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Depression as a risk factor for overall and hormone-related cancer: The Korean cancer prevention study

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Abstract

Depression has been hypothesized to be a risk factor of cancer, especially hormone related cancers. However, few studies have been conducted with large enough sample size and sufficient follow up period to rigorously estimate these associations. We aim to examine the relationship between depression and risk of registry documented overall and hormone related cancers. In this 19 year prospective cohort study of general population, 601,775 Koreans aged 30 64 years had a biennial medical evaluation by the National Health Insurance Service in either 1992 or 1994. Major and minor depression was ascertained by a 9 item depression questionnaire. At baseline, major depression was identified in 7.4% and 10.2% and minor depression in 19.3% and 21.4% in men and women, respectively. During the follow up, 49,744 cancers were identified in men and 7860 in women. Prostate cancer in men was positively related to minor depression (HR 1.13, 95% CI 1.05, 1.23), and cervical cancer in women was inversely related to major depression (HR 0.90, 95% CI 0.83, 0.98) after adjusting for potential confounders. Regarding overall cancer, major depression was positively related to overall cancer in men (HR 1.04, 95% CI 1.00, 1.08) and inversely related in women (HR 0.90, 95% CI 0.83, 0.98). There was no association between breast cancer and depression. Different direction and magnitude of association among gender and cancer subtypes suggest different psycho behavioral and biological pathways in which depression may affect later cancer development. Further studies on the association of depression and cancer and the underlying mechanisms should be conducted on specific cancer subtypes.

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Conflict of interest

No conflict declared.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2014.10.064.

Keywords

Depression; Cancer; Prostate cancer; Cervical cancer; Republic of Korea

1. Introduction

Depression, psychiatric disorder characterized by extremely low mood and loss of interest in activities of daily life, is associated with biological alterations including increased cortisol levels and absence of normal cortisol suppression response (Belmaker and Agam, 2008). The lifetime prevalence of major depressive disorder, a severe form of depression, has been estimated to affect 14.6% in high income countries and 11.1% in low income countries (Bromet et al., 2011). In US, the lifetime prevalence of major depressive disorder is more than 12% in men and 20% in women (Kessler et al., 2003). Although the prevalence of depression in Eastern countries, including Korea, is somewhat lower than Western countries (Chang et al., 2008), it has been increasing rapidly during the past decade, from 4.0% in 2001 to 6.7% in 2011 (Cho, 2011). Depression is associated with substantial morbidity not only due to the disability associated with symptoms (World Health Organization, 2008), but also associations with chronic physical illness (Pan et al., 2011; Campayo et al., 2010). Understanding the full magnitude of the relation between depression and physical health is critical for public health, given the high prevalence and associated with disability of depression worldwide.

While depression is robustly associated with chronic illnesses with an inflammatory pathway such as stroke (Pan et al., 2011), cardiovas cular disease (Nicholson et al., 2006), diabetes mellitus (Campayo et al., 2010), fibromyalgia and chronic pain (Van Houdenhove et al., 2010) associations with outcomes such as cancer remain unresolved (Spiegel and Giese Davis, 2003). A recent meta analysis reported that depression presents a small and marginally significant association with subsequent overall cancer risk, but associations among different studies show considerable heterogeneity (Oerlemans et al., 2007). Among various subtypes of cancer, hormone related cancers have received most interest due to a number of plausible pathways hypothesized (Oerlemans et al., 2007). Hormone related cancers include breast cancer, prostate cancer, and endometrial and cervical cancer, and several potential mechanisms through which depression may influence the development of these cancers have been posited. Potential mechanisms include a role of sex hormones in both cancer and depression, dysregulation of hypothalamic pituitary adrenal (HPA) axis, increased cortisol response, and immunological and inflammatory pathways, and inhibition of DNA repair mechanisms (Spiegel and Giese Davis, 2003).

Inference from the literature on depression and hormone mediated cancer has been inhibited by several major limitations of existing data, suggesting that a gap in our understanding of depres sion and cancer remains unfulfilled. First, most studies have a follow up period of less than 20 years (Aro et al., 2005; Nyklicek et al., 2003), which are not long enough to detect many tumor with slow average growth patterns (Zonderman et al., 1989; Penninx et al., 1998). Second, a relatively small sample size limits the ability to analyze the data stratified by gender and specific cancer sites. In most studies, overall cancer incidence

among the depressed subjects does not exceed 100, with studies examining the subtypes of cancer resulting in even smaller incidences (Oerlemans et al., 2007; McGee et al., 1994), thus limiting the ability to uncover the association between depression and subsequent cancers. To maximize the power, most studies did not analyze by subtypes but examined overall cancer morbidity or mortality (Zonderman et al., 1989; Chen and Lin, 2011), which might result in over or under representation of association of depression and subsequent cancer risk. Moreover, there is no report to date on stratified analysis by gender, although the prevalence and risk factors for depression and cancer differ substantially across gender (Long et al., 2010). Third, depression was usually assessed at one time point, although it is the chronicity of the condition that is thought to underlie the pathways associating depression with cancer. Only one study known to authors examined chronic depression as an exposure and reported a significant association with overall cancer incidence (Penninx et al., 1998). Finally, the biological covariates were rarely adjusted in previous studies.

While cancer incidence is relatively rare in the population, given the high prevalence of depression, even a small association may translate into a major attributable risk for hormone mediated cancers. In effort to examine the relationship between depression and subsequent hormone mediated cancer risk, we use data from Korean Cancer Prevention Study (KCPS) to resolve these limitations. This cohort includes over 600,000 subjects, which allows us to analyze it by gender and specific cancer. In this study, we aim to investigate whether persons with major and minor depression were subsequently at higher risk of developing overall and hormone mediated cancer than persons without depressive symptoms.

2. Methods

2.1. Study subjects

The KCPS is a cohort study of South Korean workers and their dependants. Eligible participants were insured by the Korean Medical Insurance Service and underwent a biennial medical assessment during 1992 1995 (baseline). Since the study used routinely obtained data, consent was not required. The study was approved by institu tional review boards at Yonsei University (Seoul, South Korea).

From the KCPS cohort, we included 1,220,697 individuals (797,959 men and 422,738 women) aged 30 64 years who participated in the biennial medical evaluation offered routinely by the Korean National Health Insurance Service from 1992 to 1995. Of the 4 years of consecutive evaluation, depression questionnaire (Chang et al., 2013) was included in 1992 and 1994 examination, with 623,419 participants. Among them, 19,050 (3.1%) with missing information were excluded. A total of 2594 people reporting a history of any form of cancer and who died in the interval between questionnaire completion and start of follow up on January 1 of the subsequent year were also excluded. Of the participants, 601,775 (502,297 men and 99,478 women) were included in the final sample.

A subgroup of 546,514 participants (458,836 men and 87,678 women) who had undertaken both biennial examinations in 1992 and 1994 survey was analyzed separately to examine the relation ship between chronic depression and later cancer incidence.

2.2. Depression ascertainment

A short questionnaire was developed to assess depression. (Table 1). The construction of the questionnaire was based on the diagnostic criteria of Major Depressive Episode in Diagnostic and Statistical Manual of Mental Disorder 4th edition (DSM IV) (American Psychiatric Association, 1994). Items contained within the questionnaire drew on the Patient Health Questionnaire 9 (PHQ 9), an instrument used widely for evaluation of depression (Spitzer et al., 1999). Study subjects reported whether they were experiencing each of the nine depressive symptoms (yes/no answer). The response was based on current rather than prior state with no specific time frame of reference. Major depression was denoted as a positive response to at least one of the first two items ("Depressed mood" or "Loss of interest"), plus positive responses to at least five of the all nine items. Minor depression was denoted by a positive response to at least one of the two items but a total of less than five positive responses to the total of nine items. Concurrent validity of the questionnaire was examined by relating data to known socio demographic and behavioral correlates of depression, and predictive validity was presented by relating the scores from the questionnaire to the occurrence of future hospitalization for depression (Chang et al., 2013). Among a subset of the sample that undertook surveys in both 1992 and 1994, additional analysis was performed to examine whether chronic depression was defined as having major depression in both 1992 and 1994 surveys.

For further analysis, we divided major depression and minor depression into four categories. Major depression was divided into severe depression (a positive response to at least one of the first two items plus positive responses to at least seven of the all nine items) and moderate depression (a positive response to at least one of the first two items plus positive responses to five or six of the all nine items). Minor depression was divided into mild depression (a positive response to at least one of the first two items plus positive responses to three or four of the all nine items) and some depression (a positive response to at least one of the first two items plus positive responses to one or two of the all nine items).

2.3. Ascertainment of cancer

Cancer incidence, the primary outcome of interest, was ascer tained by National Cancer Registry data and hospitalization records from the medical insurance claims (MIC) data. Interna tional Classification of Diseases, Tenth Revision, used to ascertain cancer incidence and site are as follows: C50 Breast; C53 Cervix; C54 Corpus uteri; C56 Ovary; and C61 Prostate. The follow up period was up to December, 2012.

2.4. Other covariates

Covariates were collected from the biennial medical evaluation offered by the Korean National Health Insurance Corporation con ducted in 1992. It was conducted by medical staff at local hospitals and followed a standard procedure. Following variables were self reported and was used as categorical variable: Age (30 34, 35 39, 40 44, 45 49, 50 54, 55 59, and 60 64), marital status (married, never married, and else), smoking status (non smoker, ex smoker, and current smoker), drinking status (non drinker, 0 25, 25 50, 50 100, and more than 100 g/day), regular exercise (regular exercise, and no exercise), and cancer family history (yes or no). Socio economic status was measured by the insurance premium paid by

the employees to their medical insurance scheme. This financial mean is calculated based on employee's income plus assets, such as ownership of property and automobiles, and was divided into four quartile groups. Physical and laboratory examinations were con ducted to collect body mass index (kg/m^2), total cholesterol, fasting blood sugar, and hypertension.

2.5. Statistical analysis

To assess the independent effects of depression status on cancer incidence, Cox proportional hazard models were used. In model, age, demographics (marital status and socioeconomic status), health behaviors (smoking status, alcohol drinking, exercise and BMI) and biological indicators of subclinical illness (total cholesterol, blood sugar and hypertension) were adjusted to express the independent effects of depression status. In Cox proportional hazard models, participants with major and minor depression were compared with participants without any depression, and participants with chronic depression were compared with participants who were not depressed in both 1992 and 1994. All analyses were performed using SAS statistical software version 9.2 (SAS Institute, Cary, NC, USA). All statistical tests were two sided and statistical significance was determined as $p>0.05$.

3. Results

The population was evenly distributed between 30 and 64 years old, with approximately five times as many men as women (Table 1). Among 502,297 men and 99,478 women, 7.4% and 10.2% were identified as having major depression, respectively. Men were mostly married, while majority of women were single. Both smoking and alcohol use were substantially more common in men.

A subgroup of sample who had undertaken biennial examina tion at both 1992 and 1994 survey was analyzed separately to examine the relationship between chronic depression and later cancer incidence. Among 458,836 men and 87,678 women, 14,931 (3.3%) men and 3947 (4.5%) women were identified with chronic depression, defined as exhibiting major depression in both 1992 and 1994 survey, respectively. Chronically depressed individuals were more likely to be neither married nor never married, lower in socioeconomic status, current smokers and heavy drinkers, and not regularly exercising (Table 2).

3.1. Depression and subsequent overall cancer incidence

A total of 49,744 cancer incidence occurred among men and 7860 among women during the 20 years of follow up (Table 3). Overall cancer in men was significantly associated with major depression (HR 1.05, 95% CI 1.01, 1.09) and minor depression (HR 1.03, 95% CI 1.01, 1.06) compared to participants with no depres sion at all, after controlling for age, smoking status, alcohol drinking, exercise, BMI, cholesterol, blood sugar, hypertension, and cancer family history. In the contrast, overall cancer in women was inversely related to major depression (HR 0.90, 0.83, 0.98) and minor depression (HR 0.99, 95% CI 0.93, 1.05). Chronically depressed sample compared to those who were never depressed showed similar results, with men demonstrating positive associa tion (HR 1.08, 95% CI 1.02, 1.14) and women showing an inverse trend (HR 0.91, 95% CI 0.80, 1.30) with chronic depression and subsequent overall cancer incidence (Table 4).

Overall cancer demonstrated clear monotonic relationship with the severity of depression (Table 5). In men, subjects with severe depression showed largest magnitude of association (HR 1.10, 95% CI 1.02, 1.18, moderate depression: HR 1.03, 95% CI 0.99, 1.08, mild depression: HR 1.04, 95% CI 1.01, 1.07, and some depression: HR 1.02, 95% CI 0.99, 1.06: p for trend 0.0483). An inverse dose response relationship between the severity of depression and overall cancer was clear in women (severe depression: HR 0.81, 95% CI 0.69, 0.96, moderate depression: HR 0.93, 95% CI 0.84, 1.02, mild depression: HR 0.98, 95% CI 0.79, 1.03, and some depression: HR 1.00 (0.91, 1.09): p for trend 0.0446).

3.2. Depression and subsequent hormone related cancer incidence

Prostate cancer in men was positively associated with major depression (HR 1.13, 95% CI 0.98, 1.29) and minor depression (HR 1.13, 1.05, 1.23). When depression was sub categorized into four levels, there was a linear trend between the severity of depression and prostate cancer (severe depression HR 1.23, 95% CI 0.94, 1.60, moderate depression: HR 1.09, 95% CI 0.84, 1.02, mild depression: HR 1.19, 95% CI 1.08, 1.32, and some depression: HR 1.07, 95% CI 0.96, 1.19).

Cervical cancer in women was inversely associated with major depression (HR 0.63, 95% CI 0.45, 0.90). Chronically depressed women showed about half hazard compared to never depressed women (HR 0.51, 95% CI 0.28, 0.93).

Breast cancer, endometrial cancer and ovarian cancer were not related to depression. (The results for association between depres sion and all subtypes of cancer except hormone related cancer are shown in Supplementary Tables 1 and 2.)

4. Discussion

In this study, we aimed to investigate the relationship between depression and the risk of developing overall and hormone mediated cancer. Overall cancer morbidity was positively asso ciated with depression in men, while inversely associated in women. Regarding hormone related cancer, depression was asso ciated with increased risk of prostate cancer in men and decreased risk of cervical cancer in women. Breast cancer, endometrial cancer and ovarian cancer were not related to depression. Differ ent directions of relationship of depression and subsequent cancer incidence between men and women may provide insights on the etiological theories for the relation between depression and cancer.

Our results on the association between depression and overall cancer in men are consistent with previous studies which have shown positive associations of small magnitude between depres sion and cancer (Oerlemans et al., 2007; Gross et al., 2010). Most of the previous studies, however, have not had sufficient sample size to rigorously demonstrate the precision of these estimates nor analyze specific cancer subtypes of lower incidence (Zonderman et al., 1989; Liang et al., 2011). The KCPS, with more than 600,000 individuals participating, confirms these previous results with statistical precision.

In this study, the incidence of prostate cancer was significantly increased in subjects with depression. In general, few studies that have examined prostate cancer as a potential

outcome of depres sion have documented positive association that did not reach statistical significance. For example, in a 24 year follow up cohort study of Baltimore, subjects with dysphoric episodes showed a hazard ratio of 1.39 (95% CI 0.51, 3.80) compared to the controls (Gross et al., 2010). In similar studies that used medical records as the depression measure, the rate ratio of subjects with major depressive disorder developing prostate cancer was 1.02 (95% CI 0.84, 1.23) and 1.33 (95% CI 0.79, 2.23) in Denmark (Dalton et al., 2002). and Taiwan (Liang et al., 2011), respectively. In another study, chronically depressed older subjects showed an increased morbidity of prostate cancer although not statistically significant (HR 1.47, 95% CI 0.20, 10.83) (Penninx et al., 1998). In a meta analysis that combined three studies, statistical pooling revealed an estimated summary adjusted relative risk of 1.60 (95% CI 0.40, 6.50). Our results, which used a sample with 260 cancer incidences among subjects with major depression, are the first to show a statistically significant association between depression and sub sequent prostate cancer risk. Furthermore, a trend of dose response relationship between depression and prostate cancer supports the robustness of association.

Literature on the effect of depression on cervical cancer is even scarcer. However, in one study conducted in Denmark, being hospitalized for depression was found to be a protective factor against cervical cancer incidence, with a standardized incidence ratio of 0.81 (95% CI 0.65, 0.99) (Dalton et al., 2002). Our result shows significantly decreased incidence of cervical cancer among women with depression. The mechanism in which depression is protective against cervical cancer is unknown. Human papilloma virus (HPV) is a necessary cause of cervical cancer (Walboomers et al., 1999), suggesting that HPV may be a mechanism through which depression influences cervical cancer risk. However, exist ing studies on the relation between depression and HPV are mixed; some studies document lower depressive and anxiety symptoms among affected men and women (Johnson et al., 2011), though other studies show that women with HPV have higher levels of psychological distress once their status is known (Graziottin and Serafini, 2009; Clarke et al., 1996). Major depres sion is known to negatively influence sexual functioning, suggest ing that women with chronic major depression may be at lower risk for HPV infection and thus subsequent development of cervical cancer. Further research into these findings is critical.

Breast cancer is one of the most extensively studied subtypes regarding its association with depression. Some reported positive association (Aro et al., 2005; Gross et al., 2010), while others showed no association or even negative relationship (Nyklicek et al., 2003). In our study, we found no association between depression and breast cancer. This result is consistent with other large sample studies that examined the relation of depression and breast cancer. For example, a study conducted in Finland with over 10,000 subjects (Aro et al., 2005) and a meta analysis of 9 studies (Oerlemans et al., 2007) also showed no evidence of depression being a significant predictor of breast cancer incidence. In one of the studies that reported a strong positive association in a 24 year cohort study ascertained breast cancer by self report (Gross et al., 2010), which may bias the association away from the null. In another study showing a positive relationship, extreme stress and severe chronic depression was found to be a significant predictor of later breast cancer (Jacobs and Bovasso, 2000), which suggests that a certain threshold of severity might exist in the relation of depression and subsequent breast cancer.

Several mechanisms may be hypothesized for the association between depression and subsequent cancer (Spiegel and Giese Davis, 2003). One plausible pathway involves the hypothalamic pituitary adrenal (HPA) axis. There is considerable evidence that cortisol, a stress hormone that is released into plasma when stress is perceived, is associated with depression. Patients with depres sion show elevated cortisol levels in plasma (Burke et al., 2005) and display aberrant response to dexamethasone suppression test (Carroll et al., 2012). At the same time, cortisol is also involved in the activation of signaling that controls cell growth and regulation of the cell cycle.

Alteration in cytokine secretion and regulation is another possible pathway in which depression may be associated with subsequence cancer. Depression is common in infectious and autoimmune dis eases, and cytokine secretion is increased in major depression (Goshen et al., 2008). Also cytokines affect the HPA axis and monoamines (Goshen et al., 2008). At the same time, dysfunctional immune responses, including increased concentrations of cytokines TNF α and IL 6, are reported in patients with cancer (Lippitz, 2013).

Cultural factors may also influence the association between depression and cancer. Prevalence of mental disorders, including depression, tends to be lower in Asian countries compared to Western world (Chang et al., 2008). This may be due to unwill ingness to disclose information about personal difficulties and result in identifying more severe cases with stronger association with subsequent physical disease.

Compared to previous studies examining the association between depression and subsequent cancer risk, this study has several important strengths. First, this is the study with the largest sample size of more than 600,000 individuals. This is the largest prospective cohort study on the effect of depression on cancer. Because of its large sample size, the analysis had enough statistical precision to identify the relationship between depression and each subtypes of cancer, stratified by gender. Secondly, a follow up period of 20 years is longer than most of the other studies (Aro et al., 2005; Nyklicek et al., 2003; Zonderman et al., 1989). Due to slow growing rate of tumors, a follow up period of less than 10 years may be too short to detect an effect of depression on cancer incidence. For example, breast cancer with an average tumor volume doubling time of 280 days needs more than 18 years to grow from the first tumor cell to a tumor that is detectable (Possel et al., 2012; Friberg and Mattson, 1997). In their meta analysis, Oerlemans et al. reported that studies with follow up period of more than ten years were more likely to show significant associa tion between depression and subsequent overall and breast cancer risk (Oerlemans et al., 2007). Thirdly, cancer was ascertained by registry independent of exposure by linkage, and not self reported. Since depression is known to color perception of subject, self report on cancer diagnosis may bias the relationship further away from the null. Fourth, chronicity was examined.

There are also limitations to be noted. The method of ascertaining depression is a common limitation in studies examining depression. In our study, we used a self reported questionnaire to assess the level of depression in this large group of subjects. Although diagnosis by specialist or standardized diagnostic interviews is thought of as more valid measure of depression, self reported questionnaires are more convenient and inexpensive, thus allowing relatively large numbers of people to be evaluated in an epidemiological

study. Moreover, in Asian countries with a culture of unwillingness to disclose informa tion about personal difficulties, anonymity provided by questionnaire may allow participants to be more freely open about their mood status. Furthermore, medical diagnosis or standardized interview generally assess only the most severe form of depression such as major depressive disorder, while self reported questionnaires that are usually devised for screening purposes may identify individuals with minimal depressive symptoms as well as those with severe mood disorders. Finally, some of the potential confounders were not included in the analysis. Screening behavior in depressed subjects may account for positive association between depression and later cancer diagnosis. Also, data on potential confounders specific to hormonal cancers, such as parity, menopause, and hormone therapy was not collected in this study.

In conclusion, depression was associated with increased risk of prostate cancer among men and decreased risk of cervical cancer among women. The KCPS, with more than 600,000 individuals participating for almost 20 years, allows for statistical power to examine the association between depression and each subtypes of cancer, stratified by gender. Different direction and magnitude of association among gender and cancer subtypes suggest different psycho behavioral and biological pathways in which depression may affect later cancer development. Further studies on the association of depression and subsequent cancer and the underlying mechanisms should be conducted on specific cancer subtypes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV0). 4th. American Psychiatric Association; Washington, DC: 1994.

Aro AR, De Koning HJ, Schreck M, Henriksson M, Anttila A, Pukkala E. Psychological risk factors of incidence of breast cancer: a prospective cohort study in Finland. Psychol. Med. 2005; 35(10): 1515–1521. [PubMed: 16164775]

Belmaker RH, Agam G. Major depressive disorder. N. Engl. J. Med. 2008; 358(1):55–68. [PubMed: 18172175]

Bromet E, Andrade LH, Hwang I, Sampson NA, Alonso J, de Girolamo G, et al. Cross-national epidemiology of DSM-IV major depressive episode. BMC Med. 2011; 9:90. [PubMed: 21791035]

Burke HM, Davis MC, Otte C, Mohr DC. Depression and cortisol responses to psychological stress: a meta-analysis. Psychoneuroendocrinology. 2005; 30(9):846–856. [PubMed: 15961250]

Campayo A, de Jonge P, Roy JF, Saz P, de la Camara C, Quintanilla MA, et al. Depressive disorder and incident diabetes mellitus: the effect of characteristics of depression. Am. J. Psychiatry. 2010; 167(5):580–588. [PubMed: 20123914]

Carroll BJ, Iranmanesh A, Keenan DM, Cassidy F, Wilson WH, Veldhuis JD. Pathophysiology of hypercortisolism in depression: pituitary and adrenal responses to low glucocorticoid feedback. Acta Psychiatr. Scand. 2012; 125(6):478–491. [PubMed: 22211368]

Chang HY, Shin YJ, Batty GD, Son DK, Yun YD, Jee SH, et al. Measuring depression in South Korea: validity and reliability of a brief questionnaire in the Korean Cancer Prevention Study. J. Affect Disord. 2013; 150:760–765. [PubMed: 23541487]

Chang SM, Hahm BJ, Lee JY, Shin MS, Jeon HJ, Hong JP, et al. Cross-national difference in the prevalence of depression caused by the diagnostic threshold. J. Affect. Disord. 2008; 106(1-2):159–167. [PubMed: 17725930]

Chen YH, Lin HC. Increased risk of cancer subsequent to severe depression–a nationwide population-based study. J. Affect Disord. 2011; 131(1-3):200–206. [PubMed: 21242002]

Cho, MJ. The Epidemiological Survey of Mental Disorders in Korea. Ministry of Health and Welfare; 2011.

Clarke P, Ebel C, Catotti DN, Stewart S. The psychosocial impact of human papillomavirus infection: implications for health care providers. Int. J. STD AIDS. 1996; 7(3):197–200. [PubMed: 8799782]

Dalton SO, Mellemkjaer L, Olsen JH, Mortensen PB, Johansen C. Depression and cancer risk: a register-based study of patients hospitalized with affective disorders, Denmark, 1969–1993. Am. J. Epidemiol. 2002; 155(12):1088–1095. [PubMed: 12048222]

Friberg S, Mattson S. On the growth rates of human malignant tumors: implications for medical decision making. J. Surg. Oncol. 1997; 65(4):284–297. [PubMed: 9274795]

Goshen I, Kreisel T, Ben-Menachem-Zidon O, Licht T, Weidenfeld J, Ben-Hur T, et al. Brain interleukin-1 mediates chronic stress-induced depression in mice via adrenocortical activation and hippocampal neurogenesis suppression. Mol. Psychiatry. 2008; 13(7):717–728. [PubMed: 17700577]

Graziottin A, Serafini A. HPV infection in women: psychosexual impact of genital warts and intraepithelial lesions. J. Sex. Med. 2009; 6(3):633–645. [PubMed: 19170869]

Gross AL, Gallo JJ, Eaton WW. Depression and cancer risk: 24 years of follow-up of the Baltimore Epidemiologic Catchment Area sample. Cancer Causes Control. 2010; 21(2):191–199. [PubMed: 19885645]

Jacobs JR, Bovasso GB. Early and chronic stress and their relation to breast cancer. Psychol. Med. 2000; 30(3):669–678. [PubMed: 10883721]

Johnson CY, Sharp L, Cotton SC, Harris CA, Gray NM, Little J. Human papillomavirus infection and anxiety: analyses in women with low-grade cervical cytological abnormalities unaware of their infection status. PLoS One. 2011; 6(6):e21046. [PubMed: 21698168]

Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA. 2003; 289(23):3095–3105. [PubMed: 12813115]

Liang JA, Sun LM, Muo CH, Sung FC, Chang SN, Kao CH. The analysis of depression and subsequent cancer risk in Taiwan. Cancer Epidemiol. Biomark. Prev. 2011; 20(3):473–475.

Lippitz BE. Cytokine patterns in patients with cancer: a systematic review. Lancet Oncol. 2013; 14(6):e218–e228. [PubMed: 23639322]

Long N, Moore MA, Chen W, Gao CM, Lai MS, Mizoue T, et al. Cancer epidemiology and control in north-East Asia - past, present and future. Asian Pac. J. Cancer Prev. 2010; 11(Suppl 2):107–148. [PubMed: 20553072]

McGee R, Williams S, Elwood M. Depression and the development of cancer: a meta-analysis. Soc. Sci. Med. 1994; 38(1):187–192. [PubMed: 8146710]

Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146,538 participants in 54 observational studies. Eur. Heart J. 2006; 27(23):2763–2774. [PubMed: 17082208]

Nyklicek I, Louwman WJ, Van Nierop PW, Wijnands CJ, Coebergh JW, Pop VJ. Depression and the lower risk for breast cancer development in middle-aged women: a prospective study. Psychol. Med. 2003; 33(6):1111–1117. [PubMed: 12946095]

Oerlemans ME, van den Akker M, Schuurman AG, Kellen E, Buntinx F. A meta-analysis on depression and subsequent cancer risk. Clin. Pract. Epidemiol. Ment. Health. 2007; 3:29. [PubMed: 18053168]

Pan A, Sun Q, Okereke OI, Rexrode KM, Hu FB. Depression and risk of stroke morbidity and mortality: a meta-analysis and systematic review. JAMA. 2011; 306(11):1241–1249. [PubMed: 21934057]

Penninx BW, Guralnik JM, Pahor M, Ferrucci L, Cerhan JR, Wallace RB, et al. Chronically depressed mood and cancer risk in older persons. J. Natl. Cancer Inst. 1998; 90(24):1888–1893. [PubMed: 9862626]

Possel P, Adams E, Valentine JC. Depression as a risk factor for breast cancer: investigating methodological limitations in the literature. Cancer Causes Control. 2012; 23(8):1223–1229. [PubMed: 22706674]

Spiegel D, Giese-Davis J. Depression and cancer: mechanisms and disease progression. Biol. Psychiatry. 2003; 54(3):269–282. [PubMed: 12893103]

Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. JAMA. 1999; 282(18):1737–1744. [PubMed: 10568646]

Van Houdenhove B, Kempke S, Luyten P. Psychiatric aspects of chronic fatigue syndrome and fibromyalgia. Curr. Psychiatry Rep. 2010; 12(3):208–214. [PubMed: 20425282]

Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J. Pathol. 1999; 189(1): 12–19. [PubMed: 10451482]

World Health Organization. The Global Burden of Disease: 2004 Update. World Health Organization; Geneva: 2008.

Zonderman AB, Costa PT Jr. McCrae RR. Depression as a risk for cancer morbidity and mortality in a nationally representative sample. JAMA. 1989; 262(9):1191–1195. [PubMed: 2761060]

Table 1

Demographic characteristics major and minor depression in 1992 in South Korea, by gender, *n* (%).

	Men				Women			
	All *n* = 502,297	**Major depression[a] 7.4%**	**Minor depression[b] 19.3%**	**Not depressed 73.3%**	**All *n*=99,478**	**Major depression[a] 10.2%**	**Minor depression[b] 21.4%**	**Not depressed 68.4%**
Age (year)								
30–34	11,4017	7.6%	14.3%	78.1%	41,444	10.2%	20.8%	69.0%
35–39	11,3663	7.9%	16.3%	75.8%	25,164	9.8%	20.6%	69.6%
40–44	86,861	7.8%	18.7%	73.5%	16,009	10.0%	21.2%	68.7%
45–49	72,509	7.6%	21.3%	71.1%	8243	11.7%	23.1%	65.7%
50–54	66,836	6.8%	24.7%	68.5%	5437	11.6%	25.6%	62.8%
55–59	39,812	6.0%	27.8%	66.2%	2616	9.0%	25.5%	65.5%
60–64	8599	5.5%	30.2%	64.3%	565	7.1%	20.2%	72.7%
Marital status								
Married	475,916	7.3%	19.3%	73.4%	10,026	10.1%	21.7%	68.2%
Never married	15,216	10.1%	15.5%	74.5%	85,396	10.6%	18.6%	70.8%
Else	8012	10.8%	23.2%	66.0%	3576	11.7%	22.1%	66.0%
Socioeconomic status								
1 St Quartile	102,577	7.9%	21.0%	71.1%	11,887	10.4%	21.6%	68.0%
2nd Quartile	92,991	7.6%	20.1%	72.3%	14,587	10.7%	21.5%	67.8%
3rd Quartile	107,286	7.6%	17.7%	74.7%	33,337	9.8%	21.4%	68.9%
4th Quartile	107,156	6.4%	19.3%	74.3%	20,947	10.2%	22.1%	67.7%
Smoking status								
Non smoker	104,435	5.6%	16.8%	77.6%	98,849	10.2%	21.4%	68.4%
Ex smoker	98,676	7.1%	20.1%	72.8%	383	13.6%	24.8%	61.6%
Current smoker	299,186	8.2%	19.9%	72.0%	246	15.0%	17.1%	67.9%
Drinking status								
Non drinker	97,612	7.1%	18.2%	75.5%	83,732	9.5%	21.0%	69.5%
0–25 g/d	282,820	6.8%	18.9%	74.3%	15,562	13.9%	23.4%	62.7%
25–50 g/d	73,124	8.3%	20.5%	71.2%	145	16.6%	25.5%	57.9%
50–100 g/d	36,973	11.5%	21.8%	66.7%	28	7.1%	32.1%	60.7%
100-g/d	11,768	14.2%	21.6%	64.2%	11	0.0%	27.3%	72.7%
Regular exercise								
Regular exercise	138,203	4.4%	16.7%	78.9%	12,480	7.4%	18.5%	74.0%
No exercise	364,094	8.6%	20.2%	71.2%	86,998	10.6%	21.8%	67.6%

[a] Major depression: (item 1 or item 2) and (at least 5 positive answers among 9 items).

[b] Minor depression: (item 1 or item 2) and (1–4 positive answers among 9 items).

Table 2

Demographic characteristics of subjects with chronic[a] major depression, *n* (%).

	Men			Women		
	All *n* = 458,836	**Chronic major depression[a] 3.3%**	**Never depressed[b] 96.7%**	**All *n*=87,678**	**Chronic major depression[a] 4.5%**	**Never depressed[b] 95.5%**
Age (year)						
30–34	103,574	3.2%	96.8%	36,435	4.3%	95.7%
35–39	103,392	3.5%	96.5%	22,275	4.3%	95.7%
40–44	79,085	3.5%	97.1%	14,132	4.2%	95.8%
45–49	66,223	3.3%	96.7%	7191	6.0%	93.9%
50–54	61,547	3.0%	97.0%	4758	5.8%	94.2%
55–59	36,988	2.4%	97.6%	2363	4.1%	95.9%
60–64	8027	2.4%	97.6%	524	3.6%	96.4%
Marital status						
Married	435,315	3.2%	96.8%	75,278	4.5%	95.5%
Never married	13,500	4.4%	95.6%	8863	4.3%	95.7%
Else	7133	5.5%	94.5%	3113	5.2%	94.8%
Socioeconomic status						
1 St Quartile	93,291	3.6%	96.4%	10,470	4.8%	95.2%
2nd Quartile	84,616	3.3%	96.7%	12,847	5.0%	95.0%
3rd Quartile	97,902	3.3%	96.7%	29,423	4.0%	96.0%
4th Quartile	99,066	2.7%	97.3%	18,523	4.5%	95.5%
Smoking status						
Non smoker	97,300	2.3%	97.7%	87,150	4.5%	95.5%
Ex smoker	90,584	2.9%	97.1%	328	4.6%	95.4%
Current smoker	270,952	3.7%	96.3%	200	7.0%	93.0%
Drinking status						
Non drinker	90,417	2.5%	97.5%	74,301	4.1%	95.9%
0-25 g/d	259,650	2.9%	97.1%	13,226	6.8%	93.2%
25-50 g/d	66,103	3.8%	96.2%	118	7.6%	92.4%
50-100 g/d	32,533	5.7%	94.3%	26	3.8%	96.2%
100-g/d	10,133	7.4%	92.6%	7	0.0%	100.0%
Regular exercise						
Regular exercise	130,010	1.7%	98.3%	11,297	2.9%	97.1%
No exercise	328,826	3.9%	96.1%	3,619	4.7%	95.3%

[a] Chronic major depression=major depression in 1992 and major depression in 1994, among those who were interviewed at both waves.

[b] Never depressed = not depressed in 1992 and not depressed in 1994.

Table 3

Hazard ratios and 95% confidence intervals for associations between cancer subtypes diagnosed between 1993 and 2012, major depression, and minor depression in 1992.

Major depression (ref: everybody else)	Number of cancer morbidity at follow-up	Number with major depression	Major depression				
			Unadjusted HR (95% CI)	Model 1	Model 2	Model 3	Model 4
Major depression							
Men							
Total cancer	49,744	3661	1.05 (1.02–1.09)	1.09 (1.06–1.13)	1.05 (1.02–1.09)	1.05 (1.02–1.09)	1.05 (1.01–1.09)
Prostate cancer (C61)	3811	260	1.01 (0.99–1.14)	1.07 (0.94–1.21)	1.12 (0.98–1.27)	1.12 (0.98–1.27)	1.13 (0.98–1.29)
Women							
Total cancer	7860	751	0.93 (0.86–1.01)	0.92 (0.85–1.00)	0.93 (0.86–1.00)	0.93 (0.86–1.00)	0.90 (0.83–0.98)
Breast cancer(C50)	2244	234	1.00 (0.88–1.15)	1.00 (0.87–1.15)	1.00 (0.87–1.14)	1.00 (0.87–1.14)	0.98 (0.98–1.14)
Cervical cancer(C53)	588	141	0.73 (0.54–1.00)	0.72 (0.53–0.99)	0.72 (0.53–0.98)	0.72 (0.52–0.98)	0.63 (0.45–0.90)
Endometrial cancer (C54)	203	47	0.77 (0.46–1.29)	0.76 (0.45–1.27)	0.77 (0.46–1.30)	0.77 (0.46–1.30)	0.69 (0.39–1.21)
Ovarian cancer (C56)	300	75	1.11 (0.76–1.62)	1.10 (0.76–1.60)	1.10 (0.76–1.60)	1.11 (0.76–1.61)	1.03 (0.68–1.56)
Minor depression							
Men							
Total cancer	49,744	11,447	1.29 (1.26–1.31)	1.06 (1.04–1.09)	1.04 (1.01–1.06)	1.03 (1.01–1.06)	1.03 (1.01–1.06)
Prostate cancer (C61)	3811	983	1.48 (1.38–1.60)	1.11 (1.03–1.19)	1.13 (1.05–1.22)	1.14 (1.06–1.22)	1.13 (1.05–1.23)
Women							
Total cancer	7860	1719	1.02 (0.97–1.08)	1.00 (0.95–1.06)	1.00 (0.95–1.06)	1.00 (0.95–1.06)	0.99 (0.93–1.05)
Breast cancer(C50)	2244	448	0.92 (0.82–1.02)	0.92 (0.83–1.02)	0.92 (0.83–1.02)	0.92 (0.83–1.02)	0.92 (0.82–1.03)
Cervical cancer(C53)	588	403	1.12 (0.92–1.36)	1.10 (0.91–1.33)	1.10 (0.91–1.33)	1.10 (0.91–1.33)	1.03 (0.84–1.27)
Endometrial cancer (C54)	203	140	1.07 (0.77–1.49)	1.07 (0.77–1.49)	1.08 (0.78–1.51)	1.08 (0.78–1.51)	1.11 (0.79–1.57)
Ovarian cancer (C56)	300	193	1.24 (0.95–1.62)	1.23 (0.94–1.61)	1.22 (0.94–1.60)	1.22 (0.94–1.60)	1.24 (0.93–1.64)

Model 1: adjusted for age, marital status, SES (demographics).

Model 2: adjusted for age, smoking status, alcohol drinking, exercise, BMl (demographics+health behaviors).

Model 3: adjusted for age, smoking status, alcohol drinking, exercise, BMI, cholesterol, blood sugar, hypertension (demos+health behaviors +biological indicators of subclinical illness).

Model 4: adjusted for age, smoking status, alcohol drinking, exercise, BMI, cholesterol, blood sugar, hypertension, and cancer family history (demos+health behaviors+biological indicators of subclinical illness + genetic liability).

Table 4

Hazard ratios and 95% confidence intervals for associations between cancer subtypes diagnosed between 1993 and 2012 and chronic depression in 1992 and 1994.

Chronic depression (ref: everybody else)	Number of cancer morbidity at follow-up	Number with chronic depression	Chronic depression				
			Unadjusted HR (95% CI)	Model 1	Model 2	Model 3	Model 4
Men							
Total cancer	45,516	1510	1.03 (0.98–1.08)	1.12 (1.06–1.18)	1.07 (1.02–1.13)	1.07 (1.02–1.13)	1.08 (1.02–1.14)
Prostate cancer (C61)	3499	99	0.87 (0.71–1.06)	1.00 (0.82–1.22)	1.05 (0.86–1.28)	1.05 (0.86–1.28)	1.05 (0.85–1.30)
Women							
Total cancer	6980	296	0.94 (0.84–1.06)	0.92 (0.82–1.04)	0.93 (0.82–1.04)	0.93 (0.82–1.04)	0.91 (0.80–1.03)
Breast cancer(C50)	1976	87	0.98 (0.79–1.21)	0.97 (0.78–1.21)	0.97 (0.79–1.21)	0.97 (0.78–1.21)	0.96 (0.76–1.21)
Cervical cancer(C53)	529	13	0.53 (0.31–0.93)	0.52 (0.30–0.91)	0.52 (0.30–0.91)	0.52 (0.30–0.91)	0.51 (0.28–0.93)
Endometrial cancer (C54)	181	6	0.73 (0.32–1.65)	0.71 (0.32–1.61)	0.74 (0.33–1.68)	0.74 (0.33–1.68)	0.81 (0.36–1.84)
Ovarian cancer (C56)	269	11	0.91 (0.50–1.66)	0.88 (0.48–1.62)	0.88 (0.48–1.61)	0.88 (0.48–1.61)	0.91 (0.48–1.72)

Model 1: adjusted for age, marital status, SES (demographics).

Model 2: adjusted for age, smoking status, alcohol drinking, exercise, BMI (demographics+health behaviors).

Model 3: adjusted for age, smoking status, alcohol drinking, exercise, BMI, cholesterol, blood sugar, hypertension (demos+health behaviors +biological indicators of subclinical illness).

Model 4: adjusted for age, smoking status, alcohol drinking, exercise, BMI, cholesterol, blood sugar, hypertension, and cancer family history (demos+health behaviors+biological indicators of subclinical illness + genetic liability).

[a]Chronic major depression=major depression in 1992 and major depression in 1994, among those who were interviewed at both waves.

Table 5

Hazard ratios and 95% confidence intervals for associations between cancer subtypes diagnosed between 1993 and 2012, by severity of depression in 1992.

	Men		Women				
	Total cancer	**Prostate cancer**	**Total cancer**	**Breast cancer**	**Cervical cancer**	**Endometrial ca**	**Ovarian cancer**
Severe depression	1.10 (1.02–1.18)	1.23 (0.94–1.60)	0.81 (0.69–0.96)	0.79 (0.58–1.08)	0.69 (0.36–1.33)	1.11 (0.45–2.71)	1.14 (0.54–2.43)
Moderate depression	1.03 (0.99–1.08)	1.09 (0.93–1.27)	0.93 (0.84–1.02)	1.05 (0.89–1.23)	0.62 (0.41–0.93)	0.56 (0.27–1.14)	0.99 (0.62–1.60)
Mild depression	1.04 (1.01–1.07)	1.19 (1.08–1.32)	0.98 (0.92–1.05)	0.90 (0.79–1.03)	0.88 (0.68–1.15)	1.08 (0.72–1.63)	1.37 (0.99–1.89)
Some depression	1.02 (0.99–1.06)	1.07 (0.96–1.19)	1.00 (0.91–1.09)	0.97 (0.81–1.15)	1.32 (0.98–1.78)	1.17 (0.70–1.97)	1.00 (0.62–1.63)
p-for-trend	0.0483	0.0931	0.0446	0.3549	0.1438	0.6827	0.6709

adjusted for age, smoking status, alcohol drinking, exercise, BMl, cholesterol, blood sugar, hypertension, and cancer family history.

Severe depression: (item 1 or item 2) and (at least 7 positive answers among 9 items).

Moderate depression: (item 1 or item 2) and (5~6 positive answers among 9 items).

Mild depression: (item 1 or item 2) and (3~4 positive answers among 9 items).

Some depression: (item 1 or item 2) and (1~2 positive answers among 9 items).

Reference: No depression (not item 1) and (not item 2).