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ORIGINAL RESEARCH

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Development of mental health disorders in endometrial cancer survivors and the impact on overall survival—a population-based cohort study

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Abstract

To better understand the risk of developing a mental health disorder and the association on outcomes in endometrial cancer patients. Endometrial cancer patients ≥18 years old diagnosed between 1997–2012 were identified from the Utah Population Database and matched with up to 5 cancer free women from the general population. Mental health disorders were identified by International Classification of Diseases ICD-9 diagnostic codes. Endometrial cancer survivors with pre-existing mental health issues were excluded. Diagnosis of a mental health disorder in endometrial cancer patients was compared with the endemic rate. The impact of a mental health disorders on overall survival (OS) and cause specific survival (CSS) was evaluated. There were 2941 endometrial cancer patients and 12,192 general population matched subjects that met criteria with a median follow up time of 7.1 years (range 0–19.2) and 7.7 years (0.4–19.2) respectively. Within the first 1.5 years from diagnosis, there was an association of endometrial cancer patients being diagnosed with a mental health disorder (Hazard radio (HR) 3.09, 95% confidence interval (CI) 2.66–3.59). However, no association was found in endometrial cancer patients being diagnosed with a mental health disorder between 1.5–3 years (HR 1.07, 95% CI 0.83–1.38) and ≥3 years (HR 1.09, 95% CI 0.95–1.26). Treatment with tri-modality (surgery, radiation and chemotherapy) and advanced disease was associated with mental health disorders. OS was worse in endometrial cancer survivors who developed an anxiety disorder (p = 0.0265). CSS was worse in endometrial cancer patients diagnosed with all mental health disorders and anxiety disorders ($p < 0.0001$, p = 0.002). Endometrial cancer patients have an increased diagnosis of mental health disorders within the first 1.5 years of cancer diagnosis compared to the general population. Endometrial cancer survivors with anxiety disorder have worse OS. Anxiety disorders and all mental health disorders have a worse CSS.

Keywords

Mental health disorders; Endometrial cancer; Cancer survivors

1. Introduction

Endometrial cancer is the most common gynecological malignancy and the 4th most common cancer in women. The incidence of endometrial cancer has also been increasing over the past decade, approximately 1.5% and 2.5% per year in White and African Americans, respectively. Although there is a large prevalence of uterine cancer in the US, 5 year survival rates are 95% for those with localized disease and 69% with regional disease [1]. The high prevalence rate, increasing incidence and high survival rates has made endometrial cancer survivorship information essential in long term management

A major survivorship issue for cancer patients is dealing with mental health disorders including anxiety and depression. Many reports have shown rates of depression in cancer patients to be as high as 50%, with up to 10–25% meeting Major Depressive disorder criteria [2–4]. While there is a plethora of literature that supports an increase in psychosocial and mental illnesses in patients with cancer, there is little data looking at the range of mental illnesses disorders in endometrial cancer patients particularly in long term follow up and how it correlates with outcomes.

The purpose of this study was to determine whether endometrial cancer survivors had a higher risk of a range of mental illness disorders compared to the endemic rate after. We also assessed if the diagnosis of mental illness disorders changed over time in endometrial cancer survivors, evaluated clinical and demographic factors that might increase risk of mental illness disorders and evaluated the effects of mental illness diagnosis on overall survival (OS) and cause specific survival

(CSS) in endometrial cancer survivors.

2. Methods

2.1 Data collection

An initial cohort of 3453 endometrial cancer survivors were identified using the Utah Population Database. Diagnosis data were available from the statewide Surveillance, Epidemiology and End Results (SEER) Utah Cancer Registry for women age 18 years and older diagnosed with invasive first primary endometrial cancer between 1997 and 2012 in the state of Utah (SEER ICD-O-3 codes: C54.0–C55.9). Endometrial cancer survivors were matched on birth year and birth state with up to five women from the general population.

Outcome data used for this study included statewide ambulatory and inpatient data from the Utah Department of Health and electronic medical record data from Intermountain Health Care and the University of Utah Health Sciences Center. Utah is considered to have a minimal percentage of residents who seek health care out of the state, based on a report by the National Association of Health Data Organizations that reviewed interstate exchange of nonresident data for health research and public health purposes [5]. Additionally, according to the US Census Bureau's state-to-state migration flow data for 2016, approximately 2.9% of Utahans left the state; thus, the outmigration rate is fairly low [6]. Data from the Utah Population Database included records from the Utah Cancer Registry, Utah driver's licenses, vital records, and the Utah Department of Health. We also identified tobacco smokers before cancer diagnosis, with the ICD-9 code for "tobacco use disorders" 305.1, "personal history of tobacco use" V15.82, ICD-10 codes for nicotine dependence, and with current procedural terminology (CPT) codes for tobacco cessation counseling based on the American Academy of Family Physicians coding guidelines [7].

A total of 100 endometrial cancer patients were excluded because their cancer was not staged, 359 because grade was missing, 49 because they were not Utah residents at the time of diagnosis, 1 because the follow-up date was same day as cancer diagnosis date, 3 because no eligible cancer-free individuals could be matched to them. There were 2941 endometrial cancer survivors and 12,192 women from the general population included in the final sample. A prism flow diagram can be seen viewed the **Supplementary Fig. 1**.

Outcome data included all available ICD-9 diagnosis codes and diagnosis dates. The Clinical Classification Software developed by the Health Cost and Utilization Project was used to categorize ICD-9 codes into four levels of specificity (mental illness only has 3 levels): From broader body systems or condition categories (for example, Diseases of the genitourinary system or Mental illness) to more detailed and specific conditions or procedures (for example, Infections of kidney or Depressive disorders) (additional details are provided in the Supplementary Methods, available online; ICD codes are provided in **Supplementary Table 1**) [8]. To validate the disease diagnoses, we previously investigated concordance between self-reported data and EMR/statewide data for various diseases (221 patients with cancer). For depression, the sensitivity was 82.6% and the specificity was 95.7%. Long-term mental illness outcomes were identified from >0 to <1.5 years, 1.5 years to <3 years, and 3 or more years after endometrial cancer diagnosis. Follow-up time was calculated from the endometrial cancer patient's first cancer diagnosis to the incident diagnosis date of mental illness, last date of follow up, or date of death. Individuals who did not have that outcome were censored at the date of last follow-up if that date fell within the analysis time period. For the matched women from the general population cohort, the follow up time started from the date of cancer diagnosis for the endometrial cancer patient they were matched to. For all levels, outcomes diagnosed prior to the cancer diagnosis were considered prevalent cases of those outcomes, and individuals were excluded from the relevant models.

2.2 Statistical analysis

Chi-square tests were used to compare baseline characteristics between the endometrial cancer survivor and general population cohorts. Multivariable Cox proportional hazard models were used to calculate hazard ratios (HR) and 95% confident intervals (CI) for long-term mental illness outcomes from >0 to <1.5 years, 1.5 years to <3 years, and 3 or more years after endometrial cancer diagnosis. Multivariable models were adjusted for matching factors, baseline body mass index (BMI), baseline Charlson Comorbidity Index (CCI) [9], and race. Cox proportional hazard models were also used to investigate risk factors such as treatment type, stage, age at diagnosis, year of diagnosis, baseline BMI and CCI among endometrial cancer survivors.

The proportional hazards assumption was checked for each time Cox proportional hazard model used. Models that were in violation of the proportional hazards assumption were then tested with flexible parametric survival models [10]. Hazard ratios from the Cox proportional hazard models were reported where there were no substantive differences.

Baseline BMI values at least one year prior to endometrial cancer diagnosis were calculated from the driver's license records for both cohorts. The height and weight was taken from the closest date prior to the date of endometrial diagnosis. For individuals missing BMI, values were imputed using a linear regression model that included cancer diagnosis, baseline CCI, race and age at endometrial cancer diagnosis as covariates. Models were run with and without the imputed values to assure that the inferences did not change due to the imputation of BMI.

Charlson Comorbidity index (CCI) is the one of most widely used methods to classify comorbid diseases of patients with ICD diagnosis codes and the total score is the sum of weights of 15 categories of these diseases (any malignancy and metastatic carcinoma are excluded in this study), from score zero which means no comorbidity disease found to high score which means a high-risk mortality [9, 11, 12]. All ICD 9 clinical modification (CM) codes from the healthcare data before cancer diagnosis are used to calculate baseline CCI.

3. Results

There were 2941 endometrial cancer survivors and 12,192 individuals in the general population cohort that met inclusion criteria with a median follow up period of 7.1 years (range 0–19.2 years) and 7.7 years (0.4–19.2 years), respectively. The cohorts differed in baseline BMI, CCI, survival status, follow up and tobacco use before diagnosis (**Supplementary Table 2**). The vast majority of subjects in both cohorts were white, with less than 5% of non-white subjects in each cohort. For endometrial cancer survivors, approximately a quarter of the patients had a normal weight (26.1%), nearly half (46.6%) were overweight at baseline and a quarter (26.9%) were obese, whereas, in the general population nearly half (47.9%) had a normal BMI, 31.6% were overweight and only 19.3% were obese ($p < 0.001$). Tobacco use before cancer diagnosis among endometrial cancer survivors was less than the general population cohort ($p = 0.01$). The prevalence of mental health disorders prior to the cancer diagnosis were similar to the endemic rate (**Supplementary Table 3**). These subjects were excluded from the analysis. Endometrial cancer was diagnosed mainly in post-menopausal women; 29% were between 50–59 years old, 28.3% were 60–69 years old and 25.8% were 70 years or greater (Table 1). At the time of diagnosis, local disease was most common, followed by regional disease and very few diagnosed with advanced disease. The majority of patients (64.4%) were treated with surgery alone, 19.7% were treated with surgery plus radiation and only 4.2% were treated with surgery, radiation and chemotherapy.

In the first 1.5 years after diagnosis, endometrial cancer patients were more likely to have a concurrent mental health disorder compared to the endemic rate in the matched general population cohort (HR 3.09, 95% CI 2.66–3.59); however, there was no significant difference seen after the first year and a half (Table 2). Within the first year and a half of diagnosis, the following mental disorders were significantly elevated compared to the general population cohort: adjustment disorders (HR 3.68, 95% CI 1.64–8.25), anxiety disorders (HR 2.47, 95% CI 2.00–3.06), mood disorders (HR 2.54, 95% CI 2.08–3.09), depressive disorders (HR 2.60, 95% CI 2.13–3.17) schizophrenia/other psychotic disorders (HR 2.71, 95% CI 1.1.7–4.33), substance abuse disorders (HR 2.06, 95% CI 1.19–3.57), and mental disorders due to general medical conditions not otherwise specified (NOS) (HR 3.17, 95% CI 1.18–8.49). After 1.5 years, no mental health disorder remained at an elevated risk compared to the general population aside from miscellaneous mental disorders.

The type of treatment endometrial cancer patients received was not associated with developing depressive disorders; whereas, mental health disorder (HR 1.91, 95% CI 1.26–2.90) and anxiety disorders (HR 2.14, 95% CI 1.21–3.78) were found to be associated in patients receiving tri-modality therapy (surgery, radiation therapy and chemotherapy) after adjusting for age, BMI, CCI and race (Table 3). The diagnosis of mental health disorder and anxiety disorders were associated with advanced stage endometrial cancer. The diagnosis of anxiety disorders increased after the year 2006, while the frequency of diagnosis for mental health disorder and depressive disorders did not change with time. Patients diagnosed with endometrial cancer between the ages of 60–79 appear to have a decreased diagnosis of depression compared to the endemic rate.

Overall survival amongst endometrial cancer patients with anxiety disorders was significantly worse than those without any mental health disorder diagnosed within the first 1.5 years ($p = 0.0265$) but was not significant for depression or all mental health disorders combined (Fig. 1). Cause specific survival was statistically worse in endometrial cancer patients diagnosed with all mental health disorders combined and anxiety disorders ($p < 0.0001$, $p = 0.002$) but not in those diagnosed with depressive disorders ($p = 0.3269$) (Fig. 2).

TABLE 1. Clinical characteristics of endometrial cancer survivors.

Characteristic	Patients (n = 2941)
Diagnosis Year	
1997–2000	630 (21.4)
2001–2005	840 (28.6)
2006–2010	1065 (36.2)
2011–2012	406 (13.8)
Age at Diagnosis	
18–49	497 (16.9)
50–59	852 (29.0)
60–69	832 (28.3)
≥70	760 (25.8)
Stage	
Local	2267 (77.1)
Regional	510 (17.3)
Advanced	164 (5.6)
Treatment	
Surgery only	1893 (64.4)
Surgery + RT	578 (19.7)
Trimodality	124 (4.2)
Other*	152 (5.2)
Missing	194 (6.6)
Location	
Urban	2526 (85.9)
Rural	413 (14.0)
Missing	2 (0.1)
Median family income	
<50,000	379 (12.9)
≥50,000	2560 (87.0)
Missing	2 (0.1)

*Abbreviations: No, number; n, number; RT, radiation therapy. *Other includes surgery and chemotherapy, chemotherapy only, radiation only, radiation and chemotherapy, and no treatment.*

TABLE 2. Adjusted hazard ratios for mental illness disorders in endometrial cancer survivors.

	>0 to <1.5 years					1.5 to <3 years					≥3 years				
	EC	GP	HR	95% CI		EC	GP	HR	95% CI		EC	GP	HR	95% CI	
Mental Illness	363	509	3.06*†	2.63†	3.57†	105	423	1.07	0.83	1.38	370	1484	1.09	0.95	1.26
Adjustment disorders	14	20	3.18*†	1.49†	6.80†	6	16	1.14	0.40	3.29	20	64	1.22	0.69	2.18
Anxiety disorders	156	269	2.34*†	1.86†	2.93†	64	243	1.11	0.82	1.50	240	899	1.01	0.85	1.19
Delirium dementia and amnestic and other cognitive disorders	48	150	1.38	0.97	1.97	31	117	1.09	0.70	1.69	155	576	1.07	0.87	1.32
Mood disorders	186	314	2.58*†	2.11†	3.16†	70	264	1.12	0.84	1.50	257	942	1.06	0.91	1.25
Bipolar disorders	10	39	1.07	0.50	2.28	7	35	0.86	0.36	2.04	27	133	0.78	0.50	1.21
Depressive disorders	187	307	2.67*†	2.18†	3.27†	70	263	1.12	0.83	1.50	256	937	1.07	0.91	1.26
Personality disorders	3	7	7.15	0.52	97.85	3	9	1.46	0.32	6.67	8	24	1.30	0.55	3.08
Schizophrenia and Other psychotic disorders	32	47	3.07*†	1.88†	4.99†	17	48	1.37	0.73	2.59	75	249	1.04	0.77	1.40
Alcohol-related disorders	9	25	1.87	0.80	4.40	8	17	2.52	0.94	6.77	20	82	1.07	0.63	1.82
Substance-related disorders	22	47	1.84†	1.03†	3.29†	10	45	0.53	0.22	1.24	42	159	0.96	0.65	1.42
Suicide and intentional self-inflicted injury	1	27	0.16	0.02	1.27	6	15	1.30	0.45	3.75	14	66	0.73	0.38	1.42
Miscellaneous mental disorders	21	61	1.47	0.86	2.51	20	63	1.21	0.69	2.12	63	165	1.61	1.16	2.24
Dissociative disorders	0	2	-	-	-	0	2	-	-	-	2	3	2.82	0.40	19.91
Eating disorders	2	3	6.50	0.30	141.48	2	5	1.63	0.30	8.95	3	13	1.46	0.34	6.17
Factitious disorders						1	0	-	-	-	1	0	-	-	-
Psychogenic disorders	1	8	0.43	0.05	3.63	3	7	1.55	0.35	6.77	7	22	1.27	0.50	3.26
Sexual and gender identity disorders	1	3	4.80	0.16	145.76	0	4	-	-	-	2	5	13.6	0.59	312.02
Sleep disorders	4	11	1.47	0.39	5.45	5	18	1.34	0.42	4.27	19	43	1.41	0.75	2.65
Somatoform disorders	5	25	0.84	0.31	2.27	6	23	0.60	0.18	2.01	23	60	1.53	0.89	2.64
Mental disorders due to general medical conditions not elsewhere classified	8	12	3.28†	1.23†	8.75†	6	9	2.68	0.85	8.48	11	28	1.91	0.83	4.36
Other miscellaneous mental conditions	2	6	0.84	0.02	35.47	1	6	0.34	0.03	3.62	3	11	1.05	0.27	4.00

[a] *Adjusted on baseline BMI, race and baseline CCI.*

**Flexible model used.*

†statistically significant.

Abbreviations: EC (+), endometrial cancer, positive for mental illness; EC, endometrial cancer, no mental illness reported; GP (+), general population, positive for mental illness; GP, general population, no mental illness reported; HR, hazard ratio; CI, confidence interval.

TABLE 3. Associations between endometrial cancer and mental health disorders.

	Mental Illness					Anxiety Disorders					Depressive Disorders				
			0–1.5 years					0–1.5 years					0–1.5 years		
	n (−)	n (+)	HR	95% CI		n (−)	n (+)	HR	95% CI		n (−)	n (+)	HR	95% CI	
Treatment Type[1]															
Surgery only	1223	220	1.00			1644	92	1.00			1537	113	1.00		
Surgery and radiation	383	77	*1.11	0.85	1.44	514	29	*1.01	0.66	1.55	469	44	1.32	0.93	1.88
Trimodality	71	25	*1.91†	1.26†	2.90†	105	14	*2.14†	1.21†	3.78†	96	11	1.59	0.86	2.97
Other treatment**	108	29	*1.48†	1.00†	2.18†	149	16	*2.20†	1.29†	3.76†	146	16	1.62	0.95	2.74
Missing	16	2				19	2				20	0			
Stage[1]															
Localized	1394	253	1.00			1870	110	1.00			1740	136	1.00		
Regional	317	63	1.13	0.85	1.49	431	28	*1.13	0.75	1.71	398	35	1.20	0.83	1.74
Advanced	90	37	2.41†	1.70†	3.41†	130	15	*2.38†	1.39†	4.09†	130	13	1.64	0.92	2.90
Baseline BMI[2]															
<18 kg/m^2	6	1	*0.89	0.12	6.45	9	0	-	-	-	9	0	-	-	-
18–25 kg/m^2	484	101	1.00			640	32	1.00			618	46	1.00		
25–30 kg/m^2	495	83	*0.82	0.61	1.10	644	45	1.32	0.83	2.08	606	52	1.11	0.75	1.66
≥ 30 kg/m^2	816	168	*0.97	0.75	1.25	1138	76	1.19	0.78	1.81	1035	86	1.00	0.69	1.45
Year of Diagnosis															
1997–2000	474	77	1.00			585	21	1.00			546	41	1.00		
2001–2005	534	115	1.28	0.96	1.71	727	39	1.46	0.86	2.49	675	54	1.05	0.70	1.58
2006–2010	584	118	1.21	0.91	1.61	838	64	2.03†	1.24†	3.33†	765	75	1.27	0.87	1.86
2011–2012	216	44	1.21	0.84	1.75	291	30	2.75†	1.58†	4.81†	292	15	0.69	0.38	1.25
Age at Diagnosis[3]															
23–50	294	68	1.00			414	30	1.00			376	41	1.00		
50–59	498	104	0.90	0.66	1.22	689	45	0.88	0.56	1.41	627	65	0.94	0.63	1.39
60–69	527	96	0.80	0.59	1.10	693	41	0.81	0.51	1.31	658	37	0.52†	0.33†	0.81†
70–79	345	52	0.69†	0.48†	0.99†	439	26	0.82	0.48	1.39	422	28	0.60†	0.37†	0.97†
80–99	144	34	1.00	0.65	1.54	206	12	0.79	0.39	1.57	195	14	0.62	0.33	1.15

TABLE 3. Continued.

	Mental Illness					Anxiety Disorders					Depressive Disorders				
% of Bachelors degree[1]															
<15%	58	12	1.00			75	4	1.00			77	1	1.00		
15%–24.9%	403	79	0.92	0.50	1.69	558	31	0.96	0.34	2.73	509	42	5.97	0.82	43.45
≥25%	1340	262	0.74	0.51	1.62	1797	118	1.11	0.41	3.01	1682	141	5.87	0.82	42.04
Missing						1	0								
Median Family below poverty[1]															
<50,000	255	52	1.00			325	19	1.00			313	27	1.00		
≥50,000	1546	301	0.95	0.70	1.27	2106	134	0.99	0.61	1.61	1955	157	0.87	0.58	1.32
CCI[4]															
0	1230	235	1.00			1551	80	1.00			1473	109	1.00		
1	351	71	*1.07	0.82	1.39	498	44	1.71†	1.18†	2.48†	467	37	1.14	0.78	1.65
≥2	220	47	*1.13	0.82	1.57	382	29	1.53	0.98	2.37	328	38	1.79†	1.22†	2.64†

**Flexible model used.*

***Includes surgery and chemotherapy only, RT and chemotherapy only, chemotherapy only, RT only.*

†statistically significant.

[1]*Adjust on age at diagnosis, BMI, CCI, and race.*

[2]*Adjust on age at diagnosis, CCI, and race.*

[3]*Adjust on BMI and CCI.*

[4]*Adjust on age a diagnosis, race, and BMI.*

Abbreviations: n, number; HR, hazard ratio; CI confidence interval; BMI, body mass index; kg, kilogram; m^2, square meter; CCI, Comprehensive Complications Index.

4. Discussion

Uterine cancer is the most common gynecological cancer and the 4th most common cancer in women in the US. With excellent long term survival outcomes in endometrial cancer patients, improving survivorship care and patient wellness is important. While there is proficient data showing an increased prevalence of mental health issues diagnosed in cancer patients, there is little information looking at the range of mental health disorders in cancer patients, nor specifically in endometrial cancer patients. Similarly, there is limited data on overall survival and mental health outcomes in endometrial cancer patients

This study utilizes the Utah Population Database to look at the occurrence of psychological disorders after a diagnosis of endometrial cancer, assess the correlating factors and analyze outcomes including OS and CSS. Overall, there was an increase in mental health disorder in patients within 1.5 years of their endometrial cancer diagnosis compared to the endemic rate. Specifically, incidence rates were increased in adjustment disorder, anxiety disorders, mood disorders—particularly depressive disorders, schizophrenia/psychotic disorders, substance-related disorders and mental disorders due to general medical conditions not otherwise classified. However, the increased risk of a mental health disorders returned to normal 1.5 years out from the cancer diagnosis.

Cross-sectional studies have reported an association between cancer diagnosis and mental health disorders, with some studies showing up to 50% of cancer patients being diagnosed with anxiety or depression [2, 3, 13]. Almost 30% of gynecological patients experience psychological distress somewhere along their cancer journey [14]. In our study, we specifically found an association between mental health disorders within the first 1.5 years from cancer diagnosis; however, in the following years, mental health disorders in endometrial cancer survivors was equivalent to the matched population. Many reasons have been postulated for an increase in mental illness diagnoses in cancer patients.

The prevalence of mental illness disorders was similar to the endemic rate prior to the endometrial cancer diagnosis. With the increase of mental illness presenting within the first 1.5 year of endometrial cancer diagnosis, the cause of the mental health disorder could be associated with the pathogenesis of the cancer. Studies of psychoneuroimmunological mechanisms have suggested biological alterations that could occur in cancer patients making them more susceptible to mental illnesses [15–17]. Inflammatory markers including natural killer (NK) cells, cytokines and interleukin (IL)-6 have been shown to be elevated in patients with mental health disorders in some cancers, while decreased in others [18, 19]. Changes in the circadian rhythm and hypothalamic-pituitary-adrenal axis have also been studied but the results have been inconsistent [13, 19]. It is also possible the mental health disorder may have been caused by some biologic effect of the tumor but there is no evidence to support this. Pain associated with the cancer/treatment has also been thought to lead to higher rates of mental health diagnoses [20]. Another explanation could be that the pre-existing mental health disorder is recognized and diagnosed as a patient establishes medical care for their cancer treatment. However, recognition and screening for mental health disorders has been found to be suboptimal in cancer patients [17, 21]. Nonetheless, regardless of the causality of the mental health disorder, a diagnosis of the mental illness disorder and proper treatment is essential to provide adequate cancer and survivorship care [22].

OS was decreased in endometrial cancer patients diagnosed with anxiety and CSS was decreased in patients with anxiety and all mental health disorders combined. This is consistent with other types of cancers showing a worse prognosis for cancer patients with a mental health disorders [15–17, 23, 24]. A mental health disorder could exacerbate the challenges every cancer patient experiences including treatment toxicities, fear of recurrence and financial burden. Patients experiencing a mental health disorders tend to have worse coping skills, increased stress and lack of support, all of which can impair treatment. Patients with untreated mental health disorders have been found to feel more barriers to cancer treatment [25] and receive inadequate treatment [26, 27]. Numerous studies have shown that patients with untreated mental health disorders have poorer health and coping styles, decreased compliance with medical care, prolonged hospital stays, and increased suicide risk, all of which can ultimately lead to increased mortality [17, 28–32]. However, it is interesting to note that all-cause mortality in general has been shown to be more than two fold higher in patients with mental health disorders than the general population [33]. Thus, whether a decrease in OS is associated solely with the mental health disorder or the extra challenges that a cancer patient with a mental health disorder may experience is a challenge to quantitate. Nevertheless, it is essential for oncology physicians to recognize mental illness and take the necessary steps to ensure the patient receives adequate treatment.

In this study, we also found tri-modality therapy to have an association with mental health disorders and anxiety disorders compared to any other treatment type and advanced disease to have an association with mental health, anxiety and depressive disorders. While tri-modality therapy may independently increase the rate of mental health disorders and anxiety, more advanced stages of endometrial cancer typically require tri-modality therapy, which could confound these data. A correlation between advanced disease and increasing depression and anxiety is logical, although, studies show mixed results [23, 25, 34].

To our knowledge, this is the largest population-based study with the longest follow-up investigating mental health disorders in endometrial cancer survivors. The Utah Population Database is unique in that is has the ability to capture survivorship medical diagnoses linked to EMRs. Thus, the Utah Population Database was able to link different mental illness diagnoses in endometrial cancer survivors. The long term follow up and extensive number of patients make this database particularly valuable. As with any population database study, there are limitations to our analysis and interpretation of the results. The subject cohort was statistically different at baseline from the general population in BMI, CCI, and tobacco use, which may be a contributing factor differences seen. There was also a lack of diversity in the population cohort. There are no patient reported outcomes and all mental health disorders, in-

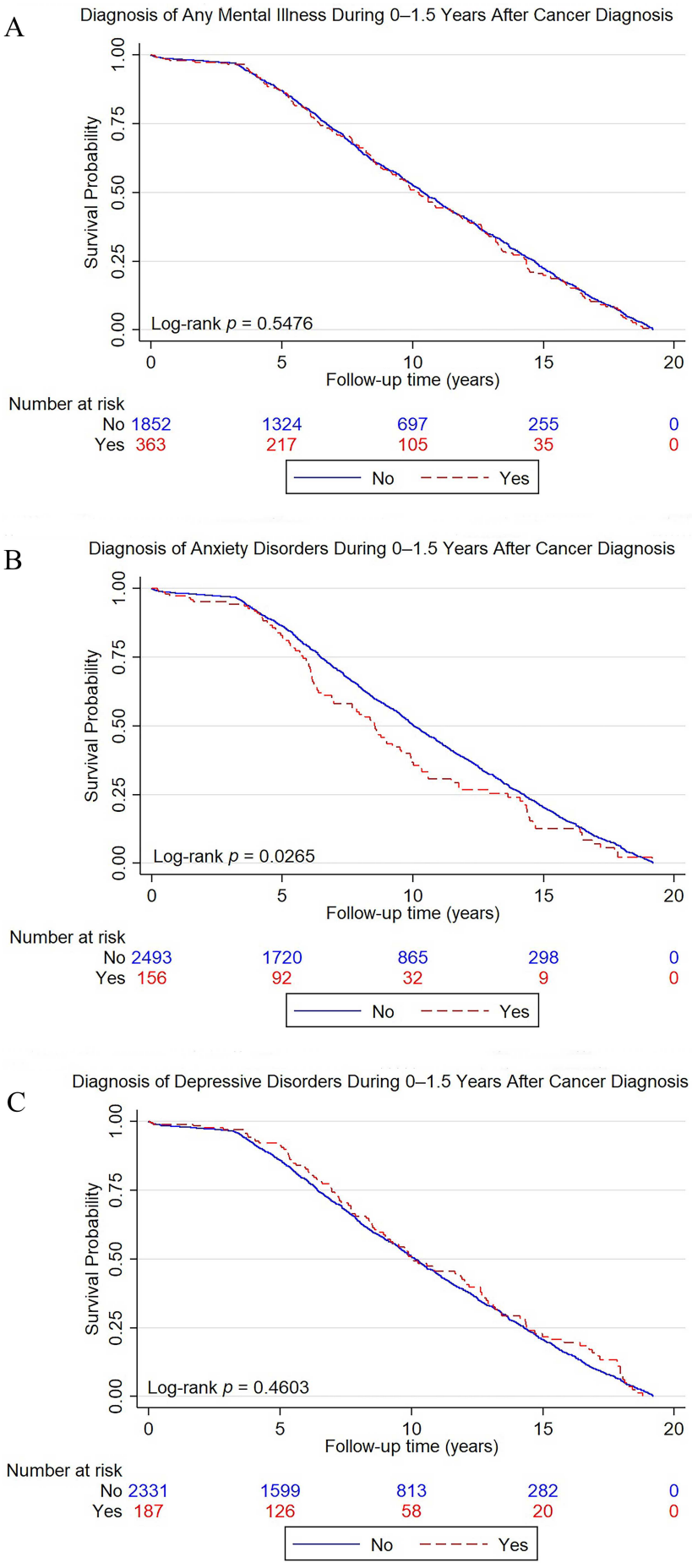

FIGURE 1. Survival Estimates for endometrial cancer survivors with a diagnosis of any mental illness during 0–1.5 years after cancer diagnosis with 20 year follow up (A) anxiety disorder (B) and with a diagnosis of depression (C).

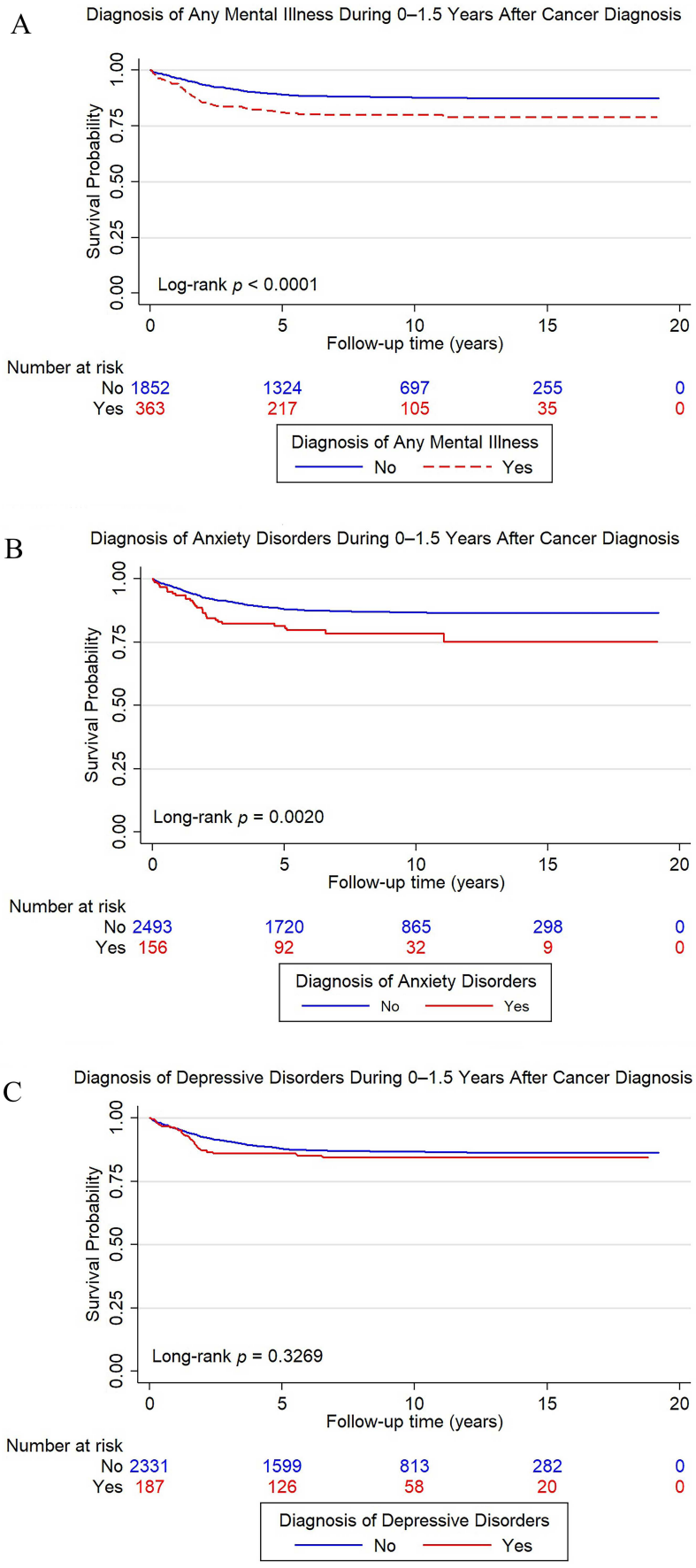

FIGURE 2. Survival Estimates for cause of death due to endometrial cancer for endometrial cancer survivors with a diagnosis of any mental illness during 0–1.5 years after cancer diagnosis with 20 year follow up (A), anxiety disorder (B) and with a diagnosis of depression (C).

cluding anxiety and depression, are solely based on a physician diagnosis and documentation in the electronic medical record (EMR). It is plausible that many endometrial cancer survivors felt anxiety and depression symptoms but did not meet DSM-V criteria and thus they never received a documented diagnosis. It is also possible an ICD-9 mental health disorder diagnosis was made without meeting strict diagnostic and statistical manual of mental disorders (DSM)-V criteria. The variation amongst physician's diagnosis of a mental health disorder could not be accounted for. There are many other psychosocial issues that do not have a DSM-V diagnosis including sexual dysfunction, stress, socioeconomic factors, that effect patients quality of life and potentially survivorship outcomes that could not be accounted for. Mental health disorders could also be affected by socioeconomic factors, which were not factored into this analysis

Regardless of the limitations, this study provides valuable information on mental health disorders in endometrial cancer patients. With a strong association between mental health disorders and endometrial cancer patients, as well as, the negative impact of anxiety on OS and CSS, it is important for oncologists to recognize and help provide appropriate management to these patients. National guidelines recommend screening for all patients prior to their oncology visit. Many screening tools are available; however, the National Comprehensive Cancer Network's Distress Management Guidelines provides a quick evaluation tool utilizing the distress thermometer and accompanying problem list [35]. Recognizing mental health disorders in cancer patients is the first step toward improvement. Future prospective studies should look at integration mental health screening tools, management of mental health issues and outcomes in cancer patients.

5. Conclusions

This study shows that within the first year and a half of endometrial cancer diagnosis there is a 2 to 3 fold increase in mental health disorders compared to the endemic rate. Endometrial cancer patients with a diagnosis of anxiety had a decrease in OS and CSS. All mental health disorders combined there was a decrease in CSS in endometrial cancer patients. Thus, it is critical for oncology physicians to recognize mental illness disorders in cancer patients and assure that patients receive adequate support and treatment.

AVAILABILITY OF DATA AND MATERIALS

The data for this project is available by applying to the Resource for Genetic and Epidemiologic Research (RGE), the oversight committee for the UPDB.

AUTHOR CONTRIBUTIONS

LB, MH and DG—designed the research study. YC, AF, JS, VD and MN—performed the research. LB, YC, MH and DG—analyzed the data. LB and YC—wrote the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Studies using the Utah Population Database data have been approved by the University of Utah's Resource for Genetic and Epidemiologic Research and its Institutional Review Board (No. 65816).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.ejgo.net/files/article/1625738632221343744/attachment/Supplementary%20material.zip.

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