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ORIGINAL RESEARCH

Risk factors for developing depression in women with cervical cancer: a nationwide population-based study in Taiwan

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Introduction: Depression might affect women with cervical cancer and can deteriorate their quality of life or even their compliance with cancer treatments. The aim of this study was to investigate the incidence of depression and risk factors for developing depression among women with cervical cancer in Taiwan.

Patients and methods: This study enrolled patients with newly diagnosed cervical cancer from the National Health Insurance Research Database in Taiwan. From a population of 21,400,826 residents, each cervical cancer patient was matched with one subject without cervical cancer according to sex, age, and comorbidities with the same diagnostic index. The International Classification of Diseases, Ninth Revision, code 180.9 was used to identify patients with cervical cancer, and 296.0X–296.1X, 296.4X–296.8X, 296.2X–296.3X, 300.4, and 311.X codes were used to identify those with depressive disorders.

Results: In total, 19,316 newly diagnosed cervical cancer patients were enrolled from January 2000 to December 2005, and the median follow-up period was 5.23 years (1.75–8.48 years). The prevalence of depressive disorder was 4.21% (813 of 19,316) in the cervical cancer cohort, and it was 3.85% (744 of 19,316) in the control cohort. The incidence risk ratio of depressive disorders was 1.35 (95% CI =1.22–1.49, $P<0.001$) among these cervical cancer patients. Cervical cancer, as an independent risk factor, was associated with developing subsequent depressive disorder. In addition, being older (≥65 years old) and the comorbidities of diabetes mellitus, ischemic heart disease, and cerebrovascular disease were also risk factors for predicting depressive disorder in cervical cancer patients.

Discussion: Cervical cancer is a prominent risk factor for the development of depression in women with cervical cancer in Taiwan. The patients with comorbidities, including diabetes mellitus, ischemic heart disease, and cerebrovascular disease, have higher risks of developing depression. However, there were no significant differences among the cervical cancer treatment modalities. In conclusion, these patients require early psychological support and intervention.

Keywords: cervical cancer, depression, risk, epidemiology, NHIRD

Introduction

Globally, cervical cancer is the third most prevalent cancer (9%, n=529,800 per year) and the fourth cause of cancer mortalities (8%, n=275,100 per year) in women.[1] Women with early-stage cervical cancer may not present with severe symptoms, and there is only occasional abnormal vaginal spotting, which might be easily neglected. Owing to the early diagnosis tool using cervical Papanicolaou smear, the incidence of invasive cervical cancer is declining gradually. However, cervical cancer is still one of the leading causes of cancer death in the developing countries, and women with this

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disorder are not only in jeopardy but also facing the enormous financial cost accompanied with cervical cancer treatments.[2] For managing women with cervical cancer, the treatment is cone biopsy or simple hysterectomy in patients with stage 1A cancer; radical hysterectomy plus pelvic lymphadenectomy in patients with stage 1B cancer; and primary external radiotherapy, brachytherapy, and concomitant chemoradiotherapy (CCRT) in patients with more advanced stages of cancer.[3] As cervical cancer survivors have fairly high 5-year survival rates, the outcomes and quality of life (QoL) for survivors are of great importance.[4] Following cervical cancer diagnosis and treatment, survivors might face the side effects and deterioration of QoL, including sleep disturbance and fatigue;[5] urologic disorders (urinary frequency, dysuria, and bladder empty difficulty);[6] gastrointestinal symptoms (nausea, vomiting, diarrhea, and bowel obstruction);[6] lymphedema;[4,7] sexual dysfunction (short and tight vagina, dyspareunia, lack of libido, and vaginal dryness);[8] menopausal symptoms and infertility;[4,9] and even psychological symptoms (depression and anxiety).[7]

Depression or major depressive disorder includes many different disorders and is characterized by low mood, difficulties in decision-making and thinking, loss of energy, loss of pleasure and interest in joyful activities, sleep and appetite annoyances, psychomotor annoyances, and suicidal thoughts.[9,10] Acute and strong pressures often arise following cancer diagnosis,[11] and the cancer patients are prone to suffer from subsequent depression,[12–15] which might influence 10%–25% of them.[16,17] In addition to physical discomfort, cancer patients commonly have to manage financial burden and emotional distress.[18,19] Depressed patients might possess noncompliance with treatment recommendations, in addition to the impact of general functions and QoL.[20] Moreover, patients who receive chemotherapy cancer treatments, such as platinum-based chemotherapy, might experience lagged symptoms, including sleep annoyances, depressed mood, and fatigue.[5]

Patients with cervical cancer have an especially high prevalence of psychiatric symptoms, and the prevalence rate of depression in cervical cancer patients is 33%–71.3% according to the retrospective observational studies.[21–24] Moreover, depression negatively affects QoL and has potentially detrimental effects on immune functions and prognosis.[8,25] In addition to the education about adherence to treatment and follow-up plans for cervical cancer survivors, comprehensive and supportive counseling is especially required to reduce psychosocial morbidity and to improve QoL.[26–29] However, the rates of diagnostic recognition of depression in women after being newly diagnosed with cervical cancer are inconclusive.[21–24] In addition, the exact mechanism of depression among these patients has not yet been documented.

The present study aimed at identifying the incidence and risk factors for developing depression in women with cervical cancer using a nationwide database in Taiwan. In addition, we also examined how depression relates to age and demographic variables to identify susceptibility.

Patients and methods

Data sources

In Taiwan, >96% of residents are covered by the National Health Insurance (NHI) program, and 93% of medical institutions are contracted to the administration of the NHI. Through the contracted institutes, the insurance beneficiaries may utilize health services.[30] The NHI Research Database (NHIRD), regarded as a population-based source, can be employed to search for a patient's date of diagnosis, medical treatments, chemotherapy, and radiotherapy. In this study, a cervical cancer patient cohort and a control cohort were identified using the encrypted NHIRD ensured by the administration of NHI and the National Health Research Institute.

Study population

This study was approved by the Institutional Review Board of Taipei Veterans General Hospital (No 2012-12-012BC), and the Board is organized under and is operated according to the International Conference on Harmonisation/World Health Organization Good Clinical Practice and the applicable regulations and laws. Cervical cancer patients were identified using the discharge codes (180.9) of the International Classification of Diseases, Ninth Revision, clinical modification (ICD-9-CM) in the Registry of Catastrophic Illness, and there were 19,316 cervical cancer patients between January 1, 2000, and December 31, 2005, who were followed up to December 31, 2006. A total of 2,315 patients were excluded due to antecedent depressive disorders before cervical cancer diagnosis. Depression was defined by compatible ICD-9-CM codes (296.0X–296.1X, 296.4X–296.8X, 296.2X–296.3X, 300.4, and 311.X) and concomitant prescription of psychotropic agents for at least 30 days.[31–33] The comorbidities, surgeries, and treatments in these cancer patients were collected for analysis.

Control cohort

Cervical cancer patients were matched with noncancer subjects by age, sex, and the existence of comorbidities

with the same index from 1,000,000 NHI beneficiaries of 21,400,826 enrollees. Outcome and mortality were predicted broadly using the Charlson comorbidity index.[34–36] Subjects with antecedent depressive disorders were excluded from the control cohort.

Statistical analyses

The incidence of depressive disorder was the main dependent variable. The two groups were followed up until the development of depressive disorder, the end of the study period (2006), or death. Incidence rates emerged per 1,000 person-years and incidence rate ratios (IRRs) were evaluated. Comparisons between the two groups were performed using the chi-squared test for categorical variables. The cumulative incidence was used with the Kaplan–Meier method. Risk factors for developing depression were identified using a Cox proportional hazard model. Sex, age, comorbidities, surgeries, cancer treatments, prescription of drugs, and drug administrations were included. Using Perl programming language (Version 5.12.2), the extraction and computation of data were performed. Data sampling, processing, and linking were performed using Microsoft SQL Server 2005 (Microsoft Corporation, Redmond, WA, USA). Statistical analyses were conducted using SPSS statistical software (Version 19.0; IBM Corporation, Armonk, NY, USA), and $P<0.05$ was considered statistically significant.

Results

Clinical characteristics of the study population

As shown in Table 1, there were 19,316 newly diagnosed cervical cancer patients from January 2000 to December 2005, and the median follow-up period was 5.23 years (1.75–8.48 years). Sex, age, and all comorbidities were matched. The age range was from 44 to 66 years, and the median age was 55.16 years. Hypertension (30.9%), diabetes mellitus (16.2%), and ischemic heart disease (13.7%) were the most frequent comorbidities. There was a longer median follow-up period for the matched group (6.44 years) than that for the cervical cancer group (5.23 years; $P<0.001$ by Mann–Whitney U test).

Incidence rates of depression

As shown in Table 2, 1,557 patients (4.0%) of the total 38,632 NHI beneficiaries were diagnosed with depression. The incidence rates were 8.1 per 1,000 person-years in the cervical cancer cohort and 6.0 per 1,000 person-years in the control cohort. The prevalence rates of depression were 4.21% (813 of 19,316) in the cervical cancer cohort and 3.85% (744/19,316) in the control cohort. There was a significantly higher cumulative incidence of depression in the cervical cancer cohort than that in the control cohort ($P<0.0001$). The IRR was 1.35 (95% CI =1.22–1.49, $P<0.0001$) in the cervical cancer cohort.

Table 1 Baseline characteristics of patients with and without cervical cancer

Demographic data	Patients with cervical cancer (n=19,316)		Matched cohort (n=19,316)		*P*-value
	N	%	N	%	
Age, years (interquartile range)	55.16 (44–66)		55.16 (44–66)		1.000
≥65	5,278	27.3	5,278	27.3	1.000
<65	14,038	72.7	14,038	72.7	1.000
Sex					
Female	19,316	100.0	19,316	100.0	1.000
Comorbidities					
Diabetes mellitus	3,137	16.2	3,136	16.2	1.000
Hypertension	5,967	30.9	5,969	30.9	0.982
Congestive heart failure	1,105	5.7	1,103	5.7	0.983
COPD	2,359	12.2	2,360	12.2	1.000
Chronic kidney disease	1,616	8.4	1,614	8.4	0.985
Cirrhosis	221	1.1	200	1.0	0.327
Autoimmune disease	1,020	5.3	1,020	5.3	1.000
Cerebrovascular disease	1,596	8.3	1,594	8.3	0.971
Ischemic heart disease	2,650	13.7	2,650	13.7	1.000
Follow-up years, median (interquartile range)	5.23 (1.75–8.48)		6.44 (3.44–9.56)		<0.001

Table 2 Incidence of depression occurrence among patients with and without cervical cancer[a]

	Patients with cervical cancer		Matched cohort		Risk ratio (95% CI)	*P*-value
	Number of events	Per 1,000 person-years	Number of events	Per 1,000 person-years		
Total	813	8.1	744	6.0	1.35 (1.22–1.49)	<0.0001
Age						
≥65	237	10.1	239	7.7	1.32 (1.10–1.58)	0.0026
<65	576	7.4	505	5.4	1.37 (1.22–1.55)	<0.0001

Note: [a]Adjusted for age, sex, diabetes mellitus, hypertension, dyslipidemia, congestive heart failure, chronic obstructive pulmonary disease, chronic kidney disease, cirrhosis, autoimmune diseases, cerebrovascular disease, and ischemic heart disease.

There were also differences in the IRR of depression in patients stratified by age, as shown in Table 2. There was a significantly higher IRR in patients aged ≥65 years or aged <65 years than that in the control cohort (IRR =1.32, 95% CI =1.10–1.58, *P*=0.0026 in age ≥65; IRR =1.37, 95% CI =1.22–1.55, *P*<0.0001 in age <65).

Risks factors for developing depression in the two cohorts

As shown in Table 3, cervical cancer was a prominent risk factor for developing depression in the two cohorts (HR =1.36 [1.23–1.50], *P*<0.001). Older age (>65 years), diabetes mellitus, cerebrovascular disease, and ischemic heart disease were associated with higher HRs for developing depression.

Treatment modalities and depression

As shown in Table 4, no treatment modality for cervical cancer was associated with a high HR of depression, and all the results were not significantly different.

Discussion

In our study, cervical cancer was a prominent risk factor for the development of depression in women with cervical cancer. In addition, comorbidities, including diabetes mellitus, ischemic heart disease, and cerebrovascular disease, were the predisposing factors for developing depression in the cervical cancer patients.

The merit of the present study is due to the claim-based data set, and the data related to medical charges, such as medication and examinations, were precise. The certification of catastrophic diseases can dispense patients from related medical charges, while it is very difficult to verify catastrophic diseases in the NHI system.[30] Biopsy is required for the catastrophic diagnosis of cervical cancer, and depression is confirmed by the prescription of anti-depressant medications for >30 days. Thus, the diagnoses of cervical cancer and depression in the present study were highly reliable and exhaustive through these restricted certification processes.[30]

In agreement with previous studies, there was also an increased risk of depression in cervical cancer patients in the present study. Other than the diagnosis of depression with antidepressant prescription records, most studies have used the outcome of depressive symptoms.[21–24] Therefore, the prevalence rate of depression following cervical cancer is much lower in the present study than that in the previous studies.

Table 3 Analyses of risk factors for depression among patients with and without cervical cancer

Predictive variables	Univariate analysis		Multivariate analysis[a]	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Cervical cancer[b]	1.35 (1.22–1.49)	<0.001	1.36 (1.23–1.50)	<0.001
Age ≥65 (≥65=1, <65=0)	1.38 (1.24–1.54)	<0.001	1.15 (1.02–1.30)	0.027
Comorbidities				
Diabetes mellitus	1.41 (1.24–1.61)	<0.001	1.16 (1.00–1.33)	0.043
Hypertension	1.37 (1.24–1.53)	<0.001	1.07 (0.94–1.22)	0.317
Congestive heart failure	1.69 (1.38–2.06)	<0.001	1.20 (0.97–1.50)	0.098
COPD	1.23 (1.06–1.43)	0.006	0.99 (0.85–1.16)	0.902
Chronic kidney disease	1.34 (1.12–1.60)	0.002	1.10 (0.91–1.33)	0.323
Cirrhosis	1.69 (1.06–2.69)	0.027	1.46 (0.92–2.33)	0.112
Autoimmune disease	1.28 (1.03–1.59)	0.026	1.11 (0.89–1.39)	0.337
Cerebrovascular disease	1.69 (1.44–2.00)	<0.001	1.34 (1.13–1.60)	<0.001
Ischemic heart disease	1.61 (1.41–1.83)	<0.001	1.27 (1.09–1.48)	0.002

Notes: [a]All factors with *P*<0.1 in the univariate analyses were included in the Cox multivariate analysis. [b]Treatment was analyzed as a time-dependent covariate in the Cox regression model.

Table 4 Analyses of risk factors for depression among patients with cervical cancer

Predictive variables	Univariate analysis		Multivariate analysis[a]	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age ≥65 (≥65=1, <65=0)	1.35 (1.16–1.57)	<0.0001	1.12 (0.94–1.34)	0.204
Comorbidities				
Diabetes mellitus	1.48 (1.24–1.77)	<0.0001	1.28 (1.05–1.55)	0.013
Hypertension	1.30 (1.12–1.50)	<0.0001	1.00 (0.83–1.19)	0.958
Congestive heart failure	1.95 (1.50–2.53)	<0.0001	1.55 (1.16–2.07)	0.003
COPD	1.16 (0.94–1.43)	0.178		
Chronic kidney disease	1.36 (1.05–1.75)	0.019	1.11 (0.85–1.45)	0.447
Cirrhosis	1.66 (0.86–3.21)	0.130		
Autoimmune disease	1.12 (0.81–1.54)	0.495		
Cerebrovascular disease	1.65 (1.31–2.08)	<0.0001	1.34 (0.34–1.02)	0.022
Ischemic heart disease	1.41 (1.17–1.71)	<0.0001	1.07 (0.86–1.33)	0.554
Treatments[b]				
Surgery alone	0.77 (0.67–0.90)	<0.001	0.87 (0.73–1.05)	0.143
Surgery with neoadjuvant and/or adjuvant chemoradiotherapy	1.16 (1.01–1.34)	0.043	1.12 (0.94–1.33)	0.206
Chemoradiotherapy without surgery	1.08 (0.92–1.26)	0.351		

Notes: [a]All factors with $P<0.1$ in the univariate analyses were included in the Cox multivariate analysis. [b]Treatment was analyzed as a time-dependent covariate in the Cox regression model.

Depressed patients present with a state of low mood and loss of enthusiasm for joyful activities, while lowered self-esteem, worthlessness, hopelessness, or suicidal ideation may affect cancer patients with depression.[37] The etiology of psychiatric symptoms in cervical cancer survivors may be related to physical stressors of surgical menopause, chemotherapy, radiotherapy, and physical discomforts associated with cancer treatments.[4–9] Thus, these mood disturbances might influence treatment compliance, reduce the QoL, and lower performance status.[8,25] Treatment with surgery plus CCRT, CCRT alone, or surgery alone is not associated with developing depression. Surgery or CCRT may cause a number of disagreeable adverse effects, often largely decreasing QoL and influencing the risk of depression.[24,38,39]

Depressed patients might experience more severe cancer-related symptoms, endure more functional impairment, use more health care resources, require a longer period to heal, and have a higher risk of suicide.[40] When patients with comorbidities are diagnosed with cervical cancer, care and prevention of depressive mood should be given special attention. In the present study, cervical cancer patients with comorbidities, including diabetes mellitus, cerebrovascular disease, or ischemic heart disease, had a higher risk of subsequent depression. Thus, early intervention of the psychiatric condition in cancer patients may reduce depression and even may improve QoL and adherence to cancer treatments.[14,26,28,41] Preventing the development of depression and other psychiatric symptoms can improve patients' QoL.[27] Moreover, there are increasing shreds of evidence that lessening psychiatric symptoms may improve the efficacy of treatment.[42] Chronic stress, including surgical stress, has a negative effect on the immune system by impairing antigen presentation, inhibiting natural killer (NK) cells, suppressing T-cell cytotoxic activities and T helper 1 (Th1) cytokines, increasing regulatory T cells,[43] and subsequently impeding the ability to combat cancer cell progression.[44–46] Thus, psychosocial intervention executed with cancer patients in active medical treatment or diagnostic phases has revealed both null and positive results regarding survival.[47–49] Moreover, psychiatric intervention for cancer survivors also significantly enhanced active coping, increased NK cell cytotoxicity, and reduced distress.[50] In addition, psychological intervention could alter neuroendocrine levels, such as cortisol levels,[51] and immune function indicators, especially Th1 cytokine production and lymphocyte proliferation.[52] There were a significantly longer time to recurrence and a longer survival over a 10-year follow-up period in early-stage melanoma patients who received 6-week cognitive–behavioral stress management than those of patients receiving standard care and surgery alone.[53] Furthermore, ~2 years after completing treatment, 57% of gynecological cancer patients stated that they had required support in coping with disease-related emotions, while 35% of patients actually had received such assistance. In addition, 73% of patients suggested that the care team should query whether cancer patients require assistance in coping with emotions.[54] It is recommended that physicians routinely inquire about patients' concerns and offer resources because cancer survivors may hesitate to raise demands.[55] However, there is a debate as to whether systematically providing patients an opportunity poses any worries or whether systematically screening depressive symptoms is more efficient and effective; however, screening

alone is clearly not sufficient. Thus, it is of great importance to offer cancer patients the implementation and availability of resources for long-term care.[56–58] In addition, it is also recommended to provide psychosocial care to survivors at treatment completion and later into survivorship. Cancer survivors suggested that they were inclined to gain specific cancer information, support services, or psychological support by themselves rather than from medical personnel after completing cancer treatment.[59] Therefore, oncology teams may provide more comprehensive survivorship care to these cancer patients through appropriate referrals to obtain adequate psychosocial resources.

There were several limitations in the present study. First, education, occupation, marital status, cancer staging, and family history of malignancy, which could be potential confounders, were not available in the analyses. Second, laboratory studies, such as estrogen, progesterone, or cortisol levels, were not available in the NHIRD. Third, we could not exclude depression diagnosed before the registry of the NHIRD (1995) and depression undiagnosed before cancer diagnosis. In addition, the status of depression could not be evaluated in the present study.

Conclusion

Cervical cancer is a prominent risk factor for developing depression following cervical cancer. Cervical cancer patients aged ≥65 years and those with diabetes mellitus, ischemic heart disease, and cerebrovascular disease also have a higher possibility of developing depression. Among the cervical cancer treatment modalities, patients showed no significant differences in the development of depression. Thus, the patients with risk factors require early psychological support and intervention to improve the QoL and the quality of care.

Disclosure

The authors report no conflicts of interest in this work.

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