Original Article

Characteristics of ovarian cancer patients with first presentation in general practice

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ABSTRACT

Introduction. Women with ovarian cancer (OC) have a poor prognosis. An improved prognosis was observed when the pathway to diagnosis begins in general practice. We aimed to investigate patient characteristics among women diagnosed with OC whose diagnostic pathway begins in general practice.

Methods. This was a population-based retrospective cohort study among Danish patients with a first-time OC diagnosis, using questionnaire data and national registers.

Results. The GP was involved in the diagnosis in 91.1% of the 313 included women with OC. Women aged 60-74 years had statistically significantly higher odds of having GP involvement than women younger than 60 years (odds ratio (OR) = 2.97 (95% confidence interval (CI): 1.09-8.08)). Women with high comorbidity had statistically significantly lower odds of having GP involvement than women with no comorbidity (OR = 0.25 (95% CI: 0.09-0.66).

Conclusions. This study found higher odds of GP involvement in the diagnosis of OC in women aged 60-74 years and lower odds of GP involvement in women with high comorbidity. The remaining patient characteristics had no significant influence on the first place of presentation for OC patients. Knowledge hereof may potentially inform future initiatives as health campaigns or postgraduate GP training thereby increasing the awareness among women and GPs alike of OC symptoms. However, the study was restricted to a limited number of patients, and future research is warranted to underpin our findings.

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Trial registration. not relevant.

Ovarian cancer (OC) has an age standardised annual incidence rate of 16.1 per 100,000 women in Denmark [1]. Around 62-68% of Danish patients with OC (including ovarian, tubal and peritoneal cancer) are diagnosed with International Federation of Gynecology and Obstetrics (FIGO) stage III-IV disease. They have a five-year survival rate of 23.4-41.0% [2], whereas patients diagnosed with FIGO stage I-II disease have a five-year survival rate of 75.5-93.3% [2].

The patient's pathway to diagnosis has profound prognostic influence [3]. International studies have shown that patients for whom general practice has been involved in their diagnostic pathway have a better prognosis than patients with emergency presentation (EP). This is seen across different types of cancer, including OC [3, 4]. Baun et al. estimated that the GP was involved in 90% of OC cases in Denmark. For 39% of the patients, the GP suspected cancer at the first presentation to general practice, and 36% were urgently referred to a cancer patient pathway (CPP) [5]. Women with vague or non-specific symptoms were more likely to experience a long

diagnostic interval and less likely to be referred for a CPP [5]. Even so, the literature is sparse concerning patient characteristics of women presenting to their GP versus women bypassing their GP in the pathway towards an OC diagnosis. Literature from the United Kingdom (UK) suggests that patients with EP are more likely to have higher age, comorbidity and lower socioeconomic status [4]. If social or health-related characteristics are associated with GP involvement in the diagnosis of women with OC in Denmark, knowledge of these characteristics may potentially support the GP's suspicion of OC and facilitate an earlier diagnosis.

The aim of this study was to investigate characteristics of women diagnosed with OC with GP involvement compared with women without GP involvement. We hypothesised that women with OC who are diagnosed without GP involvement are more likely to have a low socioeconomic status, high comorbidity and older age than women with OC who are diagnosed after their GP's involvement.

METHODS

This was a population-based retrospective cohort study among Danish women with a first-time OC diagnosis drawing on a combination of questionnaire data and register-based data.

Setting

The study was conducted in Denmark, where more than 98% of all citizens are listed with a GP [6]. Danish healthcare services are tax funded and provide universal free access to medical healthcare. The GP acts as a gatekeeper to most of the secondary healthcare services [6]. When the GP suspects cancer in a patient, the GP must refer the patient for a CPP to ensure efficient and fast diagnostics [7].

Study population

The study population consisted of patients who were registered with a first-time OC diagnosis in the Danish National Patient Register (DNPR) and who were included in one of three previously established questionnaire-based cohorts from 2010, 2013-2014 or 2016 [5] (see "Data collection").

All contacts to Danish hospitals are recorded in the DNPR with date of contact and specific diagnoses stated in line with the International Classification of Diseases, tenth revision (ICD-10). In the DNPR, patients with ICD-10 code C48 or C56.0-C57.9 were identified and further validated in the Danish Cancer Registry (DCR). Patients were included only if the ICD-10 code C48 or C56.0-C57.9 was also registered within one year of the study period in the DCR. To ensure identical age requirements across the three independent cohorts, an additional inclusion criterion was age ≥ 40 years at the time of diagnosis. The exclusion criteria were a previous diagnosis of borderline ovarian tumour (D39.1) or other cancer registered in the DCR within ten years prior to the diagnosis, except for non-melanoma skin cancer (C44).

Data collection

The three cohorts consist of three previously collected questionnaire surveys among GPs about the diagnostic process of newly diagnosed cancer patients. Data were collected in the following three time periods: Cohort 1 covered the period from 1 May 2010 to 31 August 2010, Cohort 2 covered the period from 13 October 2013 to 30 June 2014 and Cohort 3 covered the period from 1 July 2016 to 20 December 2016 [8].

In Cohorts 1 and 2, a questionnaire for each identified woman with OC was sent to her GP within 2-5 months after identification in the DNPR. In Cohort 3, the GP received the questionnaire up to one year after the patient's diagnosis, as written consent by the patients was required to collect data from her GP due to the introduction of the General Data Protection Regulation (GDPR). In all three cohorts, a reminder was sent after four weeks if the GP had not responded. If it was not possible to obtain consent from the patient due to death shortly after

diagnosis, permission to contact the respective GP was obtained from the Danish Safety Patient Authority. The GPs involved in Cohorts 2 and 3 were paid approximately 15 EUR for each completed questionnaire. The GPs in Cohort 1 received no payment. The GPs were asked to complete the questionnaires based on their medical records. All patient data were linked via the unique Danish personal identification number obtained from the Danish Civil Registration System (CRS).

Variables

GP involvement was the dependent variable and was obtained from the GP questionnaires using an explorative approach. The variable was categorised into two groups according to GP involvement in the pathway to diagnosis: "Yes" if the GP stated that the woman presented in general practice before the diagnosis with symptoms that were likely to have been caused by the patient's cancer disease according to the GP; "No" if the woman initially presented elsewhere.

The independent variables are described in the following. The women's age at the time of diagnosis was collected from the CRS and divided into three groups (< 60; 60-74 and ≥ 75 years). Statistics Denmark provided information about marital status ("married/cohabitating" or "single"), income (low, medium or high income) based on adjusted household income by the Organisation for Economic Co-operation and Development, and educational level (≤ 10, 11-15 or > 15 years of education) according to the International Standard Classification of Education, the United Nation's Educational, Scientific and Cultural Organization. Comorbidity, excluding cancer, was measured by the Charlson Comorbidity Index (CCI) score (none (score of 0), low (score of 1-2), high (score of > 2)) following the method by Quan et al. [9] and based on diagnosis registrations in the DNPR for up to ten years preceding the OC diagnosis. GP attendance was defined as the number of face-to-face consultations during the 12-24 months preceding the OC diagnosis. Data were collected from the Danish National Health Service Register and categorised into three groups (0, 1-4 or ≥ 5 visits) based on a cut-off set at the 25th and 75th percentile.

Statistical analyses

Patient characteristics were tabulated by whether the GP was involved in the diagnostics or not, and the Pearson's chi-squared test was used to assess between-group differences. Logistic regression models were used to study the association between each patient characteristic and GP involvement, and the estimates were presented as odds ratios (OR) with 95% confidence intervals (95% CI). An unadjusted model was presented followed by a fully adjusted model including all independent variables. All analyses were conducted in Stata 16.0.

Trial registration: not relevant.

RESULTS

We identified 613 women aged 18 years or more with a first-time OC diagnosis in the DNPR and who were listed with a GP (**Figure 1**). In total, 313 women met the inclusion criteria (Figure 1), corresponding to 58.7% of the eligible women (65.1% for Cohort 1, 55.1% for Cohort 2 and 62.5% for Cohort 3).

FIGURE 1 Flow chart. Inclusion of patients in the study population.
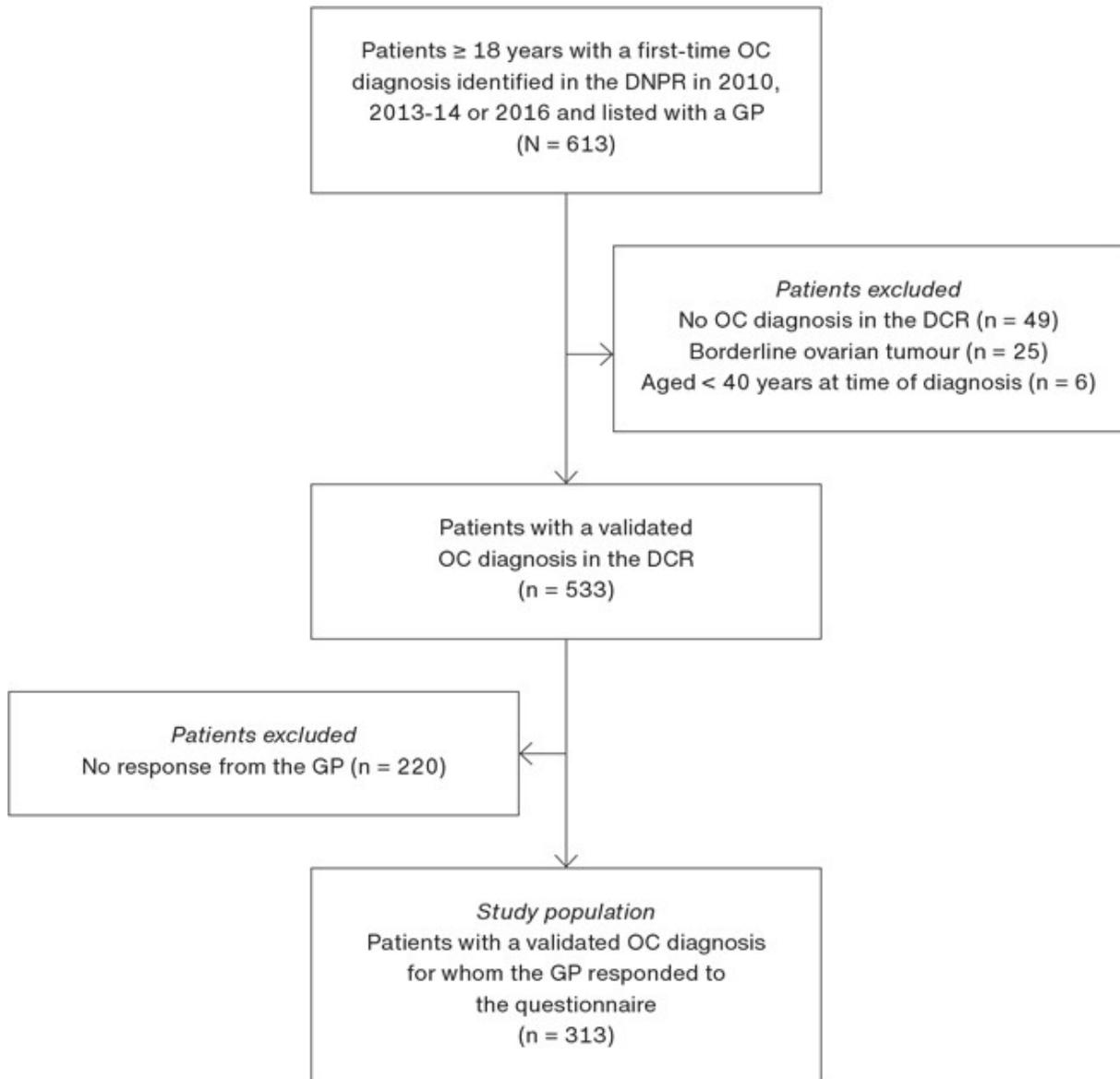
DCR = Danish Cancer Registry; DNPR = Danish National Patient Register; OC = ovarian cancer.

In total, 91.1% (285 of 313 women) consulted their GP with symptoms before their diagnosis. Hence, 28 (8.9%) women were diagnosed with OC without GP involvement; eight (2.5%) presented as EP, six (1.9%) presented at the hospital after a contact for other disease or their route was unspecified, and 14 (4.5%) presented as "Other".

The majority of women with GP involvement in the pathway to diagnosis were aged 60-74 years, married/cohabitating, had 11-15 years of education, no comorbidity and had 1-4 visits at their GP in the 12-24 months leading up to their diagnosis (**Table 1**). Women aged 60-74 years had statistically significantly higher odds of GP involvement than women aged < 60 years (OR = 2.97 (95% CI: 1.09-8.08)). Women with high comorbidity (a CCI score > 2) had statistically significantly lower odds of GP involvement than women with no comorbidity (OR = 0.25 (95% CI: 0.09-0.66)). Other patient characteristics were not statistically significantly associated with GP involvement in the pathway to diagnosis (**Table 2**).

TABLE 1 Patient characteristics by GP involvement.

	Total, N (%)	GP not involved, n (%)	GP involved, n (%)	p-value[a]
FIGO stage				0.08
Advanced	193 (61.7)	16 (57.1)	177 (62.1)	
Early	90 (28.8)	6 (21.4)	84 (29.5)	
Unknown	30 (9.6)	6 (21.4)	24 (8.4)	
Age group				0.09
< 60 yrs	90 (28.8)	10 (35.7)	80 (28.1)	
60-74 yrs	149 (47.6)	8 (28.6)	141 (49.5)	
≥ 75 yrs	74 (23.6)	10 (35.7)	64 (22.5)	
Marital status				0.65
Married/cohabiting	200 (63.9)	19 (67.9)	181 (63.5)	
Single	113 (36.1)	9 (32.1)	104 (36.5)	
Income				0.61
Low	105 (33.5)	11 (39.3)	94 (33.0)	
Middle	104 (33.2)	10 (35.7)	94 (33.0)	
High	104 (33.2)	7 (25.0)	97 (34.0)	
Education				0.66
≤ 10 yrs	105 (33.5)	11 (39.3)	94 (33.0)	
11-15 yrs	132 (42.2)	12 (42.9)	120 (42.1)	
> 15 yrs	76 (24.3)	5 (17.9)	71 (24.9)	
Comorbidity				< 0.001
None: CCI = 0	245 (78.3)	12 (42.9)	233 (81.8)	
Mild: CCI = 1-2	51 (16.3)	9 (32.1)	42 (14.7)	
High: CCI > 2	17 (5.4)	7 (25.0)	10 (3.5)	
GP contacts 12-24 mos. prior to OC diagnosis[b]				0.48
0	98 (31.3)	8 (28.6)	90 (31.6)	
1-4	143 (45.7)	11 (39.3)	132 (46.3)	
≥ 5	72 (23.0)	9 (32.1)	63 (22.1)	
Total	313 (100)	28 (100)	285 (100)	

CCI = Charlson Comorbidity Index; FIGO = International Federation of Gynecology and Obstetrics; OC = ovarian cancer.
a) Pearson's χ^2-test.
b) Number of face-to-face consultations in the 12-24 mos. before an OC diagnosis based on cut-off at the 25th and 75th percentiles.

TABLE 2 Odds ratio (95% confidence interval) of GP involvement by patient characteristics (N = 313).

	OR (95% CI)	
	unadjusted	adjusted[a]
Age group		
< 60 yrs	1.00 (reference)	
60-74 yrs	2.20 (0.83-5.82)	2.97 (1.09-8.08)*
≥ 75 yrs	0.80 (0.31-2.04)	1.52 (0.50-4.60)
Marital status		
Married/cohabiting	1.00 (reference)	
Single	1.21 (0.53-2.78)	1.48 (0.61-3.59)
Income		
Low	1.00 (reference)	
Medium	1.10 (0.45-2.72)	0.96 (0.34-2.73)
High	1.62 (0.60-4.37)	0.95 (0.33-2.75)
Educational level		
≤ 10 yrs	1.00 (reference)	
11-15yrs	1.17 (0.49-2.77)	1.25 (0.48-3.27)
> 15 yrs	1.66 (0.55-5.01)	1.79 (0.55-5.86)
Comorbidity		
None: CCI = 0	1.00 (reference)	
Mild: CCI 1-2	0.07 (0.02-0.23)	0.07 (0.02-0.23)
High: CCI > 2	0.24 (0.10-0.61)*	0.25 (0.09-0.66)*
GP contacts 12-24 mos. prior to OC diagnosis[b]		
0	1.00 (reference)	
1-4	1.07 (0.41-2.76)	1.20 (0.42-3.41)
≥ 5	0.62 (0.23-1.70)	1.05 (0.34-3.25)

CCI = Charlson Comorbidity Index; CI = confidence interval;
OC = ovarian cancer; OR = odds ratio.
*) $p < 0.05$.
a) Adjusted for age, marital status, income, educational level, comorbidity and GP attendance 12-24 mos. before diagnosis.
b) Number of face-to-face visits in the 12-24 mos. before an OC diagnosis based on cut-off at the 25th and 75th percentiles.

DISCUSSION

Main findings

For most women (91.1%), the GP was involved in their pathway to an OC diagnosis. Women aged 60-74 years had higher odds of GP involvement, whereas women with high comorbidity had lower odds of GP involvement.

Comparison with existing literature

General practitioner involvement

The high proportion of GP involvement among Danish OC patients is supported by findings in studies from the UK and Australia, where GP involvement was seen in about 90% of the patients [10, 11]. Even so, we observed a small number of OC patients with EP (2.5%) compared with a study from the UK (32%) [3]. This might be due to different definitions of GP involvement, which we based on the GP's retrospectively completed questionnaires.

Comorbidity

The finding that patients with high comorbidity are more likely to bypass the GP in cancer diagnostics across different types of cancer is supported by a study from the UK [4]. We know that comorbid patients undergo more investigation at the hospital than do patients with no comorbidity [12]. This may potentially increase the risk of bypassing the GP, either due to incidental findings or because the woman reports her OC-related symptoms to a hospital physician followed by internal referral. Moreover, comorbid patients often deal with several symptoms due to their conditions. This may mask early signs of cancer and result in a longer time interval before consulting the GP, thereby increasing the risk of EP [13]. Finally, patient barriers, e.g. transportation problems or physical access barriers, among comorbid patients [14] may potentially prolong the patient's help-seeking behaviour, which may further increase the risk of EP due to delay [13].

Age

Our findings support earlier findings that middle-aged patients are less likely to bypass the GP than are younger or older patients, as also stated in the review by Zhou et al. [15]. A UK study of young women with symptoms of possible gynaecological cancer found that these women often normalised their symptoms, thought they overreacted to their symptoms and interpreted them as a consequence of menopause, being female, poor dietary habits or hormonal contraception [16].

Socioeconomic status

Former studies have indicated that socioeconomic status influences the patient's diagnostic pathway for some cancer types, and socioeconomically deprived patients have a higher risk of EP [4]. This association was not found in the present study, which may be because of the organisation of Danish healthcare with free and equal access to healthcare; this may potentially reduce social inequality in the diagnostic pathway. Yet, it cannot be excluded that an association exists but was not found due to a low sample size.

Strengths and limitations

A key strength of the study was the identification of the study population through Danish national registers (DNPR, DCR) with almost complete information on cancer incidence in Denmark [17, 18].

Approximately 40% of the GPs did not respond to the questionnaire. However, GP response is not likely to be linked to patient characteristics. Still, in Cohort 3, the GP response depended on written patient consent. Therefore, in this cohort, non-response may be linked to a lower socioeconomic status, which may have affected the prevalence, but less so the estimates [19].

Selection bias was also limited because it was possible to include women who died shortly after their diagnosis; this group may differ from surviving women in terms of sociodemographic characteristics and GP involvement. The use of national registers to extract information on patient characteristics reduced the risk of information bias. Even so, information bias and recall bias cannot be excluded as the GPs completed the questionnaires based on their medical records and might have interpreted their notes differently when reading them the second time. Thus, the validity of the data could have been strengthened if the information from the patient journals

had been collected by the researchers.

Further limitations were that the questionnaire provided no information on the initially presented symptoms, and the small number of OC cases included in the study resulted in small strata for some categories and in wide confidence intervals.

Future implications

Women with high comorbidity and women aged < 60 years were more likely to bypass the GP on their diagnostic pathway, which former studies have linked to a poorer prognosis [3, 4]. This leaves room for improving the diagnosis of OC in both women with high comorbidity and women aged < 60 years. Several initiatives may be considered, including health campaigns or postgraduate GP training to increase the awareness of OC symptoms among women and GPs alike. The GPs may also be allowed to refer symptomatic women who do not meet the requirements for referral to the CPP for relevant diagnostic investigations, e.g. transvaginal ultrasound.

CONCLUSIONS

This study found higher odds of GP involvement in the diagnosis of OC in women aged 60-74 years and lower odds of GP involvement in women with high comorbidity. The remaining patient characteristics had no significant influence on the first place of presentation for OC patients. However, the study was restricted to a limited number of patients, and future research is warranted to underpin our findings.

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