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Increased risk for depression persists for years among women treated for gynecological cancers - a register-based cohort study with up to 19 years of follow-up

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HIGHLIGHTS

- Women diagnosed with gynecological cancer have an increased risk for depression.
- It remains increased for years after diagnosis, though most persisting (up to eight years) among women with ovarian cancer.
- Advanced disease, short education, and comorbidity is associated with antidepressant use in this patient group.

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ABSTRACT

Objective. Little is known about long-term risk of depression in women treated for gynecological cancers. We aim to investigate risk for depression among these women compared to women without a history of cancer.

Methods. We followed 16,833 women diagnosed with gynecological cancers between 1998 and 2013 and 138,888 reference women in nationwide registers for up to 19 years. Women with a history of severe psychiatric disorders, and those who had redeemed a prescription for antidepressants three years before study entry were excluded from analyses. Regression analyses were applied to compare the risk for antidepressant use among patients compared to reference women, and to investigate associations between sociodemographic as well as clinical risk factors and use of antidepressants.

Results. We found an increased risk for antidepressant use among women treated for ovarian (HR 4.14, 95% CI 3.74–4.59), endometrial (HR 2.19, 95% CI 1.97–2.45), and cervical cancer (HR 3.14, 95% CI 2.74–3.61) one year after diagnosis. This increased risk persisted years after diagnosis in all three groups, with the longest (up to eight years) found for ovarian cancer. Advanced disease was strongly associated with antidepressant use followed by short education, and comorbidity.

Conclusions. Women diagnosed with gynecological cancer have an increased risk for depression compared to reference women. The risk remains increased for years after diagnosis throughout and beyond standard oncological follow-up care. Advanced disease, short education, and comorbidity are factors associated with antidepressant use in this patient group.

1. Introduction

Depression is a severe, understudied and probably preventable late effect following treatment for gynecological cancers. Women diagnosed with these cancer types are facing diverse prognoses with five-year

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survival rates of 40% for ovarian cancer, 69% following cervical cancer and 83% for endometrial cancer [1]. Moreover, most patients go through extensive surgery and some are further treated with radiation and chemotherapy, all treatments potentially causing severe symptoms and late effects [2–5]. In order to enable prevention and early management of psychological consequences among these women, it is of utmost clinical importance to investigate risk of and risk factors for depression.

It is well established that depression is common among cancer patients [6], and we have previously shown a two-fold increased risk for hospitalization with depression among 608,591 cancer survivors in the first year after diagnosis compared to a group of 5,095,163 persons without cancer in a register-based study [7].

In worst case, having a depression decreases the patient's chance of survival following a cancer diagnosis. This is shown in a nationwide study among 45,325 women with early breast cancer diagnosed in Denmark from 1998 to 2011 with up to 13 years of follow-up, where we found that women previously treated for depression are at risk for receiving non-guideline breast cancer treatment and poorer survival [8].

Most of the recent studies on depression in women treated for gynecological cancers are cross-sectional [9–18], do not include a reference cohort [19], or comprise small sample sizes with short follow-up [20–25]. Thus, large longitudinal studies with long and comprehensive follow-up are needed on this subject.

The aim of this nationwide register-based study was to investigate if women treated for gynecological cancers have an increased risk for depression, measured as incident antidepressant use, compared to women without a history of cancer up to 19 years post diagnosis, and further to examine what demographic and clinical factors characterize the women at highest risk for depression.

2. Material and methods

We utilized data from high quality registers, and linked them on an individual level using the unique personal identification number, which is assigned to all Danish citizens [26]. This setup enabled us to conduct a nationwide cohort study with up to 19 years of follow-up including both a cohort of women diagnosed with gynecological cancers and an age-matched reference cohort.

2.1. Study population

Through the files of the Danish Cancer Registry, which contains close to complete data on all cancer cases in Denmark since 1943 [27], we identified all women 30 years or older and born after 1920 diagnosed with an incident ovarian cancer (ICD10: C56, C570-C574), endometrial cancer (ICD10: C54-C55, C58) or cervical cancer (ICD10: C53) between 1998 and 2013. We excluded women who previously had cancer. Each woman with gynecological cancer was individually matched on month and year of birth to ten women without a history of cancer using the date of cancer diagnosis as the entry date.

2.2. Antidepressant use as proxy for depression

Focus of the study was risk of depression as a consequence of cancer and treatment. We defined this as incident unipolar depression following cancer diagnosis and applied a first prescription of an antidepressant medication as a proxy measure (group N06A of the Anatomic Therapeutic Chemical (ATC) classification system). Thus, date of all redeemed prescriptions for antidepressants was obtained from The Danish National Prescription Registry, which contains high quality individual-level information on all prescription drugs sold in Danish pharmacies since 1994 [28].

We excluded women who suffered from severe psychiatric disorders that included depression as a part of the pathological picture. This included patients with a history of at least one hospital contact for organic mental disorders, behavioral disorders due to use of psychoactive substance, schizophrenia, schizotypal or delusional disorder, or manic, bipolar disorders or unipolar depression (about 5% of both cohorts). We did this by linkage to the Danish Psychiatric Central Registry, which contains data on all admissions to Danish psychiatric inpatient and outpatient facilities since 1969 [29].

Since we wanted to study risk of incident antidepressant use, we excluded all women who had redeemed a prescription for any antidepressant three years before date of diagnosis or study entry (12% of women used antidepressants prior to diagnosis/entry date in both cohorts).

2.3. Comorbidity and socioeconomics

We calculated the Charlson Comorbidity Index (CCI) [30] using data obtained from the National Patient Register, which includes information on diagnoses from all inpatient hospital admissions in Denmark since 1978 and outpatient contacts since 1994 [31].

Using the Education Register [32] and the Population Register held by Statistics Denmark, we created variables on highest attained education and cohabitation status.

2.4. Statistical analysis

All women were followed until the date of first prescription of antidepressants or one of the following censoring events: new diagnosis of primary cancer (except non-melanoma skin cancer), diagnosis of a major psychiatric disorder (not including depression), emigration, death, or December 31 2016, whichever occurred first.

We conducted all analyses separately on women diagnosed with ovarian, endometrial and cervical cancer and their appertaining reference women. Time since diagnosis was used as the underlying timeline.

To illustrate antidepressant use over time, we computed cumulative incidence and mean curves taking death as competing risk into account. Further, applying Cox proportional hazards regression we estimated hazard ratios by comparing women in the three diagnosis subgroups to the reference women. We computed overall estimates for the entire follow-up period, and by time periods since diagnosis. The analyses were stratified by age and calendar period. We calculated expected number of cases by multiplying the number of person-years of follow-up of women with gynecological cancers by the incidence rate of antidepressant use among the reference women. Excess absolute risks with accompanying 95% confidence intervals were computed by subtracting the incidence rates of depression among the reference women from the incidence rates in the patient cohorts.

To investigate risk factors for incident use of antidepressants in the patient cohorts, Cox proportional hazard regression was also applied. All covariates in the model were mutually adjusted (age, cohabitation status, educational level, comorbidity, and stage of disease), and further stratified by calendar period.

The proportional hazards assumption was evaluated by assessing log-minus-log survivor curves. Stage of disease and age violated the assumption indicating that the association between these two variables and antidepressant use differed between the first years following diagnosis and time beyond three years after diagnosis. Hence, we incorporated an interaction term with a time-dependent variable of time since diagnosis and estimated separate hazard ratios for age and stage of disease in these years.

3. Results

We included 16,833 women with gynecological cancers, covering 5702 women with ovarian cancer, 7373 with endometrial cancer, and 3758 with cervical cancer diagnosed between 1998 and 2013, and 138,888 reference women (Fig. 1). Overall, the patients contributed with 93,246 person-years and the reference women with 1,162,385

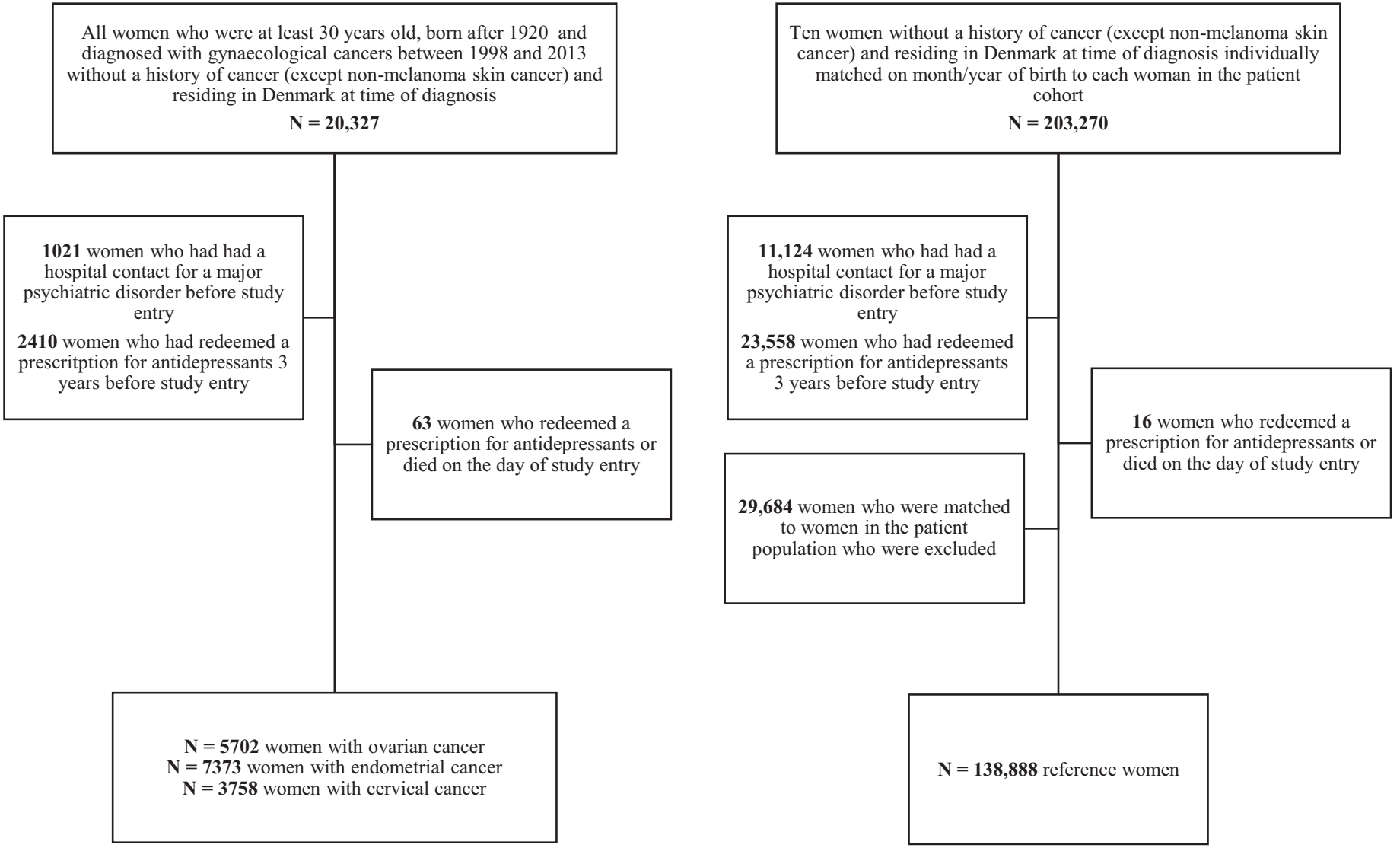

Fig. 1. Flowchart of inclusion of women diagnosed with ovarian, endometrial and cervical cancer and age-matched cancer-free reference women, Denmark, 1998–2013.

Table 1
Baseline characteristics of 16,833 women with ovarian, endometrial or cervical cancer and 138,888 age-matched cancer-free reference women, Denmark 1998–2013.

	Ovarian cancer/references ($N = 5702/N = 46,813$)	Endometrial cancer/references ($N = 7373/N = 60,223$)	Cervical cancer/references ($N = 3758/N = 31,852$)
Socio-demographics			
Age at entry, median (IQR)	64 (55, 73)/64 (55,72)	66 (59, 73)/66 (59, 73)	48 (39, 63)/47 (38, 61)
Cohabitation status			
Living alone	37%/35%	38%/37%	37%/28%
Living with a partner	63%/65%	62%/63%	63%/72%
Level of education			
Short	33%/34%	35%/35%	29%/24%
Medium	44%/44%	44%/44%	45%/46%
Higher	21%/21%	20%/19%	24%/29%
Unknown	1%/2%	1%/2%	2%/2%
Clinical characteristics			
Comorbidity			
No comorbidity	79%/81%	78%/80%	84%/87%
Cardiovascular disease	6%/5%	6%/6%	3%/3%
Cerebrovascular/neurological disease	5%/4%	5%/5%	3%/3%
Diabetes mellitus 1 or 2	4%/3%	7%/3%	3%/2%
Chronic obstructive lung disease	6%/5%	4%/5%	4%/4%
Other comorbidities	7%/7%	6%/7%	6%/5%
Stage of disease			
Localized	33%/—	78%/—	64%/—
Advanced	56%/—	13%/—	27%/—
Unknown	11%/—	9%/—	10%/—

person-years. The baseline characteristics of the populations appear in Table 1.

3.1. Risk for depression

The cumulative incidence of first antidepressant use during a period of ten years after diagnosis in all three subgroups of gynecological cancer patients and the reference women are illustrated in Fig. 2. Through the first three years following diagnosis, the cumulative incidence had a higher increase (steeper curve) for all the subgroups than for the reference women. Subsequently, this increase equalized, and for women with ovarian cancer, it became even more flat than the curve for the reference women. Three years after diagnosis the incidence reached 17% among women with ovarian cancer, 15% in those with endometrial cancer, 12% among cervical cancer patients, and 7% in the reference cohort. The cumulative incidence was similar in the three reference cohorts, thus the curves almost completely overlap each other (Fig. 2). Two thirds of both patients and reference women who had a prescription for antidepressants, redeemed at least a second prescription within the following year. The cumulative mean number of prescriptions redeemed following the initial prescription was similar among patients and reference women for the first three to five years, and thereafter less among the patients (Fig. 3).

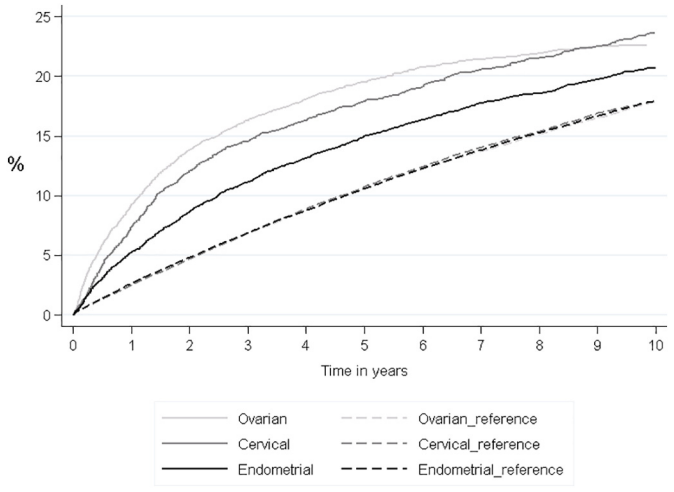

Fig. 2. Cumulative incidence of use of antidepressants among women diagnosed with ovarian, endometrial and cervical cancer and age-matched cancer-free reference women, Denmark 1998–2016.

During the first year after diagnosis, all three diagnosis groups had a significantly increased risk of antidepressant use compared to the reference cohort (Table 2). For women with ovarian cancer it was four-fold increased (95% CI 3.74–4.59), among those with endometrial cancer the risk was twice as high compared to the reference women (95% CI 1.97–2.45), and for women with cervical cancer it was three-fold increased (95% CI 2.74–3.61). This corresponds to an excess absolute risk of 850 extra antidepressants users per 10,000 person-years among women with ovarian cancer, while it was 548 and 327 extra cases for cervical and endometrial cancer patients, respectively during the first year after diagnosis. The significantly increased risk of antidepressant use decreased slightly over the following years, but persisted for up to eight years among women with ovarian cancer, five years among women with endometrial cancer, and three years for women with cervical cancer (Table 2).

3.2. Factors associated with use of antidepressants

Having advanced disease was the factor most strongly associated with first antidepressant use. This association was stable during follow-up in women with ovarian cancer. In contrast, it was considerably higher during the first years than from the third year onwards among women treated for endometrial cancer and cervical cancer (Table 3).

In all three groups, we found a pattern of higher risk of antidepressant use with lower level of education. Further, presence of comorbid diseases was associated with risk of first antidepressant use among women with endometrial and cervical cancer, but not for ovarian cancer. Women with cervical cancer who lived alone had a borderline significantly increased risk of antidepressant use when compared to those living with a partner (Table 3). Likewise, age was only found to be associated with antidepressant use among women with endometrial cancer. In this group, women younger than 50 years had an increased risk of antidepressant use the second year after diagnosis compared to women aged 50 years or more. Conversely, for the remaining follow-up time, women aged 70 or more had an increased risk of antidepressant use compared to the youngest women (Table 3).

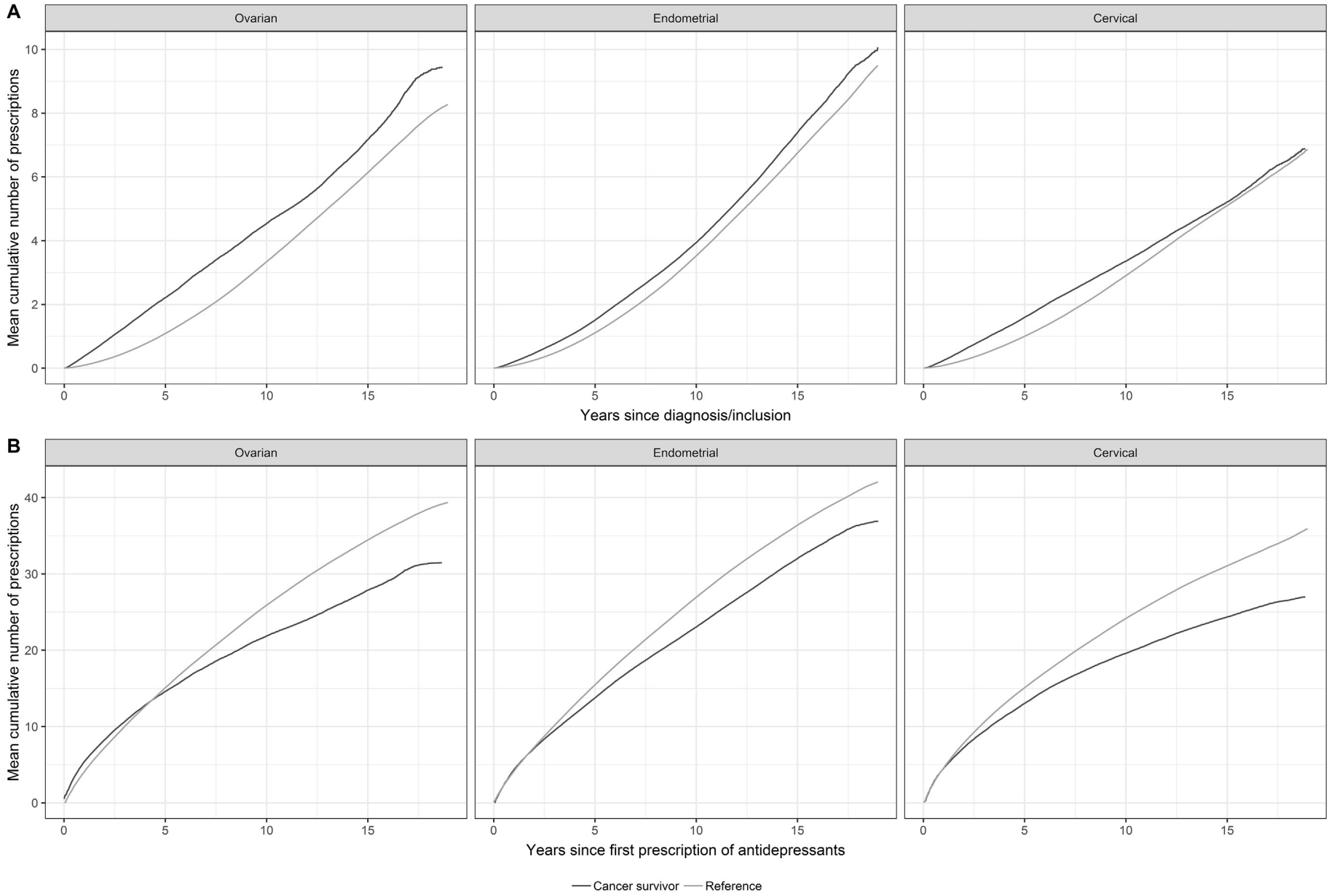

Fig. 3. Mean cumulative number of prescriptions. Panel A shows all the women by time since diagnosis/inclusion ($N = 155{,}721$), and panel B shows the women with at least one prescription by time since first prescription ($N = 29{,}810$).

Table 2
Excess absolute risks (EAR) per 10,000 person-years (PY) and hazard ratios (HR) with corresponding 95% confidence intervals (CI) for first use of antidepressants among women diagnosed with ovarian, endometrial or cervical cancer by time since diagnosis, compared with age-matched reference women without a history of cancer, Denmark 1998–2016.

	Observed	Expected	PY at risk	EAR per 10.000 PY	95% CI	HR[a]	95% CI
Ovarian cancer							
Total	1252	469	2,437	365	(332–398)	2.62	(2.47–2.78)
Time since diagnoses							
1st year	515	126	4619	850	(751–948)	4.14	(3.74–4.59)
2nd year	250	79	3315	503	(411–595)	3.27	(2.85–3.76)
3rd year	141	61	2411	301	(212–390)	2.43	(2.03–2.90)
4th year	103	50	1826	256	(160–353)	2.18	(1.77–2.67)
5th year	73	37	1444	215	(113–317)	2.06	(1.62–2.62)
6th–8th year	103	67	2803	108	(47–168)	1.65	(1.35–2.02)
9th–16th year	67	71	2635	−11	(−55–33)	1.06	(0.83–1.35)
Endometrial cancer							
Total	1487	1055	4312	91	(75–108)	1.42	(1.34–1.50)
Time since diagnoses							
1st year	403	183	6731	327	(267–387)	2.19	(1.97–2.45)
2nd year	240	140	5989	168	(115–220)	1.73	(1.51–1.99)
3rd year	179	124	5477	100	(51–150)	1.46	(1.25–1.71)
4th year	143	107	4873	74	(24–124)	1.36	(1.14–1.62)
5th year	118	94	4184	58	(5–111)	1.28	(1.05–1.54)
6th–8th year	199	199	9336	0	(−30−31)	1.02	(0.89–1.18)
9th–16th year	205	214	10,722	−9	(−36–19)	0.99	(0.86–1.14)
Cervical cancer							
Total	885	507	24,498	154	(130–178)	1.76	(1.64–1.89)
Time since diagnoses							
1st year	270	86	3361	548	(450–645)	3.14	(2.74–3.61)
2nd year	180	69	2856	388	(295–482)	2.68	(2.27–3.15)
3rd year	101	62	2560	151	(72–230)	1.66	(1.35–2.05)
4th year	60	52	2308	36	(−33–104)	1.18	(0.90–1.53)
5th year	51	45	2031	31	(−41–102)	1.17	(0.88–1.56)
6th–8th year	107	96	4821	22	(−21–66)	1.17	(0.96–1.43)
9th–16th year	116	106	6561	15	(−18–49)	1.17	(0.97–1.41)

[a] Stratified by age (as a time-dependent variable in five-year-intervals) and calendar period (as a time-dependent variable in three-year-intervals).

Among women with both low education, comorbidity and advanced disease (6% of population), 19% (95% CI, 15–22%) had been prescribed antidepressants five years after diagnosis. A similar proportion were observed among the 67% of women who had one to two of these risk factors (95% CI 19–20%) while it was 14% (95% CI, 13–15%) among women who had none of the risk factors.

4. Discussion

The risk for first antidepressant use was substantially increased among women treated for gynecological cancers compared to cancer-free women. This risk decreased over the following years, but persisted for up to eight years among women with ovarian cancer, five years among women with endometrial cancer and three years among women treated for cervical cancer. Having advanced disease was the strongest determinant of subsequent antidepressant use in all three diagnosis groups. Further, short education was also associated with increased risk for depression regardless of diagnosis group. Comorbidity was associated with antidepressant use among women with endometrial or cervical cancer, while young age only affected risk of depression in younger women with endometrial cancer the second year after diagnosis, and older women with endometrial cancer from third year and onwards. Lastly, a borderline statistically significant association between living alone and antidepressant use was found among women with cervical cancer.

To date, this is the largest population-based study with the longest follow-up time investigating depression following a gynecological cancer diagnosis. We have shown that risk of a first depression is highest close to diagnosis and decreases over the following years, but for some women it persists for several years. These results are similar to results found in our previous register-based study with up to 30 years follow-up of 608,591 cancer survivors and a comparison group of 5,095,163 persons without cancer, were we showed that the risk of hospitalization with depression remained increased for more than ten years after diagnosis among women surviving hormone-related cancers [7]. Further, we previously showed an increased risk of first antidepressant use persisting for eight years after diagnosis among 35,286 women diagnosed with breast cancer in a Danish, register-based cohort study with a reference cohort of 1,860,552 women [33].

In this present study, we observed a tendency that the cumulative mean number of prescriptions redeemed following the initial prescription was similar among patients and reference women for the first three to five years, and thereafter less among the patients. This could reflect that the patients tend to use antidepressants for shorter periods than cancer-free women, but may also to some extent reflect an increased mortality rate in these patients (due to advanced disease, comorbidity etc.).

We found that the risk of depression differed according to gynecological cancer subtype. Women with ovarian and cervical cancer had the highest risk for depression in the first year after diagnosis. For ovarian cancer, the increased risk persisted for several years, while for cervical cancer, the risk quickly decreased and lost statistical significance after three years only. This could reflect the fact that cervical cancer most often are diagnosed in early stages enabling fully remission following surgery [34], compared to ovarian cancer, which often is diagnosed in later stages demanding more extensive treatment and furthermore, more often is relapsing [35]. The lowest risk for depression was found among women with endometrial cancer. This could probably reflect that these women often are diagnosed in early stages with good chances of remission and relapse-free survival [36]. Furthermore, some of the increased risk for depression may also be explained by obesity, which is a known risk factor for endometrial cancer, and has been found to affect the women's quality of life following cancer diagnosis [37].

We found advanced disease strongly associated with risk of depression. This may have contributed to the high and prolonged risk among women with ovarian cancer, which most often is diagnosed in late stages. In contrast, endometrial and cervical cancer are more likely to be diagnosed in earlier stages, and prognoses are markedly better [1].

Table 3
Multivariate adjusted hazard ratios (HR) with corresponding 95% confidence intervals (CI) for first use of antidepressants among women diagnosed with ovarian, endometrial or cervical cancer, Denmark 1998–2016.

	Ovarian cancer ($N = 5032$[a])	Endometrial cancer ($N = 6621$[a])	Cervical cancer ($N = 3344$[a])
	HR[b] (95% CI)	HR[b] (95% CI)	HR[b] (95% CI)
Socio-demographics			
Age			
Year one			
30–49	1	1	1
50–69	1.23 (0.92–1.65)	1.03 (0.62–1.69)	1.03 (0.77–1.38)
70–	1.32 (0.96–1.82)	1.44 (0.87–2.38)	1.16 (0.81–1.65)
Year two			
30–49	1	1	1
50–69	1.17 (0.81–1.68)	0.36 (0.23–0.55)	0.84 (0.58–1.23)
70–	1.09 (0.71–1.67)	0.62 (0.40–0.97)	1.36 (0.87–2.13)
Year three to end of FU			
30–49	1	1	1
50–69	1.07 (0.84–1.36)	0.88 (0.65–1.19)	0.81 (0.63–1.03)
70–	0.99 (0.73–1.35)	1.86 (1.36–2.54)	1.29 (0.90–1.83)
Cohabitation status			
Living with a partner	1	1	1
Living alone	1.05 (0.92–1.19)	0.96 (0.86–1.08)	1.17 (1.01–1.36)
Level of education			
Higher	1	1	1
Medium	1.14 (0.97–1.33)	1.08 (0.93–1.27)	1.33 (1.10–1.60)
Short	1.39 (1.17–1.65)	1.26 (1.08–1.48)	1.57 (1.27–1.93)
Clinical characteristics			
Comorbidity			
No comorbidity	1	1	1
Comorbidity	1.07 (0.91–1.25)	1.34 (1.18–1.53)	1.32 (1.08–1.61)
Stage of disease			
Year one			
Localized	1	1	1
Advanced	1.64 (1.34–2.02)	2.59 (2.04–3.29)	2.32 (1.78–3.02)
Year two			
Localized	1	1	1
Advanced	1.50 (1.14–1.98)	1.99 (1.39–2.85)	2.30 (1.64–3.21)
Year three to end of FU			
Localized	1	1	1
Advanced	1.57 (1.30–1.91)	1.51 (1.20–1.89)	1.63 (1.28–2.07)

The underlying timeline is time since diagnosis.
[a] All the variables are mutually adjusted and further stratified by calendar period.
[b] Individuals with missing values on educational level or stage of disease are not included in analyses.

Similar results were found in a recently published German cohort study among 7000 women diagnosed with gynecological cancers [19].

We only found an association between age and risk of depression among women diagnosed with endometrial cancer. Similar to a recently published cohort study of 6526 Taiwanese women with endometrial cancer and 65,260 reference women followed for up to 11 years, we found an increased risk of depression among women younger than 50 years [38]. Considering the cancer site and the comprehensive surgical procedures (hysterectomy and salpingo-oophorectomy) most of the women undergo [36], the youngest women may experience pernicious worries related to fertility loss and symptoms of premature menopause [39].

As has been shown for many other health-related outcomes, we found that depression severe enough to warrant medical treatment was associated with both shorter education and somatic comorbidity [33,40,41].

4.1. Strengths and limitations

The use of data from registers established independently of study hypothesis, with daily update on outcome and censoring variables throughout the study period, allowed us to analyze incident depression recognized and treated by doctors. However, using register-based data also has limitations. We considered antidepressant use a proxy for clinical depression. A considerable proportion of women with symptoms of depression, do not receive medical treatment for their condition. A Scottish cross-sectional study of 3010 gynecological cancer survivors who had participated in routine screening for depression showed that most women (75%) with clinical depression did not receive any treatment for depression [12]. On the other hand, even though antidepressant medication is only prescribed by physicians in Denmark, all patients treated with antidepressants may not suffer from clinical depression but from anxiety or entirely different conditions as pain or hot flashes. However, it is estimated that 71 to 86% of persons treated with antidepressants in the general population suffer from depression [33]. Thus, a risk of misclassification of first depression exists in our study, but most likely, this will manifest as an underestimation of the incidence of depression in the population.

Another limitation in our study is the lack of available information on cancer treatment and patient-reported outcomes, which most likely are associated with risk of depression. However, since stage of disease and treatment are closely related, we assume that a possible effect of treatment and/or any late effects is included in the association found between stage of disease and risk of depression.

4.2. Conclusion

Women diagnosed with gynecological cancer are at increased risk for incident depression compared to cancer-free controls. This risk remains increased for years after diagnosis, though most persisting (up to eight years) among women with ovarian cancer. Advanced disease, short education, and comorbidity are factors associated with antidepressant use in women diagnosed with a gynecological cancer.

This knowledge is important for healthcare professionals in primary and secondary healthcare, as the increased risk persists even after end of treatment and among ovarian cancer survivors after end of follow-up care. Systematic screening for depression among women with gynecological cancers by the treating hospital departments or the general practitioner may enable early identification of patients in need for treatment.

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Interpretation of results: All authors.

Manuscript writing: All authors.

Final approval of manuscript: All authors.

Conflict of interest statement

None declared.

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