Clinical Oncology 31 (2019) 115–123

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

Influence of Prior Psychiatric Disorders on the Treatment Course of Gynaecological Cancer – A Nationwide Cohort Study

M. Iachina *†, P.M. Ljungdalh *†, R.G. Sørensen ‡, L. Kaerlev *†, J. Blaakær §, O. Trosko ¶, N. Qvist ||, B.M. Nørgård *†

* Research Unit of Clinical Epidemiology, Institute of Clinical Research, University of Southern Denmark, Odense, Denmark
† Center for Clinical Epidemiology, Odense University Hospital, Odense, Denmark
‡ Department of Obstetrics and Gynecology, Aarhus University Hospital, Skejby, Denmark
§ Department of Obstetrics and Gynecology, Odense University Hospital, Odense, Denmark
¶ Department of Psychiatry, Odense University Hospital, Odense, Denmark
|| Surgical Department, Odense University Hospital, Odense, Denmark

Received 6 June 2018; received in revised form 10 October 2018; accepted 10 October 2018

Abstract

Aims: To examine the influence of pre-existing psychiatric disorder on the choice of treatment in patients with gynaecological cancer.
Materials and methods: The analyses were based on all patients who underwent surgical treatment for endometrial, ovarian or cervical cancer who were registered in the Danish Gynecological Cancer Database in the years 2007–2014 (3059 patients with ovarian cancer, 5100 patients with endometrial cancer and 1150 with cervical cancer). Logistic regression model and Cox regression model, adjusted for relevant confounders, were used to estimate the effect of pre-existing psychiatric disorder on the course of cancer treatment. Our outcomes were (i) presurgical oncological treatment, (ii) macroradical surgery for patients with ovarian cancer, (iii) radiation/chemotherapy within 30 days and 100 days after surgery and (iv) time from surgery to first oncological treatment.
Results: In the group of patients with ovarian cancer, more patients with a psychiatric disorder received macroradical surgery versus patients without a psychiatric disorder, corresponding to an adjusted odds ratio of 1.24 (95% confidence interval 0.62–2.41) and the chance for having oncological treatment within 100 days was odds ratio = 1.26 (95% confidence interval 0.77–2.10). As for patients with endometrial cancer, all outcome estimates were close to unity. The adjusted odds ratio for oncological treatment within 30 days after surgery in patients with cervical cancer with a history of psychiatric disorder was 0.20 (95% confidence interval 0.03–1.54).
Conclusions: We did not find any significant differences in the treatment of ovarian and endometrial cancer in patients with pre-existing psychiatric diagnoses. When it comes to oncological treatment, we suggest that increased attention should be paid to patients with cervical cancer having a pre-existing psychiatric diagnosis.

Key words: Cervical cancer; endometrial cancer; oncological treatment; ovarian cancer; psychiatric disorders; surgery

Introduction

Gynaecological cancer accounted for about 16% of all new cancer cases and 14% of cancer deaths in women, globally, in 2012 [1]. The most common gynaecological cancers in Denmark are endometrial, ovarian and cervical cancer [2]. For endometrial cancer, the age-standardised incidence rate is about 13 per 100 000 and the mortality rate is less than 2% of cancer deaths in women [3]. Early diagnosis is the major factor accounting for the low mortality and nearly 80% of cases are diagnosed while the tumour is confined to the uterus [4]. Globally, ovarian cancer is the sixth most common cancer in women. Denmark and the other Scandinavian countries have the highest incidence of ovarian cancer in the world. In Denmark, about 500 new cases are diagnosed yearly and the median age of disease onset is 63 years [5]. The symptoms in ovarian cancer are unspecific and, consequently, in about 70% of cases, ovarian cancer is diagnosed in an advanced stage. Cervical cancer is the most

Author for correspondence: M. Iachina, Center for Clinical Epidemiology, Odense University Hospital, Kløvervænget 30, Entrance 216, DK-5000, Odense C, Denmark.
E-mail address: Maria.Iachina@rsyd.dk (M. Iachina).

https://doi.org/10.1016/j.clon.2018.11.006
0936-6555/

common form of gynaecological cancer in premenopausal women. It affects less than 1% of all women and almost 400 new cases are diagnosed yearly. About 100 Danish women die annually of the disease.

Age, smoking, alcohol and obesity are factors strongly associated with increased cancer mortality [6–8] and, moreover, psychiatric illness has been associated with increased tobacco use, obesity, alcohol and substance abuse [9]. Some studies have shown that patients with cancer having a psychiatric disorder are diagnosed later, and receive fewer sessions of chemotherapy, surgery and other cancer-related treatments, and that they receive their treatments significantly later than patients without a psychiatric disorder [10–15]. In 2003, Spiegel and Giese-Davis [10] argued that depression may influence the course of cancer treatment in different ways, as some symptoms of depression are similar to symptoms related to cancer, like the vegetative symptoms of sleep and appetite disturbance, fatigue and concentration difficulties. Due to an overlap in symptoms and weak social network, referral for a diagnosis of suspected cancer can potentially be delayed for patients with depression symptoms. Several factors might contribute to an increased vulnerability in patients with psychiatric disorders compared with those without psychiatric disorders, and when it comes to cancer treatment in patients with psychiatric disorders, the evidence is still sparse. Factors that might contribute to deteriorated outcomes in patients with a psychiatric disorder are less likely to adhere to preventive screening procedures, to receive treatment, to complete treatment [16] and some might refuse surgery [14,17]. Moreover, patients with a psychiatric disorder may be less effective at navigating in the complex healthcare systems [18,19].

The aim of this study was to investigate the association between psychiatric disorders prior to surgical treatment in women with gynaecological cancers and macroradical surgery, the oncological treatment and the time from surgery to oncological treatment.

Materials and Methods

Setting

This study was a population-based nationwide cohort study using data from the Danish national healthcare registries. The population-based study design was possible due to equal access to a centralised tax-funded healthcare system for all residents in Denmark. We used (i) the nationwide clinical quality database, the Danish Gynecological Cancer Database (DGCD), to identify all patients with a diagnosis of gynaecological cancer, (ii) the Danish National Patient Registry (DNPR) to retrieve information regarding relevant psychiatric diagnoses up to 10 years prior to a gynaecological cancer surgery and (iii) the Income Statistics Register to provide data on socioeconomic status.

The data were linked by a unique identifier, the civil registration number, which all Danish residents are assigned either at birth or when immigrating to Denmark. Linkage of data between registries on an individual level is therefore possible and valid [20].

The Danish National Patient Registry

The DNPR was established in 1977. This register contains data on all procedures related to the diagnostic evaluation and treatment of patient admissions in Denmark [21]. We used the DNPR to include information on oncological treatment for each patient. We also used the DNPR to identify patients with the following psychiatric disorders: schizophrenia, schizotypal disorders and affective disorders (International Classification of Diseases [ICD-10]: DF20-29: schizophrenia, schizotypal and delusional disorders [primary psychotic disorders] or DF30-39: depression and other affective disorders).

The Danish Gynecological Cancer Database

The DGCD was established in January 2005 and includes information on different types of gynaecological cancer [5]. All gynaecological departments in Denmark participating in the diagnosis and treatment of these cancers are required to report to the DGCD. The DGCD includes comprehensive information on each patient, including details on history, surgical procedures, staging and pathology. We used the DGCD to identify women with a gynaecological cancer and included relevant clinical information, such as type of surgery, tumour stage, cancer diagnosis and performance status measured as ECOG-PS. ECOG-PS is a scale that was developed by the Eastern Cooperative Oncology Group to describe the patient's level of function in terms of their ability to care for themselves, daily activity and physical ability. It varies from 0 for 'fully active' to 5 for 'dead'.

The Income Statistics Registry

Using the Income Statistics Registry [22], we included information on the socioeconomic status for each patient at the time of cancer surgery. The socioeconomic class was defined as the household income in the year the patient received surgical treatment for gynaecological cancer, adjusted for the number of people in the household. The socioeconomic class was divided by the median into two groups, low and high.

Study Population

The study population included all women who were registered in the DGCD with the diagnosis of endometrial, ovarian or cervical cancer within the period 1 January 2007 to 18 September 2014, and who received surgery. We divided the study population by type of cancer (three mutually exclusive groups): ovarian cancer, endometrial cancer and cervical cancer.

Exposed and Unexposed Cohorts

The exposed cohorts comprised patients, treated with surgery for the gynaecological cancer, who had at least one psychiatric diagnosis (schizophrenia, or schizotypal or affective disorders) within the period of 10 years to 120 days before the date of surgery. This group is now referred to as the group of patients with a psychiatric disorder. The unexposed cohorts comprised all patients, treated with surgery for the gynaecological cancer, who did not have a psychiatric diagnosis (schizophrenia, or schizotypal or affective disorders) within the 10 years. This group is now referred to as the group of patients without a psychiatric disorder. To avoid the psychiatric diagnosis being present solely as a result of the patient's knowledge of having a cancer, psychiatric disorders diagnosed less than 120 days before the date of the cancer diagnosis were excluded.

Outcomes

The primary outcome was the effect of psychiatric disorders on the course of gynaecological cancer treatment with specific attention on (i) receiving a presurgical (neoadjuvant) oncological treatment; (ii) receiving macroradical surgery, i.e. no visible tumour left (complete cytoreductive surgery). This outcome was only calculated for patients with ovarian cancer, as more than 90% of patients with endometrial and cervical cancer receive macroradical surgery; (iii) receiving either radiation or chemotherapy within 30 days after surgery; (iv) receiving either radiation or chemotherapy within 100 days after surgery [23]; (v) time from surgery to the first oncological treatment given within 100 days.

According to Danish guidelines for the treatment of cervical cancer, adjuvant radiation therapy and concomitant treatment with cisplatin should be given if one of the following criteria is met: (i) positive lymph nodes, (ii) invasion of parametria, (iii) resection edge is not free. Moreover, adjuvant radiation therapy and concomitant treatment with cisplatin is recommended for patients with negative lymph nodes if one of the following criteria is met: (i) tumour is greater than 3 cm and invasion depth is greater than two-thirds, (ii) tumour is greater than 2 cm, invasion depth is greater than one-third and vascular invasion. According to these guidelines, about 25% of the cervical cancer patients should receive adjuvant therapy [24].

Statistical Analyses and Confounders

We used an approximation of the Fisher exact test to compare the baseline characteristics of women with the different types of gynaecological cancer with and without a psychiatric disorder.

We used a logistic regression model to estimate the ratio for receiving macroradical surgery in patients with ovarian cancer and a psychiatric disorder versus those without a psychiatric disorder, adjusted for relevant confounders. We also used a logistic regression model to estimate the effect of a psychiatric disorder on receiving oncological treatment within 30 days and 100 days after surgery, adjusted for relevant confounders.

A Cox regression model was used to estimate the effect of a psychiatric disorder on the time from surgery to the start of oncological treatment. We used a time window of 100 days from the date of surgery. Patients who did not survive 30 days or 100 days after surgery were excluded from the corresponding analyses.

The specific confounders were included as follows: age at the time of a gynaecological cancer diagnosis and clinical tumour stage according to low (clinical tumour stage I and II) or high (clinical tumour stage III and IV). Year of surgery was divided into two time intervals, 2007–2010 and 2011–2014. The patient's socioeconomic status was defined from the patient's personal income in the year of the gynaecological cancer surgery. The personal equivalent disposable income for our study population was from 56 000 DKK (7500 EUR) to 693 000 DKK (93 000 EUR) per year with a median about 200 000 DKK (26 900 EUR). The socioeconomic class was divided according to low being lower than the median and high as being equal to or higher than the median. Education was defined into categories of (i) basic school, (ii) high school or short cycle tertiary or (iii) higher education including bachelor, masters and doctoral levels. The ECOG-PS was grouped into categories by reported normal activity, yes = 0 and no = 1, smoking by no = 0 and yes = 1, body mass index (BMI) by BMI < 25, BMI ≥ 25 and BMI < 30, BMI ≥ 30; and alcohol abuse as no versus yes.

For each outcome variable in the multivariate model, confounders were included corresponding to a biological rationale and to *a priori* decisions.

In subanalyses we restricted our exposed cohorts only to include those patients who had at least one psychiatric diagnosis within the period of 5 years to 120 days before the date of surgery.

Approvals

The DGCD operates under Danish law on data protection, with licenses granted by the Danish Data Protection Agency and the Danish Health and Medicines Authority. This specific study has been approved by the Danish Data Protection Agency (jr. nr. 2008-58-0035).

According to Danish law, ethical approval is not required for purely registry-based studies.

Results

From the DGCD, we extracted information on 9442 patients and nearly all received a surgical treatment, providing us with a total of 9309 patients. Patients with ovarian cancer comprised 3059 patients, 5100 patients had endometrial cancer and 1150 had cervical cancer. Eighty-five women with ovarian cancer, 136 with endometrial cancer and 31 with cervical cancer had a diagnosis of psychiatric disorder within 10 years before the cancer diagnosis. Table 1 shows the baseline characteristics of the cohorts. For each

Table 1
Baseline characteristics of women diagnosed with ovarian, endometrial or cervical cancer in 2007–2014 according to psychiatric disorders

	Ovarian cancer ($N = 3059$)		Endometrial cancer ($N = 5100$)		Cervical cancer ($N = 1150$)	
	With psychiatric disorder	Without psychiatric disorder	With psychiatric disorder	Without psychiatric disorder	With psychiatric disorder	Without psychiatric disorder
n	85	2974	136	4964	31	1119
Age, mean (SD)		*		*		
	57.6 (15.9)	62.3 (15.1)	59.1 (16.4)	62.6 (15.2)	57.5 (18.5)	60.6 (14.3)
Stage						
Low	36 (42.4%)	1041 (35.0%)	52 (38.2%)	1822 (6.7%)	28 (90.3%)	992 (88.7%)
High	49 (57.7%)	1933 (65.0%)	8 (5.9%)	301 (6.1%)	3 (9.7%)	104 (9.3%)
Missing			76 (55.9%)	2841 (57.2%)	0	23 (2.1)
BMI						
Normal	41 (48.2%)	1517 (51.0%)	55 (40.4%)	1669 (33.6%)	14 (45.2%)	620 (55.4%)
Overweight	26 (30.6%)	802 (26.9%)	32 (23.5%)	1434 (28.9%)	14 (45.2%)	285 (25.5%)
Obese	14 (16.5%)	452 (15.2%)	45 (33.1%)	1716 (34.6%)	3 (9.7%)	190 (16.9)
Missing	4 (4.7%)	203 (6.8%)	4 (2.9%)	145 (2.9%)	0	24 (2.1%)
ECOG-PS		*				
Low	46 (54.1%)	1427 (47.9%)	83 (61.0%)	2998 (60.4%)	24 (77.4%)	819 (73.2%)
High	37 (43.5%)	1535 (51.6%)	52 (38.2%)	1935 (38.9%)	3 (9.7%)	133 (11.9%)
Missing					4 (12.9%)	167 (14.9%)
Year				*		
2007–2010	54 (63.5%)	1833 (61.6%)	68 (50.0%)	2904 (58.5%)	22 (70.8%)	663 (59.3%)
2011–2014	31 (36.5%)	1141 (38.4%)	68 (50.0%)	2060 (41.5%)	9 (29.0%)	456 (40.8%)
Socioeconomic class		*		*		*
Low	55 (64.7%)	1357 (45.6%)	82 (60.3%)	2236 (45.0%)	19 (61.3%)	473 (42.3%)
High	25 (29.4%)	1345 (45.2%)	36 (26.5%)	2198 (44.3%)	12 (38.7%)	549 (49.1%)
Missing	5 (5.9%)	272 (9.2%)	18 (13.2%)	530 (10.7%)	0 (0%)	97 (8.7%)
Education						
Low	34 (44.0%)	1113 (37.4%)	62 (45.6%)	1799 (36.2%)	13 (41.9%)	387 (34.6%)
Medium	29 (34.1%)	1044 (35.1%)	41 (30.2%)	1705 (34.4%)	11 (35.5%)	414 (37.0%)
High	19 (22.4%)	588 (19.8%)	22 (16.2%)	999 (20.1%)	6 (19.4%)	243 (21.7%)
Missing	3 (3.5%)	229 (7.7%)	11 (8.1%)	461 (9.3%)		
Smoking						
No	67 (78.8%)	2327 (78.2%)	118 (86.8%)	4190 (84.4%)	25 (80.7%)	772 (68.9%)
Yes	15 (17.7%)	562 (18.9%)	17 (12.5%)	734 (14.8%)	6 (19.4%)	339 (30.3%)
Missing	3 (3.5%)	85 (2.9%)	1 (0.7%)	40 (0.8%)	0 (0.0%)	8 (0.7%)
Alcohol		*				
No	65 (76.5%)	1963 (66.0%)	94 (69.1%)	3266 (65.8%)	22 (70.9%)	731 (65.3%)
Yes	18 (21.2%)	721 (24.2%)	28 (20.6%)	1294 (26.1%)	8 (25.8%)	304 (7.2%)
Missing			14 (10.3%)	404 (8.1%)		

*$P < 0.05$.
SD, standard deviation; BMI, body mass index; ECOG-PS, Eastern Cooperative Oncology Group-performance status.

cancer type, about 2.8% of the study population had at least one former hospital contact with a psychiatric diagnosis. For all three types of cancer, the mean age of patients with a psychiatric disorder was younger than in patients without a psychiatric disorder. For patients with ovarian cancer, a total of 42.4% of the patients with a psychiatric disorder had low tumour stage versus 35% in patients without a psychiatric disorder; the difference was not statistically significant. There was a significant difference in the socioeconomic class distribution across the psychiatric groups for all three cancer types. For patients with ovarian cancer, only 29.4% of the patients with a psychiatric disorder belonged to a high socioeconomic class versus 45.2% of the patients without a psychiatric disorder; the corresponding proportions were 26.5% versus 44.3% for patients with endometrial cancer and 38.7% versus 49.1% for patients with cervical cancer.

From the study population, only 97 received a presurgical (neoadjuvant) oncological treatment (26 patients with ovarian cancer, 61 patients with endometrial cancer and 10 patients with cervical cancer); none of them had a prior psychiatric disorder. Therefore, we did not carry out further analyses according to presurgical oncological treatment.

Sixty-nine patients with endometrial cancer did not survive 30 days after surgery (three with a psychiatric disorder and 66 without a psychiatric disorder) and 223 did not survive 100 days after surgery (11 with a psychiatric disorder and 212 without a psychiatric disorder). In total, 117 patients with ovarian cancer did not survive 30 days after surgery (two with a psychiatric disorder and 115

without a psychiatric disorder) and 278 did not survive 100 days after surgery (four with a psychiatric disorder and 274 without a psychiatric disorder). Seven patients with cervical cancer did not survive 30 days after surgery (all without a psychiatric disorder) and 38 did not survive 100 days after surgery (all without a psychiatric disorder). Those patients were excluded from the analyses 30 and 100 days of postsurgical oncological treatment, respectively.

Table 2 shows the results for patients with ovarian cancer according to macroradical surgery and postsurgical (adjuvant) oncological treatment, as well as time from surgery to oncological treatment within 100 days after surgery. A larger number of patients with a psychiatric disorder received macroradical surgery versus patients without a psychiatric disorder (61.2% versus 54%), corresponding to an adjusted odds ratio of 1.24 (95% confidence interval 0.62–2.41). The results indicated no significant difference in the ratio for oncological treatment within 30 days or within 100 days after surgery (adjusted odds ratio 1.12 [95% confidence interval 0.62–2.03] and 1.26 [95% confidence interval 0.77–2.10], respectively). Figure 1 shows the Kaplan–Meier estimates of the oncological treatment within 100 days after surgery. The figure, and the hazard ratios presented in Table 2, show no significant difference according to the time from surgery to oncological treatment in patients with a psychiatric disorder versus those without.

Table 3 shows the results for patients with endometrial cancer according to postsurgical oncological treatment. The results indicated that there were no significant differences in the ratios for postsurgical oncological treatment for patients with endometrial cancer (adjusted odds ratio 0.82 [95% confidence interval 0.38–1.77] for oncological treatment within 30 days and within 100 days adjusted odds ratio 1.05 [95% confidence interval 0.55–1.98]). There was no difference in the median duration from the time of surgery to the oncological treatment between those with and those without a psychiatric diagnosis (adjusted hazard ratio 1.03 [95% confidence interval 0.60–1.76]).

Table 4 shows the results for patients with cervical cancer according to postsurgical oncological treatment, as well as the median for the duration in days from the time of surgery to oncological treatment within 100 days after surgery. Patients with a psychiatric disorder had a statistically non-significantly lower chance of receiving the oncological treatment within 30 days, as well as 100 days, after surgery (adjusted odds ratio 0.20 [95% confidence interval 0.03–1.54] and adjusted odds ratio 0.40 [95% confidence interval 0.12–1.36], respectively). Figure 1 illustrates that patients with a psychiatric disorder waited longer for oncological treatment after surgery than patients without a psychiatric disorder, but the estimated difference was not statistically significant (adjusted hazard ratio = 0.42 [0.14–1.35]).

We also carried out sub-analyses where the exposed cohorts were restricted to comprise patients who had at least one psychiatric diagnosis within the period of 5 years before the date of surgery; the results were similar to those from the main analyses (data not shown). Moreover, we carried out an additional analysis without tumour stage as an adjustment variable; the estimated effect of psychiatric disorder was very similar to our main result.

Discussion

Our study showed that patients with ovarian cancer and a pre-existing psychiatric disorder did not have a lower ratio for macroradical surgery and oncological treatment compared with patients without a psychiatric disorder. The ratio for oncological treatment for patients with

Table 2
Distribution of treatment by psychiatric disorder status for patients with ovarian cancer and risk estimates from logistic regression analyses (for type of surgery and chance of receiving oncological treatment) and Cox regression analyses (days from surgery to first oncological treatment)

Ovarian cancer	With psychiatric disorder	Without psychiatric disorder	Crude OR/HR (95% CI)	Adjusted OR/HR (95% CI)*
Macroradical surgery ($n = 3059$)			1.52 (0.90; 2.53)	1.24 (0.62; 2.41)
Yes	52 (61.2%)	1607 (54.0%)		
No	21 (24.7%)	986 (33.2%)		
Oncological treatment within 30 days after surgery ($n = 2942$)			1.06 (0.60; 1.87)	1.12 (0.62; 2.03)
Yes	15 (18.1%)	492 (17.2%)		
No	68 (82.0%)	2367 (82.8%)		
Oncological treatment within 100 days after surgery ($n = 2781$)			1.18 (0.73; 1.91)	1.26 (0.77; 2.10)
Yes	24 (29.6%)	711 (26.3%)		
No	57 (70.4%)	1989 (73.7%)		
Time from surgery to oncological treatment within 100 days			1.14 (0.76; 1.72)	1.21 (0.79; 1.84)
Median (25% fractal; 75% fractal)	17.5 (6; 43)	15 (6; 43)		

OR, odds ratio; HR, hazard ratio; CI, confidence interval.
* Adjusted for age, tumour stage, year of surgery, socioeconomic class, body mass index, Eastern Cooperative Oncology Group-performance status, smoking, alcohol consumption and level of education.

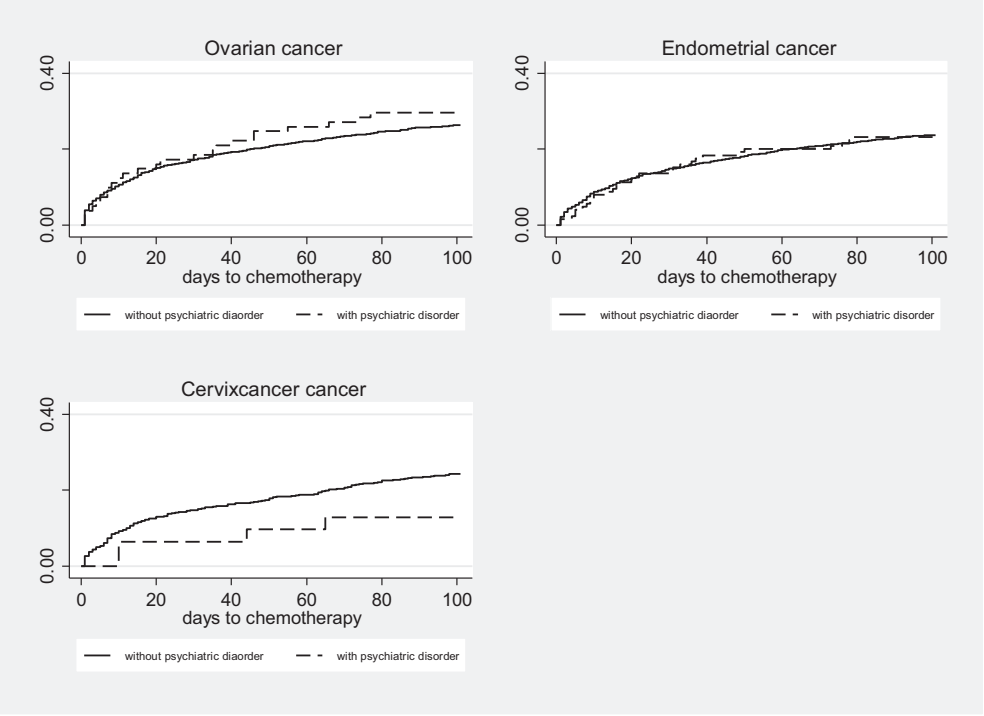

Fig 1. Kaplan–Meier estimates for chemotherapy within 100 days after surgery, by psychiatric groups.

Table 3
Distribution of treatment by psychiatric disorder status for patients with endometrial cancer and risk estimates from logistic regression analyses (chance of receiving oncological treatment) and Cox regression analyses (days from surgery to first oncological treatment)

Endometrial cancer	With psychiatric disorder	Without psychiatric disorder	Crude OR/HR (95% CI)	Adjusted OR/HR (95% CI)*
Oncological treatment within 30 days after surgery ($n = 5028$)			0.96 (0.59; 1.57)	0.82 (0.38; 1.77)
Yes	19 (14.3%)	723 (14.8%)		
No	114 (85.7%)	4172 (85.2%)		
Oncological treatment within 100 days after surgery ($n = 4876$)			0.97 (0.64; 1.48)	1.05 (0.55; 1.98)
Yes	29 (23.2%)	1127 (23.7%)		
No	96 (76.8%)	3624 (76.3%)		
Time from surgery to oncological treatment within 100 days			0.97 (0.67; 1.40)	1.3 (0.60; 1.76)
Median (25% fractal; 75% fractal)	20 (9; 37)	19 (6; 49)		

OR, odds ratio; HR, hazard ratio; CI, confidence interval.
* Adjusted for age, tumour stage, year of surgery, socioeconomic class, body mass index, Eastern Cooperative Oncology Group-performance status, smoking, alcohol consumption and level of education.

endometrial cancer was not influenced by a pre-existing psychiatric disorder. When it comes to oncological treatment for patients with cervical cancer and a pre-existing psychiatric disorder we found a tendency towards a reduced ratio for oncological treatment.

In this study we examined the effect of a pre-existing psychiatric disorder on postsurgical treatment in patients with gynaecological cancers. The study was restricted to women with ovarian, endometrial and cervical cancer who had received surgical treatment. About 3% of the study population had at least one hospital contact with a psychiatric diagnosis preceding the cancer diagnosis. This corresponds to the general Danish female population [25,26]. We did not find that patients with ovarian cancer with a pre-existing psychiatric disorder had a lower chance of receiving a macroradical surgical treatment or oncological treatment. For patients with endometrial cancer, we did not find a statistically significant lower chance for oncological treatment either. However, in patients with cervical cancer, our data suggest (although our results were not statistically significant) that patients with a pre-existing psychiatric diagnosis had a lower chance of receiving oncological treatment compared with patients without a psychiatric diagnosis. Other studies have shown that patients with both

Table 4
Distribution of treatment by psychiatric disorder status for patients with cervical cancer and risk estimates from logistic regression analyses (and chance of receiving oncological treatment) and Cox regression analyses (days from surgery to first oncological treatment)

Cervical cancer	With psychiatric disorder	Without psychiatric disorder	Crude OR/HR (95% CI)	Adjusted OR/HR (95% CI)*
Oncological treatment within 30 days after surgery ($n = 1143$)			0.38 (0.09; 1.63)	0.20 (0.03; 1.54)
Yes	2 (6.5%)	169 (15.2%)		
No	29 (93.6%)	943 (84.8%)		
Oncological treatment within 100 days after surgery ($n = 1112$)			0.46 (0.16; 1.34)	0.40 (0.12; 1.36)
Yes	4 (12.9%)	262 (24.2%)		
No	27 (87.1%)	819 (75.8%)		
Time from surgery to oncological treatment within 100 days			0.49 (0.18; 1.33)	1.42 (0.14; 1.35)
Median (25% fractal; 75% fractal)	27 (10; 54.5)	17 (6; 52)		

OR, odds ratio; HR, hazard ratio; CI, confidence interval.
* Adjusted for age, tumour stage, year of surgery, socioeconomic class, body mass index, Eastern Cooperative Oncology Group-performance status, smoking, alcohol consumption and level of education.

cancer and psychiatric disorders have a lower chance of receiving oncological treatment compared with patients with cancer without psychiatric disorders [27,28]. Results from the present study indicate the same tendency for patients with cervical cancer. Moreover, we found a potential delay in the time for oncological treatment in patients with cervical cancer having a pre-existing psychiatric disorder. However, it is important to emphasise that our study included only 31 patients who had received surgery for cervical cancer and who had a pre-existing psychiatric diagnosis. If about 25% of these patients received post-operative treatment, it would concern only seven to eight patients. Owing to the small numbers involved, the non-statistically significant trend for all cervical cancer analyses in this study could be due to chance alone.

In general, patients with a psychiatric disorder have an increased sensitivity to stress factors, which might cause a depression episode in this patient group. Depression affects the patient's cognitive function and might therefore reduce compliance to oncological treatment. This could explain both the lower ratio of oncological treatment and the potential delay. Moreover, it could be difficult for women with psychiatric disorders to follow the national screening programme for cervical cancer, which might be caused by a general lack of disease knowledge. In general, they are younger and their psychiatric disorder might not be as well treated at the time of diagnosis as in the older age groups.

Our study has several strengths. To our knowledge, this is the first study, based on nationwide data, providing adjusted risk estimates for treatment outcomes in patients with gynaecological cancers. The validity of our results depends on the size of the study, accurate classification of exposure and the outcome data, and the ability to take into account the influence of confounders. We used DGCD to identify gynaecological cancer patients and multiple studies reported that data in the DGCD are both valid and complete, and provide a solid base for research [5]. Using exclusively nationwide register data leads to a high completeness of the study populations and minimises the risk for selection bias due to independently collected data. In the DNPR we had access to mandatory registration of all in- and outpatient diagnoses and in general the validity of the diagnoses in the DNPR is high. Our outcome data on treatment procedures in the DNPR have both very high completeness and validity [21]. Also, our outcome data were obtained independently of the hypothesis examined, preventing differential misclassification of our outcome assessment. The information on several important confounders was an important strength. As we expected for all cancer types, women with a psychiatric disorder were younger, had a lower socioeconomic status and lower education level.

Our study also has limitations. The limitation of register data is that they do not contain detailed information about health behaviour and details according to treatments. In patients with psychiatric disorders we included all patients who had been diagnosed with schizophrenia, schizotypal disorders and affective disorders within 10 years before cancer diagnosis. Some of them could have been cured of their psychiatric disorder long before they had a cancer diagnosis. Restricting the period to patients with a psychiatric disorder within 5 years before cancer diagnosis did, however, not change our results. Also, we included only psychiatric patients with hospital contact as it was not possible for us to have access to data from general practitioners. A psychiatric diagnosis only given by general practitioners would therefore not be detected in our study and these patients would be categorised as unexposed. Such cases could potentially lead to an underestimation of the effect of psychiatric disorders on cancer treatment. Another weakness in our study is that we could not carry out a separate analysis according to different groups of psychiatric disorders because of the small number of patients with psychiatric disorders.

Most patients receiving a cancer diagnosis might react with depressive symptoms, as this is a powerful stress factor [29]. We therefore only looked at pre-existing psychiatric disorders that were diagnosed within the period of 10 years–120 days before the date of surgery.

In 2013, the Danish Health Authorities introduced a need-based follow-up programme instead of the earlier timetabled follow-up programme. This means that women with a low risk of gynaecological cancer receive less attention at the hospital and the resources are redirected to women with a special need for close follow-up.

Possible explanations to the variation in treatment between women with a psychiatric diagnosis prior to cancer and women without can be lack of referral if the patients are considered not fit for treatment due to individual psychical or psychological factors or inability to adhere to treatment. It is also important to notice that some psychotropic drugs can interact with specific drugs used in oncological treatment, resulting in severe side-effects and in some cases death [30]. Specific psychotropic drugs, such as clozapine, have been found to cause blood dyscrasia, such as leukopenia or neutropenia, which can result in life-threatening infections [31,32]. This is another factor for clinicians to consider before initiating treatment. Another suggested possibility is that depression is an indication of global brain dysfunction. This central nervous system dysregulation produces a greater risk for morbidity, which weakens a patient's chance of receiving an oncological treatment [33]. Moreover, depression has a double feedback loop whereby it promotes poor function and poor function in return promotes depression, which makes models delineating the exact mechanism of how depression influences diagnosis and makes treatment problematic [34].

The positive finding in our study is that we did not find any difference in the treatment of patients with ovarian and endometrial cancer who had a pre-existing psychiatric disorder. Although our results are reassuring regarding patients with ovarian and endometrial cancer, they should be examined in other study populations. Until our results on patients with cervical cancer are confirmed, special attention should be given to patients with cervical cancer having a pre-existing psychiatric disorder when it comes to oncological treatment.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgement

The study was supported by a grant from the Free Research Funds from the Odense University Hospital Research Fund.

References

[1] Constantinou P, Tischkowitz M. Genetics of Gynaecological Cancers. *Best Pract Res Clin Obstet Gynaecol* 2017;42:114–124.
[2] Rieger E, Touyz SW, Wain GV. The role of the clinical psychologist in gynecological cancer. *J Psychosom Res* 1998;45(3):201–214.
[3] Hubbard JL, Holcombe JK. Cancer of the endometrium. *Semin Oncol Nurs* 1990;6(3):206–213.
[4] Rieger PT. Cancer biology and implications for practice. *Clin J Oncol Nurs* 2006;10(4):457–460.
[5] Sørensen SM, Bjørn SF, Jochumsen KM, Jensen PT, Thranov IR, Hare-Bruun H, *et al.* Danish gynecological cancer database. *Clin Epidemiol* 2016;8:485–490.
[6] Siemiatycki J, Krewski D, Franco E, Kaiserman M. Associations between cigarette smoking and each of 21 types of cancer: a multi-site case-control study. *Int J Epidemiol* 1995;24:504–514.
[7] Yancik R. Cancer burden in the aged: an epidemiologic and demographic overview. *Cancer* 1997;80:1273–1283.
[8] Doll R, Peto R, Wheatley K, Gray R, Sutherland I. Mortality in relation to smoking: 40 years' observations on male British doctors. *BMJ* 1994;309:901–911.
[9] Lasser K, Wesley JB, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. Smoking and mental illness: a population based prevalence study. *Am Med Assoc* 2000;284:2606–2610.
[10] Spiegel D, Giese-Davis J. Depression and cancer: mechanisms and disease progression. *Biol Psychiatr* 2003;54(3):269–282.
[11] Giese-Davis J, Collie K, Rancourt KM, Neri E, Kraemer HC, Spiegel D. Decrease in depression symptoms is associated with longer survival in patients with metastatic breast cancer: a secondary analysis. *J Clin Oncol* 2011;29:413–420.
[12] Steel JL, Geller DA, Gamblin TC, Olek MC, Carr BI. Depression, immunity, and survival in patients with hepatobiliary carcinoma. *J Clin Oncol* 2007;25:2397–2405.
[13] Prasad SM, Eggener SE, Lipsitz SR, Irwin MR, Ganz PA, Hu JC. Effect of depression on diagnosis, treatment, and mortality of men with clinically localized prostate. *Cancer J Clin Oncol* 2014;32:23.
[14] Farasatpour M, Janardhan R, Williams CD, Margenthaler JA, Virgo KS, Johnson FE. Breast cancer in patients with schizophrenia. *Am J Surg* 2013;206(5):798–804, https://www-sciencedirect-com.proxy1-bib.sdu.dk/science/article/pii/S0002961013002250?_rdoc=1&_fmt=high&_origin=gateway&_docanchor=&md5=b8429449ccfc9c30159a5f9aeaa92ffb&ccp=y - !.
[15] Iglay K, Santorelli ML, Hirshfield KM, Williams JM, Rhoads GG, Lin Y, *et al.* Diagnosis and treatment delays among elderly breast cancer patients with pre-existing mental illness. *Breast Cancer Res Treat* 2017;166(1):267–275.
[16] DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Arch Intern Med* 2000;160(14):2101–2107.
[17] Tunzi M, Spike JP. Assessing capacity in psychiatric patients with acute medical illness who refuse care. *Prim Care Companion CNS Disord* 2014;16(6). https://doi.org/10.4088/PCC.14br01666.
[18] Irwin KE, Henderson DC, Knight HP, Pirl WF. Cancer care for individuals with schizophrenia. *Cancer* 2014;120(3):323–334.
[19] Manderbacka K, Arffman M, Suvisaari J, Ahlgren-Rimpiläinen A, Lumme S, Keskimäki I, *et al.* Effect of stage, comorbidities and treatment on survival among cancer patients with or without mental illness. *Br J Psychiatr* 2017;211(5):304–309.
[20] Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011;39:22–25.
[21] Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011;39(Suppl. 7):S30–S33.
[22] Thygesen LC, Daasnes C, Thaulow I, Hansen HB. Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation and archiving. *Scand J Public Health* 2011;39:12–16.

[23] Lydiksen L, Jensen-Fangel S, Blaakaer J. Is it possible to define an optimal time for chemotherapy after surgery for ovarian cancer? *Gynecol Oncol* 2014;133(3):454–459.
[24] Fuglsang K, Petersen L, Blaakær J. *Staging in cervical cancer continuously based on a clinical examination*. Nice: European Society of Gynecologic Oncology (ESGO); 24–27 October 2015.
[25] Mors O, Perto GP, Mortensen PB. The Danish Psychiatric Central Research Register. *Scand J Public Health* 2011; 39(Suppl. 7):54–57.
[26] Dansk Depression Database National Report 2016. Available at: http://www.kcks-vest.dk/kliniske+kvalitetsdatabaser/dansk+depressionsdatabase.
[27] Iachina M, Brønserud MM, Jakobsen E, Trosko O, Green A. History of depression in lung cancer patients: impact of delay. *Clin Oncol* 2017;29(9):585–592.
[28] Kaerlev L, Iachina M, Trosko O, Qvist N, Ljungdalh PM, Nørgård B. Cancer stage and oncological treatment in colon and rectum cancer patients with previous hospital contacts for serious psychiatric disorders. A nationwide Danish cohort study. *BMC Cancer* Oct 29;18(1):1050.
[29] Thompson DS, Shear MK. Psychiatric disorders and gynecological oncology: a review of the literature. *Gen Hosp Psychiatr* 1998;20(4):241–247.
[30] Yap KY, Tay WL, Chui WK, Chan A. Clinically relevant drug interactions between anticancer drugs and psychotropic agents. *Eur J Cancer Care* 2011;20(1):6–32.
[31] Idanpaan-Heikkila J, Alhava E, Olkinuora M, Palva I. Letter: clozapine and agranulocytosis. *Lancet* 1975;2(7935):611.
[32] Stubner S, Grohmann R, Engel R, Bandelow B, Ludwig WD, Wagner G, *et al*. Blood dyscrasias induced by psychotropic drugs. *Pharmacopsychiatry* 2004;37(Suppl. 1):S70–S78.
[33] Goodwin JS, Zhang DD, Ostir GV. Effect of depression on diagnosis, treatment, and survival of older women with breast cancer. *J Am Geriatr Soc* 2004;52(1):106–111.
[34] Blazer DG, Hybels CF, Pieper CF. The association of depression and mortality in elderly persons: a case for multiple, independent pathways. *J Gerontol A Biol Sci Med Sci* 2001;56A. M505–9.