The Association Between Depression and Invasive and In-situ Cervical Tumors: A Large Population Based Cohort Study

Ravit Bassal PhD[1,2], Varda Shalev MD[2,3], Vered H. Eisenberg MD[3,4], Orit Stein-Reisner MD[5], and Eduardo Schejter MD[6]

[1]Israel Center for Disease Control, Ministry of Health, Sheba Medical Center, Tel Hashomer, Israel
[2]Department of Epidemiology and Preventive Medicine, School of Public Health, Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[3]Maccabi Institute for Research and Innovation, Tel Aviv, Israel
[4]Department of Obstetrics and Gynecology, Sheba Medical Center, Tel Hashomer, Israel
[5]Maccabi Healthcare Services, Tel Aviv, Israel
[6]Women Health Center, Maccabi Healthcare Services, Tel Aviv, Israel

ABSTRACT **Background:** Depression has been shown to be associated with cervical tumors (CTs), an association mostly demonstrated in studies in which temporality could not have been ascertained.

Objectives: To study the association between depression and CTs and the influence of co-morbidities of this association in a large cohort study.

Methods: A retrospective computer-based cohort study was conducted. The cohort included 357,450 female members of Maccabi Healthcare Services. The cohort was classified as depressed or non-depressed using the International Classification of Diseases 9/10 codes. For each subgroup, demographic characteristics, behavioral characteristics, co-morbidities, and CTs diagnosis were obtained. The burden of co-morbidities was defined as the sum of major co-morbidities. We used zero-inflated negative binomial regression analysis due to over-dispersion to estimate the relative risk (RR) for CTs with 95% confidence interval (95%CI).

Results: Depression was diagnosed in 15,789 women. Among this group, CTs were diagnosed in 1585 (10.0%). Among the 341,661 non-depressed, CTs were diagnosed in 4185 (1.2%). After adjustment to age and socioeconomic status, the association between depression and CTs was RR=9.2 (95%CI 8.7–9.9, *P*-value < 0.0001). The association between depression and CTs increased as the burden of clinical conditions increased (*P*-value < 0.0001).

Conclusions: Women with depression are at a higher risk for CTs, especially among those who have several co-morbidities. Tighter gynecology surveillance is crucial among these women.

IMAJ 2023; 25: 490–494

KEY WORDS: cervical tumors, depression, relative risk, risk factors

Depression is common in the world according to the Global Health Data Exchange. The prevalence of depressive disorders among women in 2019 was 4.5% (95%CI 4.1–5.0%) [1].

Cervical tumors (CTs) begin with changes in healthy cells and accumulate to abnormal cells growth with no growth control to the level of the tumor. Abnormal squamous cells invading 2/3 of the cervix leads to cervical intraepithelial neoplasia 3 (CIN3) and invasion of the whole cervix leads to squamous cell carcinoma. Tumors of the glandular cells lead to adenocarcinoma. Risk factors for cervical cancer include multiple sexual partners, early sexual activity, other sexually transmitted infections, weak immune system, smoking, and exposure to miscarriage prevention drugs [2].

Depression has been shown to be associated with several chronic diseases and various types of cancer [3-6]. Previous studies have shown that depression and anxiety were also associated with CTs [7,8]. However, most studies investigated the association between depression and CTs were cross-sectional or case-control studies that usually examined the occurrence of depression after the diagnosis of CTs, thus temporality could not have been ascertained [9,10].

The aim of this study was to evaluate the association between depression and CTs in a large, retrospective cohort study and to assess the risk to develop CTs in women with co-morbidities.

PATIENTS AND METHODS

STUDY DESIGN AND STUDY POPULATION

We conducted a retrospective cohort study, including 357,450 women members of Maccabi Health Services (MHS). In Israel, by law, every resident must be registered in one of the four health maintenance organizations (HMOs). MHS is the second largest HMO in Israel, covering 25% of the population [11].

EXPOSURE

Women aged 21 years or older between 1 January 1998 and 30 September 2017 who were diagnosed with depression using the International Classification of Diseases (ICD) 9/10 codes [Appendix 1, online version only] or who purchased antidepressants for more than 3 months during that time, were classified as depressive. The date depression was diagnosed or the first date antidepressant medication was purchased was established as the date of depression diagnosis. Women diagnosed with a disease in which depression is part of the syndrome but not the leading phenomenon, were excluded from the cohort. A random, computer-based representative sample of MHS women not diagnosed with depression or who did not purchase antidepressants for more than 3 months after 1 January 1998, served as the control group. The follow-up of depressed and non-depressed women continued until the occurrence of one of the following endpoints: the diagnosis of CTs or 30 September 2017, the end of the follow-up.

OUTCOME

CTs included diagnosis of cervical cancer, CIN3, and adenocarcinoma in situ (AIS), according to the MHS cancer registry and were obtained using SNOMED codes [Appendix 2, online version only]. Only CT diagnosed 1 year after the diagnosis of depression was included to allow for a minimal latency period.

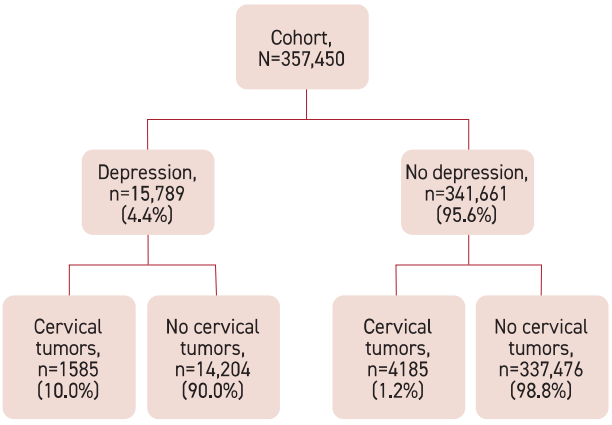
COVARIATE

The following covariates were obtained:

- *Demographic characteristics* included age at CT diagnosis or at the end of the follow-up and socioeconomic status (SES). SES was determined using the socioeconomic residential classification of the Israeli Central Bureau of Statistic, range between 1 (lowest) and 20 (highest) [12].
- *Behavioral characteristics* included smoking status and number of Pap tests performed (< 1 vs. ≥ 1) in the last 3 years (for those diagnosed with CTs, 3 years before the diagnosis and for those who were not diagnosed with CTs, 3 years before the end of follow-up).
- *Clinical characteristics* included diagnosis of diabetes, infertility, weight disorders (overweight and underweight), hypertension, autoimmune disease, hormonal treatment (hormone replacement therapy [HRT] and non-HRT), inflammatory bowel disease (IBD), immune deficiency, immune suppressant, sexually transmitted diseases (herpes, gonorrhea, chlamydia, acquired immune deficiency syndrome, and syphilis), thyroid disease, and cancer (non-cervical). Clinical conditions were obtained using the computerized registries of MHS (for those diagnosed with CTs, one year before the diagnosis and for those who were not diagnosed with CTs, one year before the end of follow-up). The appearance of a clinical condition was defined only if the diagnosis appeared at least one year before the diagnosis of CT. For each clinical condition, the date of diagnosis was also obtained. The burden of clinical conditions was defined as the sum of clinical conditions during the follow up.

The study was approved by the Maccabi Health Services ethics committee (reference number 0026–17-BBL).

Figure 1. Cohort selection flow chart



DATA ANALYSIS

Descriptive analyses were presented as frequencies for categorical variables and mean ± standard deviation (SD) for continuous variables. For categorical variables and continuous variables, Pearson's chi-square and Student's *t*-test were used, respectively, to evaluate differences between depressed and non-depressed women. To evaluate the association between depression and CTs and the association by exposure to covariates, the zero-inflated negative binomial univariate and multivariate regression models were used due to over-dispersion [13]. Relative risk (RR) and 95% confidence interval (95%CI) were calculated. We also evaluated the association between depression and CTs by the sum of clinical conditions. *P*-value < 0.05 was considered statistically significant. Statistical analyses were performed using SAS 9.2 Enterprise Guide version 7.12 HF5 software (SAS Institute Inc., Cary, NC, USA).

RESULTS

The cohort included 357,450 women. Depression was diagnosed in 15,789 (4.4%) [Figure 1]. Women with depression were significantly older (mean age 68.9 ± 15.6 vs. non-depressed 53.8 ± 19.2 years, *P*-value < 0.0001), from higher SES (12.3 ± 3.6 vs. non-depressed 11.6 ± 3.8, *P*-value < 0.0001), less likely to smoke (0.9% vs. non-depressed 23.6%, *P*-value < 0.0001), and less likely to perform a Pap test 3 years before diagnosis (62.0% vs. non-depressed 53.9%, *P*-value < 0.0001) [Table 1].

Table 1. Description of the cohort (N=357,450)

	Depressed n=15,789 (%)	Non-depressed n=341,661 (%)	*P*-value
Demographic characteristics			
Age in years: n, mean ± SD	15,789, 68.9 ± 15.6	341,661, 53.8 ± 19.2	< 0.0001
SES: n, mean ± SD	14,689, 12.3 ± 3.6	316,352, 11.6 ± 3.8	< 0.0001
Behavioral characteristics			
Smoking	148 (0.9)	80,682 (23.6)	< 0.0001
< 1 Pap test performed in the last 3 years (vs. ≥ 1)	1535 (62.0)	40,797 (53.9)	< 0.0001
Clinical conditions			
Diabetes	152 (1.0)	5067 (1.5)	< 0.0001
Infertility	108 (0.7)	7807 (2.3)	< 0.0001
Weight disorders	673 (4.3)	41,610 (12.2)	< 0.0001
Hypertension	374 (2.4)	12,728 (3.7)	< 0.0001
Autoimmune disease	17 (0.1)	13,105 (3.8)	< 0.0001
Hormones consumption	172 (1.1)	26,276 (7.7)	< 0.0001
Hormones replacement treatment	1582 (10.0)	77,793 (22.8)	< 0.0001
Inflammatory bowel disease	29 (0.2)	639 (0.2)	0.9240
Immune deficiency	245 (1.6)	824 (0.2)	< 0.0001
Immune suppressant	1582 (10.0)	77,793 (22.8)	< 0.0001
Sexually transmitted diseases	745 (4.7)	28,675 (8.4)	< 0.0001
Thyroid disease	341 (2.2)	15,036 (4.4)	< 0.0001
Cancer (any)	0 (0.0)	4759 (1.4)	< 0.0001

SD = standard deviation

Depressed women had significantly lower rates of clinical conditions, excluding IBD and immune deficiency.

Of the depressed women, CTs were diagnosed in 1585 (10.0%) while among the non-depressed, CTs were diagnosed in 4185 (1.2%) [Figure 1].

Before adjustment for age and SES, which were found to be confounders in the association between depression and CTs, the association was RR=8.2 (95%CI 7.7–8.7) and after adjustment, the association was RR=9.2 (95%CI 8.7–9.9; *P*-value < 0.0001).

Table 2 shows the association between depression and CTs by exposure to behavioral characteristics and clinical conditions, adjusted for age and SES. The association between depression and CTs was higher among those who were exposed to smoking and performed fewer than one Pap test in 3 years as well as those with the following clinical conditions: diabetes, infertility, weight disorders, hypertension, autoimmune disease, hormones consumption, hormones replacement treatment, inflammatory bowel disease, immune deficiency, immune suppressant, sexually transmitted diseases, and thyroid disease. In the multivariable analysis, included age, SES, weight disorders, hypertension, HRT, immune deficiency, and thyroid disease, the risk to develop CTs among depressed was RR=11.1; 95%CI 10.4–11.9.

The mean number of clinical conditions among depressed women was significantly lower (mean ± SD: 0.4 ± 1.2) than non-depressed women (mean ± SD: 0.8 ± 1.6) (*P*-value < 0.0001).

Table 3 describes the occurrence of cervical malignancies among depressed and non-depressed by the burden of clinical conditions. A significant increase (*P*-value < 0.0001) in the relative risk to develop CTs was observed as the number of clinical conditions increased [Table 3].

DISCUSSION

We demonstrated that depression was a risk factor for developing CTs and as the number of clinical conditions increased, the risk of developing CTs was stronger.

The association between depression and CTs was already demonstrated by others [7-10]. There are several possible explanations for the association between depression and CTs. First, depression encourages body inflammation, followed by a decrease in immune-surveillance and the body's ability to detect and remove human papillomavirus (HPV) infection, which is the leading etiology for CTs [14-16]. Second, depressed women might be less likely to notice symptoms associated with cervical malignancies. Last, depressed women are more likely to be under tighter follow-up and health supervision, thus more likely to be diagnosed. Goodkin et al. [17] described the association between psychosocial factors and cervical cancer as complicated.

We have shown a strong association between depression and CTs among women experiencing multiple clinical conditions.

Table 2. Univariable analysis for the association between depression and cervical tumors by behavioral characteristics and clinical condition, adjusted for age and socioeconomic status

		Relative risk	95% confidence interval	*P*-value
Behavioral characteristics				
Smoking	Yes	69.7	58.4–83.2	< 0.0001
	No	8.9	8.3–9.6	< 0.0001
Number of Pap tests performed in the last 3 years	< 1	12.4	10.5–14.7	< 0.0001
	≥ 1	6.5	5.4–8.0	< 0.0001
Clinical conditions				
Diabetes	Yes	23.8	19.1–29.5	< 0.0001
	No	9.1	8.5–9.7	< 0.0001
Infertility	Yes	26.7	21.0–34.1	< 0.0001
	No	8.8	8.3–9.5	< 0.0001
Weight disorders	Yes	35.9	32.5–39.7	< 0.0001
	No	6.2	5.7–6.7	< 0.0001
Hypertension	Yes	22.6	19.7–25.8	< 0.0001
	No	9.0	8.4–9.7	< 0.0001
Autoimmune disease	Yes	59.9	36.2–99.3	< 0.0001
	No	9.3	8.7–9.9	< 0.0001
Hormones consumption	Yes	19.5	15.7–24.2	< 0.0001
	No	8.9	8.4–9.6	< 0.0001
Hormones replacement treatment	Yes	22.7	21.3–24.2	< 0.0001
	No	0.0	0.0–0.1	< 0.0001
Inflammatory bowel disease	Yes	37.3	19.7–70.5	< 0.0001
	No	9.1	8.5–9.7	< 0.0001
Immune deficiency	Yes	4.4	3.6–5.4	< 0.0001
	No	8.1	7.6–8.7	< 0.0001
Immune suppressant	Yes	22.7	21.3–24.2	< 0.0001
	No	0.0	0.0–0.1	< 0.0001
Sexually transmitted diseases	Yes	18.4	16.8–20.2	< 0.0001
	No	5.8	5.4–6.4	< 0.0001
Thyroid disease	Yes	28.1	24.3–32.4	< 0.0001
	No	8.1	7.5–8.7	< 0.0001
Cancer (any)	Yes	–	–	–
	No	9.1	8.5–9.7	< 0.0001

Table 3. Cervical tumors among depressed and non-depressed by the burden of clinical conditions (N=357,450)

Burden of clinical conditions	Depressed		Non-depressed		Relative risk	95%CI	*P*-value
	N	CTs (%)	N	CTs (%)			
0	14,206	2 (0.0)	262,049	1061 (0.4)	Ref.	–	–
1	1	1 (100.0)	1574	25 (1.6)	95.8	11.3–813.0	< 0.0001
2	288	288 (100.0)	15,546	837 (5.4)	14.1	12.3–16.3	< 0.0001
3	487	487 (100.0)	23,937	937 (3.9)	22.1	19.7–24.8	< 0.0001
4	415	415 (100.0)	20,281	742 (3.7)	25.2	22.2–28.6	< 0.0001
5	248	248 (100.0)	11,679	386 (3.3)	29.1	24.7–32.3	< 0.0001
6	104	104 (100.0)	4770	154 (3.2)	30.3	23.4–39.1	< 0.0001
7	34	34 (100.0)	1431	38 (2.7)	36.9	22.8–59.7	< 0.0001
8	6	6 (100.0)	345	5 (1.4)	78.4	18.2–336.9	< 0.0001

95%CI = 95% confidence interval, CT = cervical tumor

We substantiated our findings by demonstrating a dose response effect. As the number of clinical conditions increased, the association between depression and CTs was significantly stronger (*P*-value < 0.0001). The dose response effect may reflect the magnitude of the impact of multiple clinical conditions on the immune system to detect and remove HPV infection [18,19] but may also be explained by the tighter follow-up and health supervision, thus the higher likelihood to be diagnosed.

To the best of our knowledge, this is the first study investigating the association between depression and CTs in a very large cohort, with a well-structured registry, in which temporality was demonstrate.

Certain limitations are noteworthy in our study. We included in the outcome variable both CIN3 and cervical cancer, although different risk factors were observed for each [7]. There was a lack of data on HPV infection as HPV testing was not commonly used in Israel during the study period. The absence of the data affected our ability to test whether depression was not a direct risk factor for CTs but only a modifier in the association between HPV and CTs. Some variables that are known to have a role in the association between depression and CTs, such as the number of sexual partners, educational level, and sexual habits, were unavailable. The absence of these variables decreased our ability to understand the association between depression and CTs. Data regarding sexual abuse and intimate partner violence, which are associated with both depression and CTs [20-23], were not included, pursuant to intrusiveness. Prescription of antidepressants is not specific and common in different physical conditions; thus, information bias should be considered. Women with multi-morbidity may have a higher use of healthcare services, which may increase the opportunities for diagnosis, either with depression or with cancer. Last, since the rate of smoking among depressed women was low, we did not include smoking as a potential confounder in the association between depression and CTs.

The strong association between depression and CTs shows that physicians and gynecologists play a crucial role in the primary and secondary prevention of CTs. The combination of mental and clinical condition, as well as behavioral characteristics, may help identifying women with a higher risk for developing CTs.

CONCLUSIONS

Depressed women are at a higher risk for developing CTs, especially those who are exposed to multiple clinical conditions.

Correspondence

Dr. R. Bassal
Israel Center for Disease Control, Sheba Medical Center, Tel Hashomer 5262100, Israel
Email: rbassal@gmail.com

References

1. Evaluation IoHMa. Global Health Data Exchange (GHDx) Global Burden of Disease Study 2019 (GBD 2019) Data Resources. [Available from http://ghdx.healthdata.org/gbd-results-tool?params=gbd-api-2019-permalink/d780dffbe8a381b25e1416884959e88b]. [Accessed 2 October 2022].
2. Mayo Clinic. Cervical cancer. [Available from https://www.mayoclinic.org/diseases-conditions/cervical-cancer/symptoms-causes/syc-20352501]. [Accessed 2 October 2022].
3. Clarke DM, Currie KC. Depression, anxiety and their relationship with chronic diseases: a review of the epidemiology, risk and treatment evidence. *Med J Aust* 2009; 190: S54-60.
4. Linkins RW, Comstock GW. Depressed mood and development of cancer. *Am J Epidemiol* 1990; 132: 962-72.
5. Massetti GM, Thomas CC, King J, Ragan K, Buchanan Lunsford N. Mental health problems and cancer risk factors among young adults. *Am J Prev Med* 2017; 53: S30-s9.
6. Patten SB, Williams JV, Lavorato DH, Modgill G, Jetté N, Eliasziw M. Major depression as a risk factor for chronic disease incidence: longitudinal analyses in a general population cohort. *Gen Hosp Psychiatry* 2008; 30: 407-13.
7. Bassal R, Schejter E, Bachar R, et al. Risk factors for cervical cancer and CIN3 in Jewish women in Israel - two case control studies. *Asian Pac J Cancer Prev* 2016; 17: 2067-73.
8. Coker AL, Bond S, Madeleine MM, Luchok K, Pirisi L. Psychosocial stress and cervical neoplasia risk. *Psychosom Med* 2003; 65: 644-51.
9. Yang YL, Liu L, Wang XX, Wang Y, Wang L. Prevalence and associated positive psychological variables of depression and anxiety among Chinese cervical cancer patients: a cross-sectional study. *PLoS One* 2014; 9: e94804.
10. Gray NM, Sharp L, Cotton SC, et al. Psychological effects of a low-grade abnormal cervical smear test result: anxiety and associated factors. *Br J Cancer* 2006; 94: 1253-62.
11. Israel National Insurance. Security IS. Periodical Surveys – Membership in Health Maintenance organizations [Available from https://www.btl.gov.il/Publications/Pages/default.aspx]. [Accessed 2 October 2022]. [Hebrew].
12. Central Bureau of Statistics. Characterization and classification of local authorities by the socioeconomic level of the population in 2008. Local Councils and Municipalities - Rank, Cluster Membership, Population, Variable Values, Standardized Values and Ranking for the Variables Used in the Computation of the Index [Available from https://www.cbs.gov.il/he/publications/Pages/2013]. [Accessed 2 October 2022]. [Hebrew].
13. Héroux J, Moodie EE, Strumpf E, Coyle N, Tousignant P, Diop M. Marginal structural models for skewed outcomes: identifying causal relationships in health care utilization. *Stat Med* 2014; 33: 1205-21.
14. Bortolato B, Hyphantis TN, Valpione S, et al. Depression in cancer: The many biobehavioral pathways driving tumor progression. *Cancer Treat Rev* 2017; 52: 58-70.
15. Krishnadas R, Cavanagh J. Depression: an inflammatory illness? *J Neurol Neurosurg Psychiatry* 2012; 83: 495-502.
16. Lutgendorf SK, Andersen BL. Biobehavioral approaches to cancer progression and survival: Mechanisms and interventions. *Am Psychol* 2015; 70: 186-97.
17. Goodkin K, Antoni MH, Sevin B, Fox BH. A partially testable, predictive model of psychosocial factors in the etiology of cervical cancer I. Biological, psychological and social aspects. *Psycho-Oncology* 1993; 2: 79-98.
18. Dugué PA, Rebolj M, Garred P, Lynge E. Immunosuppression and risk of cervical cancer. *Expert Rev Anticancer Ther* 2013; 13: 29-42.
19. Herbert TB, Cohen S. Depression and immunity: a meta-analytic review. *Psychol Bull* 1993; 113: 472-86.
20. Cesario SK, McFarlane J, Nava A, Gilroy H, Maddoux J. Linking cancer and intimate partner violence: the importance of screening women in the oncology setting. *Clin J Oncol Nurs* 2014; 18: 65-73.
21. Coker AL, Hopenhayn C, DeSimone CP, Bush HM, Crofford L. Violence against women raises risk of cervical cancer. *J Womens Health (Larchmt)* 2009; 18: 1179-85.
22. Coker AL, Sanderson M, Fadden MK, Pirisi L. Intimate partner violence and cervical neoplasia. *J Womens Health Gend Based Med* 2000; 9: 1015-23.
23. Lindert J, von Ehrenstein OS, Grashow R, Gal G, Braehler E, Weisskopf MG. Sexual and physical abuse in childhood is associated with depression and anxiety over the life course: systematic review and meta-analysis. *Int J Public Health* 2014; 59: 359-72.