

## Risk of Ovarian Cancer in Women Seeking Primary Care with Symptoms

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### Abstract

**Objective:** To recognise and measure ovarian cancer signs in women receiving primary care.

**Design:** Case-control research that included the primary care records of the participants for the year prior to diagnosis.

**Setting:** Devon, England has 39 general practitioners.

**Participants:** 212 women over 40 had an initial ovarian cancer diagnosis between 2000 and 2007; 1060 controls with similar age and general practise.

**Main outcome measures:** From conditional logistic regression analysis, odds ratios and positive predictive values for symptoms.

**Results:** In a multivariate study, seven symptoms were linked to ovarian cancer. There were 2.5 percent (1.2 percent to 5.9 percent) and 240 (46 to 1200) for abdominal distension, 0.5 percent (0.2 percent to 0.9 percent) and 24 (9.3 to 64) for postmenopausal bleeding, 0.6 percent (0.3 percent to 1.0 percent) and 17 (6.1 to 50) for loss of appetite, and 0.2 percent (0.1 percent to 0.3 percent) and 16 (5.6 to 48) for increased urogenital flow, respectively. At least one of these seven symptoms was reported to primary care prior to diagnosis in 181 (85%) cases and 164 (15%) controls. Abdominal distension, frequent urination, and abdominal discomfort continued to be independently related with an ovarian cancer diagnosis when 180 days of symptoms were excluded.

**Conclusions:** Often months before the disease is discovered, women with ovarian cancer report their symptoms to their primary care physician. This study gives doctors and those who create guidelines a solid evidence framework for choosing which patients to investigate.

**Keywords:** Postmenopausal bleeding; Urogenital flow; Abdominal distension; Frequent urination; Abdominal discomfort

### Introduction

Over 200 000 new cases of ovarian cancer are diagnosed each year around the world, accounting for 4% of all malignancies in women. Among all gynaecological malignancies, it has the worst prognosis, with a five-year survival rate of just approximately 35% overall. Compared to late tumours, early cancers (FIGO (International Federation of Gynecology and Obstetrics) stage I or II) have a survival rate of 80–90% (FIGO III and IV). Only 30% of patients are currently diagnosed in these early stages [1]. Since there is now no reliable screening method, improving the ability to recognise cancer symptoms is the best hope for an earlier diagnosis. 5 Such symptoms are typically reported to primary care.

Current referral guidance in the United Kingdom recommends urgent investigation only for abnormal vaginal bleeding and palpable masses, though these recommendations are not required. Several recent studies have shown that symptoms are common, though they frequently go unrecognised by women and doctors. Abdominal pain, abdominal distension, pelvic pain, incontinence, and bloating are just a few of the symptoms that are commonly overlooked by women and doctors [2]. However, nearly all studies of symptomatic ovarian cancer have relied on patient interviews after diagnosis, a technique that frequently results in recollection or selection bias. Furthermore, since 95 percent of women who visit their primary care provider have a symptom that could be an indicator of ovarian cancer, the symptoms that have been discovered are equally frequent in non-malignant illnesses.

Only three researches, all of which used American medical data to identify symptoms, were based in primary care. For abdominal

discomfort, an estimated 0.3 percent positive predictive value was calculated. Clinicians can utilise positive predictive values to help them decide whether to conduct further testing on a woman who exhibits a symptom [3]. In order to determine the positive predictive values for ovarian cancer for each significant symptom in primary care, both alone and collectively, we designed this case-control study to be large enough.

### Methods

#### Participants

We identified women under 40 who were diagnosed with primary ovarian cancer in England between 2000 and 2007. Invited to participate were all 50 general practises in Exeter, mid-Devon, or east Devon. A total of 97 500 female patients, aged 40 to 69, and 3000 patients older than 70, were among the 39 who were accepted [1].

We found cases by performing a computer system search for the practise. We located histology records and only included women who had negative histology results if the records also included a specialist

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diagnosis supported by substantial clinical evidence [4]. In cases where there was no histological confirmation, the date of diagnosis was assumed to be the date of the positive histology results or the date provided by the specialist.

Using computerised random numbers, five controls for each instance were matched by age (to one year) and experience. If the controls were still living at the time of the matching case's diagnosis, they were considered eligible [3]. Cases and controls were removed if the medical record was not available, there was no entry in the records in the year prior to diagnosis, the woman had undergone bilateral oophorectomy or ovarian cancer prior to diagnosis, or she resided outside the research area. Reserve controls were used in place of ineligible controls [5].

### Data gathering and coding for medical purposes

We created anonymized photocopies of each cancer patient's complete medical history from the year before to diagnosis, and we did the same for the matched controls. Using the primary care-2 international categorization and new codes for symptoms including bloating, three researchers who were unaware of each woman's health categorised all symptoms, whether or not they had previously been linked to ovarian cancer [2]. 13 With 17 chapters covering several body systems and up to 30 pertinent symptoms in each, this classification system is the most symptom-based of the primary care coding systems. For each exercise, the same researcher coded both the cases and the controls in order to reduce the impact of any differences in coding styles among observers. All coders recoded 246 randomly chosen symptom codes to look at variation. It was 0.79 for the dependability coefficient (95 percent confidence interval 0.75 to 0.83) [6].

### Analysis

Only symptoms that appeared in at least 5% of patients or controls were examined. With a P value 0.1, univariable conditional logistic regressions revealed symptoms for multivariate analyses [7]. We utilised a P value of 0.01 as the significance criterion for the multivariable analyses because 99 of these were found. At this point, eight clinical groups having a common theme, such as urine symptoms, were formed from the symptoms [4]. Multiple variable conditional logistic regressions were used to analyse each group. Following this initial study, the symptoms still linked to cancer were reorganised into two bigger groups (abdominal symptoms and other symptoms), and more modelling was done. The likelihood ratio test was used to confirm that none of the deleted symptoms significantly contributed to the final model by adding each one separately. The final model was evaluated using five clinically realistic interactions.

Using the likelihood ratio and the country's overall incidence of cancer in 2005, we determined the positive predictive values for both single symptoms and pairs of symptoms [3]. 16 For women older than 40, this frequency was 35.7/100 000, for those between 40 and 69 it was 29.6/100 000, and for those over 70 it was 68.6/100 000. Since 10.8% of eligible controls and all women in cases received primary care consultations, respectively, we divided positive predictive values by 0.892 to obtain the value for the consulting population. We stratified analyses by age (40-69 and 70) if all cell values in the 22 table were at least five. State 10 was used to perform the analyses.

Abdominal pain was employed in the sample size calculation. According to earlier studies, 10% of adults without cancer sought medical attention for stomach pain [5]. 17 18 19 percent was the lowest number previously reported for cases in primary care. With a two-

sided 5 percent and 90 percent power, 210 cases were needed to detect this difference.

## Results

### Cases and controls

43 women were excluded from the 255 women with ovarian cancer records that were found by the computer searches. Eight of them were under 40 at the time of diagnosis, 12 had merely suspected ovarian tumours (six also had other cancers and six had benign ovarian illness), six had ovarian metastases, and six had ovarian cancers that had previously been detected before 2000 recurred [8]. Seven diagnoses were made outside the study region, three participants departed the study area and their notes could not be located, and one participant accidentally submitted the erroneous date of birth for the study, rendering her controls worthless because they were 13 years younger [5]. There were 212 instances remained, 113 (53 percent) of which were women whose deaths occurred at the time of the study but whose notes could still be found. Up to 2006 and 2007, when there were 44 and 52 qualified instances, respectively, we discovered 12-26 eligible cases annually.

Of the 212 cases, histology findings were obtained for 169 (80%), albeit 94 of these only had the descriptors carcinoma or adenocarcinoma. 66 (88%) of the 75 samples with the cell type indicated were epithelial, while nine (12%) were non-epithelial [4]. Borderline tumours were present in 13 women. For 164 (77%) patients, staging information was available; of them, 46 (28%) had FIGO stage I, seven (4%) stage II, 73 (45%) stage III, and 38 (23%) stage IV. While 60 (59%) of the 101 women aged 40-69 years with staging were in stages III or IV, 51 (81%) of the 63 women above the age of 70 with staging data were in stages III or IV (2 P=0.004).

One had previously had ovarian cancer, 50 had undergone an oophorectomy, and 128 (10.8 percent of those qualified for the research by every other criterion) had no consultations during the relevant one-year period. There were 1239 controls who met the inclusion criteria, but 179 were ineligible. (7.2%) of the controls also passed away at the time of the study although their notes could still be found [9].

We identified 99 factors that were significantly (P 0.1) related with ovarian cancer and included them in a multivariable analysis. Lists the univariable analyses of those symptoms that were later discovered in the multivariable analysis to be independently linked with an ovarian cancer diagnosis.

In the final multivariable model seven symptoms persisted. Abdominal distension and higher urine frequency have one antagonistic interaction, which means that when both symptoms are present, the overall effect is smaller than would be expected from multiplying the odds ratios together [6]. 181 (85%) of cases and 164 (15%) of controls experienced at least one of the symptoms. Three sensitivity analyses produced unfavourable findings. Odds ratios were comparable for cancers diagnosed before and after the adoption of the quality and outcomes framework, for those with and without histology, for stage I or II tumours compared with stage III and IV tumours, and for cancers diagnosed with and without histology (a payment scheme for UK general practitioners, which encouraged recording of cancer diagnoses).

Early signs of ovarian cancer were discovered using multivariable analysis using data excluding the previous 180 days. In this model, there were no interactions.

The positive predictive value for ovarian cancer for each symptom that was independently related in multivariable analysis whether it was reported alone in combination with another symptom, or a second time (shown on diagonal). The univariable positive predictive values and multivariable odds ratios (with 95 percent confidence intervals) for abdominal distension, loss of appetite, increased urinary frequency, and abdominal pain, respectively, were 2.5 percent (1.2 percent to 5.9 percent), 240 (46 to 1200), 0.6 percent (0.3 percent to 1.0 percent), and 17 (6.1 to 50), respectively [5]. While the combination of abdominal distension and loss of appetite was technically speaking undefined, it was present in 20 cases but not in any controls. Because of this, the positive predictive value was calculated as >5%. The sample sizes for postmenopausal and rectal bleeding were too small to calculate positive predictive values in combinations, but the univariable values were 0.5 percent (95 percent confidence interval: 0.2 percent to 0.9 percent) for postmenopausal bleeding and 0.2 percent (0.1 percent to 0.4 percent) for rectal bleeding, respectively [10]. All of the symptoms had larger positive predictive values in patients under the age of 70, reflecting the increased incidence of ovarian cancer in older women, with the exception of urine frequency.

## Discussion

We discovered seven symptoms connected to ovarian cancers that were independently reported to primary care. When we limited our analysis to symptoms reported at least 180 days before to diagnosis, three of these symptoms—abdominal pain, abdominal distension, and urine frequency—remained linked to the outcome. All of the symptoms have previously been documented in studies on secondary care [11]. This is encouraging given the significant number of diverse symptoms that were reported to general practice and included in the study's analyses. We determined the likelihood of ovarian cancer over the whole spectrum of significant symptoms in primary care, the environment where diagnostic labs are most common.

## Possibilities and constraints

This study was conducted in 39 different practices; therefore there will unavoidably have been some difference in how symptoms were recorded. This effect should have been reduced by practice matching controls and using the same coder for each exercise. If ovarian cancer is a possibility, doctors may take more detailed notes on symptoms [10]. In that case, the study's positive predictive values would have been exaggerated. Prior estimates only included one positive predictive value, which was 0.3% for abdominal discomfort. Our comparable number is encouraging since it indicates that recording bias may have only had a little impact [12]. One-fifth of the women in this study had none of the seven symptoms noted in their notes. According to interview research, just 7% of women actually have no symptoms. The discrepancy may be attributable to failure to inform the doctor of symptoms or failure to document them, or, more likely, to both. Furthermore, characteristics of symptoms, such as their severity or duration, are rarely captured by retrospective approaches. But according to earlier studies using medical records, women with cancer appear to have no symptoms in a mean of 22% of cases (range: 19–26%). We were able to record more symptoms thanks to our methodology than in earlier trials.

Through computer searches, we found the cases; however, some cases may have been overlooked. According to the national incidence rate, we should have found about 35 new cases annually within the study population. For the first five years, the number was lower than this, but it started to rise in 2006—possibly as a result of the quality and outcomes framework, which prompted UK general practitioners to start a cancer

register [13]. If the cases we did discover are not indicative of all the women who get ovarian cancer, then this discrepancy won't matter. The age distribution is consistent with national statistics, the histology and staging are consistent with previous case series and thus any bias brought about by missed cases was probably not very significant.

## Symptoms

All symptoms, with the exception of abdominal distension, showed positive predictive values under 1%. These low results are a result of the frequent stomach complaints in the "healthy" population as well as the uncommon occurrence of ovarian cancer. However, the 2.5 percent risk of ovarian cancer associated with abdominal distension obviously calls for more study [14]. Over a third of women also mentioned this symptom. Furthermore, even after we excluded the last six months from the analysis, it continued to be linked to cancer. As previously mentioned, it was equally prevalent in cancers in stages I and II as it was in advanced cancer. However, abdominal distension is not recommended for immediate inquiry according to current guidelines; if it were, some women's diagnosis would be made much sooner.

The symptom of bloating is related. The records of bloating presumably represent a verbatim notation of the word the woman used because this is not a common medical term in the UK. Women, on the other hand, use the phrase to refer to either intermittent or persistent (or progressive) distension. The latter is used more frequently. In this study, people with a history of abdominal distension will include those women who, when the precise symptom was identified, switched from using the term "bloating" to the phrase "distension." The term "bloating" may still be used by other physicians. Patients who claim to have distension but are actually experiencing sporadic edema are less likely to do so [15]. As a result, the abdominal distension variable is presumably very "pure," consisting mostly of patients with persistent distension, as opposed to the bloating variable, which probably includes some women who are more accurately defined as having distension. The majority of earlier investigations accepted the word bloating without further clarification and discovered that it was connected to ovarian cancer. However, one small study discovered that intermittent distension was not connected to cancer when the two meanings were separated. Only if we acknowledge that some of individuals diagnosed with bloating actually had persistent distension, are our findings consistent with this. The substantially reduced odds ratios and positive predictive values demonstrate that, even if true intermittent distension does entail some risk, it is significantly lower than chronic distension [16].

Abdominal pain was reported by more than half of women, and this was true whether the women had early-stage or advanced malignancies. Some ladies had it for a number of months prior to diagnosis. However, compared to abdominal distension, the positive predictive value was only 0.3 percent. The low risk, but not zero risk, symptom is a classic problem for people in primary care. Even when a second symptom (other than distension) was present, the combination was still considered to be low risk. We are unable to determine whether lower abdominal or pelvic pain was particularly significantly associated with cancer since the exact location of the pain was rarely specified in the medical records. Despite the fact that women would typically not be offered further testing based only on stomach pain due to this low risk, general practitioners must take into account the remote probability of ovarian cancer [17]. Therefore, a thorough clinical examination is necessary in cases when a definite diagnosis cannot be made, and this is followed by evaluation and investigation. The yield in a newly published trial of ovarian cancer screening was about one malignancy

per 2000 women screened. A reassuringly low false positive rate was also present. Since the yield will be substantially higher in the symptomatic women, general practitioners should absolutely look into low-risk but not no-risk pregnant women.

Urinary frequency emerged as the third cancer-related symptom when the last 180 days were excluded. This symptom has been linked to ovarian cancer in the past, but there is no conclusive evidence linking it to early or advanced disease. In comparison to stomach pain or distension, it was less common and carried a lower risk. Naturally, other, more widespread reasons of frequent urination will be looked into first, but ovarian cancer must be kept in mind as a diagnostic possibility and investigated [18].

The majority of symptom reporting to general practitioners takes place in the three months prior to diagnosis, even though these three symptoms were linked to cancer 180 days before diagnosis. From this study, we are unable to determine if accelerating the diagnosis by this [12] much would have therapeutic advantages; all we can say is that some women may be able to receive a diagnosis up to three months earlier.

Although the primary initial concerns are uterine and colorectal malignancies, respectively, postmenopausal and rectal bleeding are grounds for prompt evaluation in contrast to abdominal distension, abdominal pain, and frequent urination [9]. Early tumours exhibited both of these symptoms a little more frequently. This might reflect rapid investigation, albeit for a different cancer. But because these two signs were so uncommon, this early inquiry will only find a tiny fraction of ovarian malignancies.

Numerous other symptoms, such as constipation and diarrhoea, were linked in univariable analyses in addition to the seven that remained connected to cancer following multivariable analysis. These have previously been discussed in case studies [19]. However, the existence of additional symptoms diminished the predictive value of these symptoms. For primary care, this makes things a little easier. Doctors shouldn't be overly concerned with isolated gastrointestinal symptoms; it might be challenging enough to remember to investigate ovarian cancer when experiencing abdominal pain.

## Conclusion

Currently, identifying cancer in women who have symptoms is the only practical option for hastening the diagnosis of ovarian cancer. Even in early tumours that may be treatable, symptoms are typical and frequently reported. Our findings are encouraging in that regard since they suggest that early ovarian cancer may be detectable using symptoms. Particularly, abdominal distension is a frequent, serious symptom that requires quick evaluation. Other symptoms call for more conventional primary care techniques, such as examining a patient's history, performing an examination, and taking cancer into account. Although it is not silent, ovarian cancer is not being heard.

## Acknowledgement

None

## Conflict of Interest

The author declares has no conflict of interest.

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