Submitted: 23 October, 2023 Accepted: 15 November, 2023 Published: 30 May, 2024 DOI:10.22514/jomh.2024.073

ORIGINAL RESEARCH

JOMH Journal of Men's Health

Interaction effects between depression and gender on risk of cancer

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Abstract

Despite the recognized association between depression and cancer risk, there remains a paucity of research exploring the gender-specific variations in this relationship. Our study using prospective cohort data, aimed to investigate the relationship between depression and cancer risk, and to discern how this association varies by gender. Utilizing the Korea Genome and Epidemiology Study (KoGES) prospective cohort data, our primary exposure variables were depression and sex. The occurrence of cancer served as the main outcome of interest. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox regression analysis. To assess the interaction effects of depression and sex on cancer incidence, an interaction analysis was conducted. In cox proportional logistic regression analysis, depression was not associated with cancer risk (HR: 1.14, 95% CI, 0.85–1.51). However, for interaction analysis, in the male group, depression was not identified as a risk factor for cancer, with a HR of 0.88 (95% CI, 0.52–1.48). Conversely, in the female group, depression was associated with a heightened risk of cancer, demonstrating an HR of 1.35 (95% CI, 1.06–1.90) (p for interaction < 0.10). In our study, while depression emerged as a risk factor for cancer in females, it paradoxically appeared to have a protective effect against cancer in males. This underscores the importance of adopting sex-specific strategies in treating depression, potentially aiding in tailoring cancer risk reduction approaches, particularly for males.

Keywords

Depression; Gender; Cancer

1. Introduction

Cancer stands as a formidable adversary in the global health landscape, claiming millions of lives annually and posing relentless challenges to medical and public health communities alike [1]. According to the World Health Organization, in 2020 alone, nearly 10 million lives were extinguished by this complex disease, a number exacerbated by rapidly aging populations and increasing adoption of lifestyle behaviors that potentiate cancer risk [2]. From an economic lens, the ramifications are daunting; cancer care expenditures have skyrocketed, crossing an unprecedented US$ 1.16 trillion every year. For regions grappling with limited health infrastructure, particularly low- and middle-income countries, the weight of this challenge is even more pronounced, marked by strained resources and late diagnoses [3, 4]. As researchers unravel the complexities of cancer's origins, it's evident that the disease results from an intricate dance between genetic predispositions, environmental factors and lifestyle choices [5, 6]. Traditionally recognized risk factors, ranging from genetic makeup and age to exposure to harmful agents and lifestyle practices, have been at the forefront of preventive strategies. However, as the tapestry of cancer research continues to expand, emergent evidence is shining light on less conventional risk determinants [7, 8]. Among these, the role of psychosocial factors, notably depression, is gaining attention, suggesting a deeper nexus between mental health and cancer susceptibility [9, 10].

Depression stands as one of the paramount mental health challenges globally, with its prevalence steadily on the rise [11, 12]. Rooted in diverse causes—from stress and genetics to chemical imbalances and environmental triggers—depression casts a wide net of influence. Recent studies have increasingly highlighted the robust association between depression and physical health, especially chronic diseases. The relationship between cancer and depression, in particular, has garnered significant attention [9, 13]. It's suggested that depression might elevate the risk of cancer onset and that a notable fraction of cancer patients experience symptoms of depression [14]. Indeed, research indicates that up to one-third of cancer patients may suffer from depression at some point during their illness, significantly impacting their treatment adherence, recovery and overall quality of life [15]. The physical and psychological stresses induced by depression are believed to influence the inception and progression of cancer [13]. While it's not posited that depression directly causes

cancer, there's evidence suggesting that it might negatively impact cancer patients' survival rates, treatment outcomes, and overall quality of life. Such intricate interactions underscore the need for a deeper understanding of the relationship between depression and cancer.

Furthermore, an intriguing dimension of this relationship is the role of gender [16]. Both depression and cancer manifest differently across genders due to a myriad of biological, psychological and sociocultural factors. Some studies suggest that men and women might experience and express depressive symptoms differently, which could, in turn, influence how their bodies respond to stressors linked to cancer risks [17]. Moreover, the biological differences, hormonal fluctuations, and even societal roles might mediate the potential link between depression and cancer risk in both genders [18]. Recognizing and understanding these gender-specific nuances can pave the way for more tailored preventive strategies and interventions. Thus, exploring the gendered interplay between depression and cancer risk becomes paramount in providing a comprehensive view of this multifaceted relationship.

Thus, our study using prospective cohort data, aimed to investigate the relationship between depression and cancer risk, and to discern how this association varies by gender.

2. Methods

2.1 Study design and data sources

The Korean Genome Epidemiology Study (KoGES) began two separate prospective cohort research projects in 2001. These projects were carried out in two distinct areas: Ansung, a rural region with around 176,000 inhabitants in 2010, and Ansan, an urban center housing close to 715,000 people that same year. Participants from both cohorts are Korean men and women, aged 40 to 69, who all come from a homogeneous ethnic background. Comprehensive methodologies, such as the methods of sampling and inclusion criteria, can be found in earlier works. During 2001 and 2002, Ansung identified 7129 suitable participants, while Ansan identified 10,957. From these, 5018 individuals in Ansung (comprising 2239 men and 2779 women) and 5020 in Ansan (made up of 2523 men and 2497 women) took part in initial examinations. These participants underwent regular evaluations until the study's conclusion, with the final, 9th evaluation taking place between 2019 and 2020. Interviewers, who follow a uniform set of instructions, undergo refresh training biennially. Throughout the study, cohort members were monitored at consistent intervals, including planned visits to the sites every other year.

2.2 Study population and definition of cancer

KoGES data included biennial follow-up assessments of patient information, beginning with the baseline survey in 2003–2004. For the analysis, we excluded participants who were reported physician diagnosed cancer and who were not reported depression history at the time of baseline survey. Participants who did not have a history of cancer at the time of the baseline survey, and during the biennial follow-up surveys commencing from 2005–2006, and those who reported being diagnosed with a cancer were classified as having a cancer.

2.3 Depression and other risk factors

Depression was categorized based on the beck depression inventory (BDI) scores. Participants were classified into 4 categories: no or slight depression (0–13), mild depression (14–19), moderate depression (20–28), and severe depression (29–63) [19]. We also collected demographic characteristics, including age, sex, marital status and education year; comorbidities, including hypertension and diabetes mellitus (DM) and health-related behavior, including body mass index (BMI), alcohol intake, smoking, physical activity and insomnia. Additionally, we measured and presented the serum levels of C-reactive protein (CRP).

2.4 Statistical analysis

We calculated descriptive statistics for the baseline characteristics of the study participants by depression and depression status. The baseline characteristics of participants from the KoGES were compared using the Wilcoxon rank sum test for continuous variables and the chi-square test for categorical variables. The crude 19-year (2001 to 2020) incidence rates of stroke were calculated as the number of risk cases per 1000 person-years based on the depression and gender. The hazard ratios (HRs) and 95% confidence interval (CIs) obtained from Cox proportional hazard regression models with fixed covariates were used to estimate the relative risks for 19-year cumulative stroke incidence based on depression and gender. Additionally, to investigate the impact of depression and gender on cancer risk, we conducted an interaction analysis between the two factors. We tested the multicollinearity between covariables in the model. All statistical analyses were performed using SAS version 9.4 software (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1 Demographic findings

During the 15 years of follow-up, we documented 299 cases of new-onset cancer (7.8 cases per 1000 person-years). The characteristics of the study participants according to history of depression status and severity of depression are presented in Table 1. Patient's demographics among the study participants, those diagnosed with depression had a significantly higher proportion of females, representing 57.3% compared to 45.0% in the non-depressed group. The occurrence of current smokers was noticeably higher in the group with depression. Insomnia symptoms were also more prevalent among individuals with depression, with 46.0% of them reporting insomnia compared to 34.9% in the group without depression. As for the cancer incidence, the data did not show a significant difference between those with and without depression, registering 10.5% and 9.0% respectively (p = 0.25). When participants were categorized based on the severity of their depression, ranging from no symptoms to mild, moderate and severe, there was no observed statistically significant variation in the risk of developing cancer across these groups (p = 0.60).

TABLE 1. Demographics of study population by depression and depression status.

Variables	All	Depression			Depression status				
	N (%)	No	Yes	*p*-value	No	Mild	Moderate	Severe	*p*-value
All	3222 (100.0)	2613 (100.0)	609 (100.0)		2613 (100.0)	327 (100.0)	162 (100.0)	120 (100.0)	
Age, year, mean (SD)	52.4 (7.37)	52.1 (7.19)	53.7 (7.98)	0.021	52.1 (7.19)	53.0 (7.61)	55.0 (8.41)	53.8 (8.20)	0.031
Sex, female	1524 (47.3)	1175 (45.0)	349 (57.3)	<0.001	1175 (45.0)	180 (55.0)	99 (61.1)	70 (58.3)	<0.001
Married, yes	2977 (92.4)	2442 (93.5)	535 (87.8)	<0.001	2442 (93.5)	293 (89.6)	141 (87.0)	101 (84.2)	<0.001
Educational period >9 years	2077 (64.5)	1757 (67.2)	320 (52.5)	0.003	1757 (67.2)	182 (55.7)	88 (54.3)	50 (41.7)	0.004
Comorbidity									
Hypertension	521 (16.2)	418 (16.0)	103 (16.9)	0.575	418 (16.0)	52 (15.9)	31 (19.1)	20 (16.7)	0.769
Diabetes mellitus	204 (6.3)	159 (6.1)	45 (7.4)	0.231	159 (6.1)	28 (8.6)	9 (5.6)	8 (6.7)	0.361
Body mass index									
<18.5 (under-weight)	26 (0.8)	20 (0.8)	6 (1.0)		20 (0.8)	4 (1.2)	2 (1.2)	(0.0)	
18.5–24.9 (normal)	1808 (56.1)	1442 (55.2)	366 (60.1)	0.069	1442 (55.2)	185 (56.6)	102 (63.0)	79 (65.8)	0.141
>25.0 (over-weight)	1388 (43.1)	1151 (44.0)	237 (38.9)		1151 (44.0)	138 (42.2)	58 (35.8)	41 (34.2)	
Health-related behavior									
Alcohol intake, yes	1678 (52.1)	1363 (52.2)	315 (51.7)	0.845	1363 (52.2)	168 (51.4)	83 (51.2)	64 (53.3)	0.981
Smoking									
Current smoker	574 (17.8)	458 (17.5)	116 (19.0)		458 (17.5)	62 (19.0)	32 (19.8)	22 (18.3)	
Former smoker	757 (23.5)	649 (24.8)	108 (17.7)	<0.001	649 (24.8)	63 (19.3)	27 (16.7)	18 (15.0)	0.021
Never smoker	1891 (58.7)	1506 (57.6)	385 (63.2)		1506 (57.6)	202 (61.8)	103 (63.6)	80 (66.7)	
Physical activity, vigorous	1624 (50.4)	1341 (51.3)	283 (46.5)	0.031	1341 (51.3)	158 (48.3)	77 (47.5)	48 (40.0)	0.007
Insomnia, yes	1193 (37.0)	913 (34.9)	280 (46.0)	<0.001	913 (34.9)	148 (45.3)	76 (46.9)	56 (46.7)	<0.001
CRP (mg/dL), median (q1, q3)	0.65 (0.34–1.40)	0.64 (0.34–1.37)	0.68 (0.35–1.49)	0.214	0.64 (0.34–1.37)	0.71 (0.35–1.49)	0.75 (0.34–1.79)	0.58 (0.36–1.14)	0.911
Total cancer cases	299 (9.3)	235 (9.0)	64 (10.5)	0.247	235 (9.0)	32 (9.8)	19 (11.7)	13 (10.8)	0.611

SD: standard deviation; CRP: C-reactive protein.

In Table 2, when analyzing demographic characteristics by sex, male participants demonstrated a significantly lower risk of developing cancer, with an incidence of 7.2%, in contrast to 11.5% in female participants, a difference that was statistically significant ($p < 0.01$).

3.2 Main outcomes

In the group without depression, there were 235 cases of cancer, reflecting an incidence rate of 7.5 per 1000 person-years and the group with depression demonstrated a cancer incidence rate of 9.2 per 1000 person-years. To explore the impact of exposure variables on cancer incidence, a Cox proportional logistic regression analysis was conducted, adjusting for all confounding variables. Following adjustment, depression was associated with a hazard ratio (HR) of 1.14 (95% CI, 0.85–1.51) in comparison to the non-depression group. However, in the male group, there were 6.1 cases of cancer per 1000 person-years, whereas in the female group, the rate was higher, with 9.8 cases per 1000 person-years. To investigate the potential influence of gender on cancer incidence, a Cox proportional logistic regression analysis was performed, accounting for all potential confounders. After making these adjustments, females exhibited a significantly higher risk, with a hazard ratio (HR) of 1.89 (95% CI, 1.28–2.80) for cancer incidence compared to males (Table 3).

3.3 Interaction analysis

Utilizing the Cox proportional regression for interaction analysis, sex-specific association between depression and cancer risk were observed. In the male group, depression was not identified as a risk factor for cancer, with a HR of 0.88 (95% CI, 0.52–1.48). Conversely, in the female group, depression was associated with a heightened risk of cancer, demonstrating an HR of 1.35 (95% CI, 1.06–1.90) (p for interaction < 0.10) (Table 4).

4. Discussion

Our study elucidates the intricate relationship between depression and cancer risk, unveiling a gender-specific dimension that has significant clinical and public health implications. The primary findings indicate that while depression was not associated with an elevated risk of cancer in males (HR: 0.88; 95% CI, 0.52–1.48), females with depression had a 35% increased risk (HR: 1.35; 95% CI, 1.06–1.90). This pronounced gender disparity underscores the importance of considering sex-based differences when examining depression as a potential risk factor for cancer.

Several merits stem from this research. Firstly, the identification of depression as a risk factor specifically in females can inform targeted preventive measures and screenings, allowing healthcare providers to more effectively address cancer risks in this population. By recognizing the heightened vulnerability among depressed females, clinicians can prioritize mental health interventions, not just for psychiatric well-being, but also as a potential avenue for cancer risk mitigation.

The relationship between depression and the risk of developing cancer has been a topic of investigation for many decades. Several studies have suggested a possible link between the two, although the nature of this relationship remains a subject of debate. Some research has pointed towards an increased risk of cancer among individuals with depression [20, 21]. This potential association might be attributed to biological mechanisms where the stress and physiological changes associated with depression might impact the immune system, potentially making an individual more susceptible to cancer [22]. Additionally, behavioral factors could play a role: individuals with depression might engage more frequently in behaviors that are known cancer risk factors, such as smoking, excessive alcohol consumption, and lack of physical activity. Furthermore, there's evidence suggesting that people with depression might experience barriers in accessing medical services, leading to delays in cancer diagnosis and treatment [23].

However, it's essential to note that several other studies have found no definitive association between depression and cancer risk [24–27]. These discrepancies could arise from variations in study designs, sample populations, and measurement techniques. Moreover, the directionality of the relationship is complex; while depression might increase the risk for certain cancers, a cancer diagnosis can also significantly elevate the risk of developing depression due to the immense stress and lifestyle changes associated with the disease. In our study, we also found no association between depression and the risk of cancer. Even when we categorized depression by its severity, there was no increased risk for cancer among those with severe depression [27]. This underscores the importance of viewing the relationship between depression and cancer with nuance, considering multiple factors, and not drawing premature conclusions.

Depression's influence as a risk factor for diseases can vary based on sex, and this is evident in various health conditions. For instance, depression seems to heighten the risk of cardiovascular disease more prominently in female than in male [28]. Similarly, females with depression are found to have an increased risk of stroke compared to their male counterparts [29]. The underlying reasons might be a complex interplay of hormonal changes, especially post-menopause, combined with the physiological impacts of depression. Furthermore, post-menopausal female with depression might face a greater risk of osteoporosis, possibly due to the convergence of hormonal shifts and behavioral factors associated with depression, such as reduced physical activity or inadequate nutrition. Notably, our recent study on cancer revealed a sex-specific nuance. While depression emerged as a potential risk factor for cancer in female, it did not show the same effect in male, emphasizing the necessity of a sex-specific approach when assessing the relationship between depression and health outcomes.

Our investigation into the relationship between depression and cancer risk has revealed a significant correlation for females, with depression acting as a notable risk factor for the onset of cancer. In contrast, this relationship was not observed in males. This sex-specific link might be attributed to different pathological characteristics of depression between sexes or perhaps varying biological responses to depression. The findings of our study underscore the vital importance of tailored mental health care, especially for female patients. Recognizing depression as a potential risk factor for cancer in females

TABLE 2. Demographics of study population by sex.

Variables	All	Sex		
	N (%)	Male	Female	*p*-value
All	3222 (100.0)	1698 (100.0)	1524 (100.0)	
Depression status				
No	2613 (81.1)	1438 (84.7)	1175 (77.1)	<0.001
Mild	327 (10.1)	147 (8.7)	180 (11.8)	
Moderate	162 (5.0)	63 (3.7)	99 (6.5)	
Severe	120 (3.7)	50 (2.9)	70 (4.6)	
Age, year, mean (SD)	52.4 (7.37)	52.2 (7.16)	52.7 (7.59)	0.051
Married, yes	2977 (92.4)	1646 (96.9)	1331 (87.3)	<0.001
Educational period >9 years	2077 (64.5)	1252 (73.7)	825 (54.1)	<0.001
Comorbidity				
Hypertension	521 (16.2)	282 (16.6)	239 (15.7)	0.481
Diabetes mellitus	204 (6.3)	120 (7.1)	84 (5.5)	0.069
Body mass index				
<18.5 (underweight)	26 (0.8)	13 (0.8)	13 (0.9)	0.241
18.5–24.9 (normal weight)	1808 (56.1)	930 (54.8)	878 (57.6)	
>25.0 (overweight)	1388 (43.1)	755 (44.5)	633 (41.5)	
Health-related behavior				
Alcohol intake, yes	1678 (52.1)	1253 (73.8)	425 (27.9)	<0.001
Smoking				
Current smoker	574 (17.8)	544 (32.0)	30 (2.0)	<0.001
Former smoker	757 (23.5)	743 (43.8)	14 (0.9)	
Never smoker	1891 (58.7)	411 (24.2)	1480 (97.1)	
Physical activity, vigorous	1624 (50.4)	894 (52.7)	730 (47.9)	<0.001
CRP (mg/dL), median (q1, q3)	0.65 (0.34–1.40)	0.70 (0.38–1.45)	0.59 (0.30–1.36)	0.382
Insomnia, yes	1193 (37.0)	524 (30.9)	669 (43.9)	<0.001
Total cancer cases	299 (9.3)	123 (7.2)	176 (11.5)	<0.001

SD: standard deviation; CRP: C-reactive protein.

TABLE 3. Cox-proportional logistic regression analysis for study outcomes.

Potential risk factors	Numbers at risk	Cancer events	Person-years	Incidence rate per 1000 PYS	Model 1 HR (95% CI)	Model 2 aHR (95% CI)	Model 3 aHR (95% CI)
Depression							
No	2613	235	31,344.9	7.5	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	609	64	6938.8	9.2	1.12 (0.85–1.48)	1.13 (0.85–1.50)	1.14 (0.85–1.51)
Depression Status							
No	2613	235	31,344.9	7.5	1.00 (reference)	1.00 (reference)	1.00 (reference)
Mild	327	32	3771.4	8.5	1.07 (0.73–1.55)	1.07 (0.74–1.56)	1.08 (0.74–1.57)
Moderate	162	19	1796.0	10.6	1.19 (0.74–1.91)	1.19 (0.74–1.92)	1.20 (0.74–1.94)
Severe	120	13	1371.4	9.5	1.18 (0.67–2.08)	1.20 (0.68–2.12)	1.21 (0.69–2.14)
Sex							
Male	1698	123	20,246.5	6.1	1.00 (reference)	1.00 (reference)	1.00 (reference)
Female	1524	176	18,037.2	9.8	1.58 (1.24–1.98)	1.59 (1.25–2.02)	1.89 (1.28–2.80)

PYS: person-years; aHR: adjusted hazard ratio; CI: confidence interval.
Model 1: adjusted for age and sex.
Model 2: Model 1 + adjusted for married status, education period, hypertension, and diabetes mellitus.
Model 3: Model 2 + adjusted for body mass index and health-related behavior including alcohol intake, smoking and physical activity.

TABLE 4. Interaction analysis between depression and sex for study outcome.

	Depression		
	No	Yes	*p* value
		aHR (95% CI)	<0.001
Male	ref.	0.88 (0.52–1.48)	
Female	ref.	1.35 (1.06–1.90)	

aHR: adjusted hazard ratio; CI: confidence interval; ref.: reference.

can have profound implications for both cancer prevention and depression management, emphasizing the need for early diagnosis and targeted intervention strategies. As we continue to delve deeper into the intricacies of this relationship, our study's results can serve as a catalyst for more comprehensive research, which in turn could reshape how we approach both mental health and cancer care in the future.

Our study presents several inherent limitations that should be carefully weighed. The most notable is the determination of depression. Instead of relying on a clinician's diagnosis, we based our assessment on the individual's self-reported Beck Depression Inventory (BDI) test, which might not provide a holistic clinical understanding of depression. Additionally, we did not make distinctions between different types of cancer that might exhibit varied prevalence among males and females. This lack of differentiation might mask specific relationships between depression and individual cancer types, especially when considering sex-based variations. While we used data from the KoGES dataset, it's worth noting that this might not wholly represent the broader Korean demographic due to potential biases such as certain age groups, regions or specific subsets. The longitudinal design of our research might have introduced certain biases, with the potential for shifts or alterations emerging during the study or between follow-up periods. The constraints of the KoGES dataset further limited our investigation, potentially causing us to overlook pivotal covariates that could have a considerable impact on our findings. Our study also sidestepped specific intricacies of some conditions. For instance, we did not differentiate between types of strokes or delve deeply into the nuances of secondhand smoke (SHS) and alcohol consumption, mirroring our approach to cancer types. Relying on self-reported data introduces another layer of complexity, as aspects like SHS exposure, alcohol intake, or past medical histories might be subject to recall or reporting inconsistencies. We also need to acknowledge that external variables, not captured by the KoGES dataset, or more recent medical advancements post-collection, could influence our results. Lastly, given the potential limitation in the number of cases, our study might occasionally lack the statistical vigor to detect subtle variations or outcomes. All these aspects should guide any interpretation and extrapolation of our findings.

5. Conclusions

In our study, depression, as assessed by the BDI test, was not found to be an independent risk factor for cancer development overall. However, the observed sex-specific differences underscore the potential importance of adopting sex-specific approaches in the treatment and management of depression to mitigate cancer risk, particularly among females.

AVAILABILITY OF DATA AND MATERIALS

Data in this study were from the Korean Genome and Epidemiology Study (KoGES; 6635-302), National Institute of Health, Korea Disease Control and Prevention Agency, Republic of Korea.

AUTHOR CONTRIBUTIONS

EJ and HHR—conceptualization, investigation, software, writing original draft, writing review and editing; EJ, HLK and HHR—data curation; EJ, SMJ and HHR—formal analysis, supervision; EJ—methodology. All authors have read and agreed to the published version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was reviewed and approved by the Institutional Review Board of Chonnam National University Hospital (CNUH-2018-297). The requirement for informed consent from patients was waived because the study was a retrospective analysis of existing data.

ACKNOWLEDGMENT

We express our sincere gratitude to all the dedicated staff members at the hospital who played an instrumental role in the collection of data for this study.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Eujene Jung, Soon Mi Jang, Hyun Lee Kim, Hyun Ho Ryu. Interaction effects between depression and gender on risk of cancer. Journal of Men's Health. 2024; 20(4): 76-82. doi: 10.22514/jomh.2024.073.