer symptoms, including any differences between early and advanced cancer patients.

Results:

38% of the women with early stage and 20% with advanced stage disease were <50 years of age (OR: 1.04; 95% C.I: 1.00-1.07, P=0.03). The duration of symptoms was the same regardless of cancer stage (70% early vs.60% late) presenting within 3 months of onset. All women with advanced cancer had experienced at least one symptom whilst 90% of women with early cancer were asymptomatic. The most common presenting symptom with early stage disease was vague abdominal pain (51%), also experienced by 44% of women with advanced stage disease.

- **Outcome: symptoms in early stage disease vs. advanced cancer:**
    - Abdominal swelling: 32% vs. 62% (OR 2.8: 95% C.I: 1.3-5.8, P=0.01)
    - Bloating: 10%v.s.13%
    - Abdominal pain: 51% vs. 44%
    - Abdominal pressure: 4%v.s.8%
    - Abdominal discomfort: 7% vs. 11%
    - Abnormal vaginal bleeding: 17% vs. 12%
    - Urinary symptom: 5% vs. 9%

Follow-up: N/A

General comments:

This paper reported the results of a retrospective cohort study comparing the symptomatology between early and advanced ovarian cancer. The cohort was from the Gynaecological Cancer database at Royal Hospital for Women at Australia. Data on the presenting symptoms were collected from medical records. The two groups were compared for each variable using logistic regression analysis.

Points to be considered:

- This was probably the only cohort study which compared early and advanced ovarian cancer.
- The study selectively compared stage IA and IB with IIIC but no other stages were included.
- There was a probability of bias due to recording symptoms from medical records although this may have reduced recall bias.
- Abdominal swelling, reported in advanced cancer significant more often when compared to early disease, might also have been due to ascites.
- There was no good quality evidence from this study to answer the topic question

Author(s): Bankhead *et al.* (2008)

Design: Prospective, qualitative cohort study

Country: United Kingdom

Inclusion criteria:

Women referred to hospital with suspected ovarian cancer; women recently diagnosed with ovarian cancer from hospital clinics.

Exclusion criteria: N/A

Population: Women with ovarian cancer: N=44. Mean age: 59 years. Women without ovarian cancer: N=80. Mean age: 48 years

Intervention(s) and comparator(s):

Outcomes: Symptoms in women with and without ovarian cancer.

Results:

44/124 women had malignancies (ovarian (N=40), primary peritoneal (N=2) or unknown (N=2)). 59 women had benign gynaecological pathologies and 21 had normal findings.

Multivariate analysis revealed the following symptoms as independent variable with ovarian cancer:

- **Outcome: symptoms of ovarian cancer v controls:**
    - Abdominal distension ± bloating OR: 5.2 (95% C.I: 1.3-20.5)
    - Bloating alone OR: 0.4 (95% C.I: 0.0-0.4)
    - Early satiety OR: 5.0 (95% C.I: 1.6-15.7)
    - Loss of appetite OR: 3.2 (95% C.I: 1.1-9.2)
    - Postmenopausal bleeding OR: 9.2 (95% C.I: 1.1-76.1)
    - Progression or worsening of the symptoms OR: 3.6 (95% C.I: 1.3-9.8)

The discriminatory power of the model was 81.5% which means 66% of the women with ovarian cancer and 90% of women without ovarian cancer were correctly identified.

Follow-up: N/A

Notes:

This paper described the results of a cohort study conducted in four hospitals in United Kingdom. All women were referred with suspected ovarian cancer. The study participants were interviewed

before diagnosis or shortly after diagnosis and a thematic analysis of the data was conducted. The emergent symptoms were then quantitatively analysed and the symptoms for women with and without ovarian cancer were compared. 63/124 women were interviewed prior to the diagnosis and remaining women were interviewed shortly after diagnosis.

The authors concluded that change could be effected at the primary care level if general practitioners could distinguish between persistent and fluctuating distension. This is because persistent distension is an associated symptom in women with ovarian cancer and fluctuating distension or bloating is associated with women without ovarian cancer. This, they felt, would lead to more rapid and appropriate referrals for women with suspected ovarian cancer.

The authors emphasised that their qualitative study showed that the terminology used to describe symptoms did not always accurately describe the symptoms that the women experienced. They used the example of persistent and fluctuating distension which was commonly described by women as bloating.

Things to be considered from these results:

1. This study differed from other studies since medical records or a symptom checklist was not used. Instead, the authors conducted a qualitative analysis to identify symptoms and then quantified the symptoms, comparing women with and without ovarian cancer.

2. The interview was conducted before their diagnosis or shortly after diagnosis which eliminated recall and survivor bias.

3. The authors performed a subgroup analysis of the frequency of symptoms in women interviewed after diagnosis and concluded that systematic bias was not introduced.

4. The sample size was small in order to manage the qualitative analysis effectively.

5. The model was not tested on an independent set of data and needs further validation.

Author(s): Hamilton *et al.* (2009)

Design: Primary care based, retrospective case-control study

Country: United Kingdom

Inclusion criteria:

Cases: Women diagnosed with primary ovarian cancer between 2000 and 2007 and age>40 years.

Controls: Women without cancer, age and practice matched to the cases and randomly selected.

Exclusion criteria:

Women whose medical records was unobtainable, no entry in records in the year before diagnosis, women who had previous oophorectomy, or they lived outside the study area at the time of diagnosis.

Population:

Cases: N=212; median age = 67 years.

Controls: N=1060; median age = not given

Intervention(s) and comparator(s): N/A

Outcomes: To evaluate and identify symptoms of ovarian cancer in women in primary care

Results:

The data on the symptoms was collected from the medical records at primary care for one year before diagnosis. The researchers were blinded to the status of each woman. The symptoms were coded using international classification of primary care-2.

Univariate logistic regression, with P<0.1, identified symptoms for multivariate analysis. Using multivariable analysis the following seven symptoms were identified as independently associated with ovarian cancer.

Abdominal distension OR: 240 (95% CI: 46-1200),

Abdominal pain OR: 12 (95% CI: 6.1-22),

Postmenopausal bleeding OR: 24 (95% CI: 9.3-64),

Loss of appetite OR: 17 (95% CI: 6.1-50),

Urinary frequency OR: 16 (95% CI: 5.6-48),

Rectal bleeding OR: 7.6 (95% CI: 2.5-23),

Abdominal bloating OR: 5.3 (95% CI: 1.8-16).

One antagonistic interaction abdominal distension and increased urinary frequency suggesting if both symptoms are present, it is less likely to be ovarian cancer.

The calculated the positive predictive value (PPV) by combing two symptoms or same symptom reported second time. The combination of abdominal distension and loss of appetite had highest PPV of >5%, followed by abdominal distension reported twice with PPV of 4.3%.

They also calculated the odds for symptoms excluding 6months from the diagnosis. Three symptoms, abdominal distension (OR: 18, 95% CI 2.1-160), urinary frequency (OR: 3.1, 95% CI 1.3-7.3) and abdominal pain (OR: 2.6, 95% CI 1.5-4.6) was noted.

Follow-up: N/A

Notes:

This paper described the results of a retrospective case control study conducted in the United Kingdom using data from women aged more than 40 years diagnosed with ovarian cancer between 1994 and 1999. The data is from the primary care records. Data were extracted from the GP records and were not linked to the cancer registry. The controls were age and practice matched to the cases

The authors concluded from their study that symptoms of ovarian cancer in women in primary care were similar to those in hospital series. Abdominal distension with positive predictive value of 2.5% warrants rapid investigation

Points to consider from these results:

1. This is probably the only study in United Kingdom done at the primary care level and hence carries more valuable information on initial presentation.

2. The researchers have been blinded to the diagnosis and thereby reducing bias.

3. This is a retrospective study which has an inherent risk of bias since patient records were selected for inclusion.

4. All the women in this study were aged 40 years or over and hence younger women, possibly with earlier disease stages, were unrepresented.

5. There may be a bias in only including women who presented to the primary care. Some women might present directly to hospital as emergencies.

Author(s): Rossing *et al.* (2010)

Design: Case control study

Country: USA

Inclusion and exclusion criteria:

Women diagnosed with primary invasive or borderline epithelial ovarian cancer between 2002 and 2005 identified through a population based registry (SEER). Control subjects (with at least one ovary and no history of ovarian cancer) were selected by stratified random sampling from the same registry.

Population: 594 women with primary invasive ovarian cancer, 1313 healthy controls and 217 women with borderline ovarian cancer.

Intervention(s) and comparator(s):

Women were interviewed in person about their symptoms before diagnosis, which was on average 9 months before the interview. Control subjects were asked about symptoms before a reference date in the past, on average ten months before their interview.

Outcomes:

Women were asked to report five categories of symptoms: nausea; bloating or feeling of fullness; diarrhoea or constipation; pelvic or abdominal discomfort, pressure or pain; and a need to urinate more frequently or urgently than usual.

Only symptoms that were present at some point during the year before the diagnosis or reference date, at a frequency of at least daily for at least a week, were recorded.

Symptoms were analysed individually and as components of a symptom index (Goff, 2007) and consensus recommendations (Twombly *et al.*, 2007).

Results:

	Invasive ovarian cancer (N=594)	Control (N=1313)
Any symptom	504/594 (85%)	336/1313 (26%)
Nausea	83/594 (14%)	58/1313 (4%)
Diarrhoea or constipation	199/594 (33%)	132/1313 (10%)
Pelvic or abdominal pain	362/594 (61%)	96/1313 (7%)
Bloating or feeling full	381/594 (64%)	122/1313 (9%)
Urinary frequency or urgency	250/594 (42%)	152/1313 (12%)
Symptom index (Goff *et al.*, 2007)	400/594 (67%)	80/1313 (6%)
Consensus criteria (Twombly *et al.*, 2007)	386/594 (65%)	94/1313 (7%)

Subgroup analyses according to stage, age and symptom severity are also available

Author(s): Pavlik *et al.* (2009)

Design: Prospective case series

Country: USA

Inclusion criteria:

Subgroup of 450 women enrolled in a prospective screening study for ovarian cancer, who had abnormal transvaginal ultrasound (TVS) findings and underwent surgery. Only women who returned confident responses to the symptom index questionnaire were included (272/450).

Exclusion criteria:

Women who had died, had withdrawn from the study, who were unwilling to take the symptoms survey or who were not confident in their answers (178/450).

Population:

272 women. 32 with primary invasive ovarian cancer, 17 with low malignant potential or granulosa cell tumours, 192 with benign ovarian pathology.

Intervention(s) and comparator(s):

Women completed the Goff *et al.* (2007) symptom index questionnaire. They also had to rate their confidence in their replies (from 0 – no confidence to 5 - absolutely sure of accuracy). Only

women with confidence of 3 (pretty sure) or more were included.

Transvaginal ultrasound (TVS) findings were also reported using a morphology index – the sum of the volume score (1 to 5) and the structure score (1 to 5).

Outcomes: Rate of symptoms, TVS morphology index.

Results:

	Invasive ovarian cancer (N=30)	**Benign or low malignant potential ovarian pathology (N=242)**
Symptom index + (Goff *et al.*, 2007)	6/30 (20%)	21/242 (9%)
TVS morphology index >3	27/20 (90%)	107/242 (44%)
TVS morphology index >4	22/30 (73%)	62/242 (27%)
Symptom index AND TVS >3	5/30 (17%)	7/242 (3%)
Symptom index AND TVS >4	5/30 (17%)	5/242 (2%)
Symptom index OR TVS >3	28/30 (93%)	121/242 (88%)
Symptom index OR TVS >4	23/30 (77%)	78/242 (32%)

Notes:

Unclear whether the questionnaire was completed as part of the screening study or following diagnosis. Combined low malignant potential tumours and benign ovarian pathology in their analysis.

Unlike the other case-control studies, all the included women had some form of ovarian pathology and had surgery. Exclude from any meta-analysis for this reason.

Author(s): Kim *et al.* 2009

Design: Case control study

Country: South Korea.

Inclusion criteria: Women visiting a single gynaecology department between 2007 and 2008. Controls had to have an intact uterus and at least one ovary.

Exclusion criteria: Women with a history of gynaecological cancer were excluded from the control group.

Population: 116 women with epithelial ovarian cancer, and 209 controls (74/209 controls had benign ovarian cysts).

Intervention(s) and comparator(s):

Women completed a questionnaire based on the Goff *et al*. (2007) symptom index. The study added an extra question about urinary symptoms.

In women with benign cysts the questionnaires were done before surgery. In women with ovarian cancer they were done during hospital stays for surgery or chemotherapy. In the remaining controls they were done during clinic visits for a routine Pap smear test. Investigators were available to help women with any questions they did not understand.

Outcomes: Individual symptoms (see below) and symptom index. The symptom index was considered positive if a woman had any of the symptoms present for less than one year but occurring more than 12 times per month.

Results:

	Ovarian cancer (N=116)	**Benign cyst (N=74)**	**Healthy control or benign cyst (N=209)**
Symptom index +	76/116	23/74	32/209
Pelvic/abdominal pain	20/116	10/74	11/209
Increased abdominal size / **bloating**	56/116	11/74	11/209
Urinary urgency / **frequency**	33/116	8/74	13/209
Difficulty eating / **feeling full**	42/116	10/74	14/209

Author(s): Andersen (2010)

Design: Case control study

Country: USA

Inclusion criteria:

Women with ovarian cancer. Healthy controls were identified via a screening study in high risk women.

Exclusion criteria:

Women with a history of gynaecological cancer were excluded from the control group.

Population:

74 women with ovarian cancer (6 with mucinous tumours, 6 with clear cell carcinoma, 7 with

endometrioid cancer, 5 with other adenocarcinoma and 50 with serous cancer), 137 healthy controls.

Intervention(s) and comparator(s):

The target condition was the identification of ovarian cancer; the reference standard was histopathology for the women with ovarian cancer. Reference standard was not reported for the controls - it was probably negative screening tests for ovarian cancer since these women were identified via a screening study.

Outcomes: Serum samples and symptom questionnaires were collected prior to surgery (and diagnosis) in women who had surgery. Controls had serum samples and symptom questionnaires collected on a quarterly basis as part of a screening study.

Results:

Serum HE4

The HE4 threshold for positivity was the upper 95% percentile of the control group. Authors do not report the numeric value of this cut-off threshold. Using this definition fixes the specificity of HE4 at 95%.

sensitivity (95% C.I.) was 0.77 (0.66, 0.86), specificity was 0.95 (0.90, 0.98)

Serum CA125

The CA125 threshold for positivity was the upper 95% percentile of the control group. Authors do not report the numeric value of this cut-off threshold. Using this definition fixes the specificity of CA125 at 95%.

Sensitivity was 0.81 (0.70, 0.89), specificity was 0.95 (0.90, 0.98)

Symptom index (SI)

The symptom index was considered positive if the patient had at least one of the following symptoms for less than 1 year but more than 12 times per month: bloating or increased abdominal size, abdominal or pelvic pain, difficulty eating or feeling full quickly.

Sensitivity was 0.64 (0.52, 0.74), specificity was 0.88 (0.82, 0.93)

Combined tests

HE4 or CA125 positive: sensitivity was 0.89 (0.80, 0.95), specificity was 0.90 (0.83, 0.94)

HE4 or SI positive: sensitivity was 0.92 (0.83, 0.97), specificity was 0.85 (0.78, 0.90)

CA125 or SI positive: sensitivity was 0.92 (0.83, 0.97), specificity was 0.83 (0.76, 0.89)

HE4 or CA125 or SI positive: sensitivity was 0.95 (0.87, 0.99), specificity was 0.80 (0.72, 0.86)

SI and (HE4 or SI) positive: sensitivity was 0.58 (0.46, 0.70), specificity was 0.99 (0.95, 1.0)

Subgroup analyses of test accuracy according to age (<50 years versus 50 or more years), risk status and stage were also done.