Depression in patients with colorectal cancer

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ABSTRACT

أن المرضى الذين يعانون من سرطان القولون والمستقيم يتعرضون للضغط النفسي بسبب معرفتهم للتشخيص والتغييرات العضوية والاجتماعية الناجمة عن هذا المرض، مما يزيد من مخاطر الإصابة بمرض الاكتئاب. الاكتئاب يسبب عجز هائل ويضيف معاناة زائدة إلى معاناتهم الأصلية ومن المعروف أن الاكتئاب يغير وظائف المناعة والغدد الصماء التي تزيد من قابلية التعرض لمرض سرطان القولون والمستقيم وكذلك يؤثر على مسار المرض بمرور الوقت واستجابته للعلاج وقد راجعنا نسبة انتشار أعراض وأمراض الاكتئاب في جميع أنحاء العالم وفي المملكة العربية السعودية، مع التركيز على المرضى الذين يعانون من مرض عضوي وعلى وجه الخصوص مرضى سرطان القولون والمستقيم. وراجعنا نسبة تشخيص الاكتئاب وكيفية علاجه ومساره المحتمل مع مرور الوقت ومراجعة آثار الاكتئاب على حدوث عجز وظيفي و طول العمر ووظائف المناعة. وأخيراً ناقشنا الاحتياجات البحثية وتقديم توصيات بشأن الدراسات البحثية ذات الأولوية العليا للنهوض بفهمنا لمرض الاكتئاب لدى مرضى سرطان القولون والمستقيم في المملكة العربية السعودية.

Patients with colorectal cancer (CRC) experience psychological stress due to the diagnosis and the physical and social changes brought on by the illness, increasing the risk of depressive disorder. Depression causes tremendous disability and adds to the suffering that patients must already endure. It is known to alter immune and endocrine functions that affect vulnerability to CRC, its course over time, and its response to treatment. We review the prevalence of depressive symptoms and disorders worldwide and in the Kingdom of Saudi Arabia (KSA), focusing on patients with medical illness and those with CRC, in particular. We examine how often depression is diagnosed, how it is treated, and its likely course over time, and review the effects of depression on functional disability, longevity, and immune functions. Finally, we discuss research needs and make recommendations on highest priority research studies to advance our understanding of depressive disorder in CRC patients in KSA.

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According to Ibrahim et al,[1] colorectal cancer (CRC) is the second most common cancer in the Kingdom of Saudi Arabia (KSA) surpassed only by breast cancer. Colorectal cancer is the most common form of cancer among men in KSA, with one-third of patients under age 50 when diagnosed in the hospital.[2] As of 2002, approximately 2.8 million persons were living with CRC within 5 years of diagnosis (based on the National Cancer Registry, KSA). Furthermore, among Saudi males between 1999 and 2003, the rates of CRC have been rising with an annual percentage change of 20.5% (based on the latest available data), with projections of further increases due to the aging of the Saudi population (projections that have been recently confirmed[3]). Given the many challenges that this illness presents, CRC is often accompanied by depression. The purpose of this review is to highlight the importance of depression among Saudi patients with CRC and recommend research needed in this area.

Prevalence of depression. Depression is common around the world. Using the Composite International Diagnostic Interview (CIDI), a survey of 18 high and low-to-middle income countries recently reported a lifetime prevalence of 15% for major depressive disorder, and a 12-month (point) prevalence of 6%.[4] Note that these rates apply to healthy, community-dwelling populations. Among low-to-middle income countries, lifetime prevalence ranged from 7% in

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China to 18% in Brazil, among high-income countries, lifetime prevalence ranged from 7% in Japan to 21% in France. For low-to-middle income countries, point prevalence ranged from 4% in China to 10% in Brazil; for high-income countries, it ranged from 3% in Japan to 8% in the United States (US). Only 2 Middle Eastern countries were included in this international study: Israel and Lebanon. In both countries, the lifetime prevalence was 10-11%, and the point prevalence was 6%. An independent survey of the US population (National Co-morbidity Study) research using the CIDI reported that the lifetime prevalence of depression (major depression and dysthymia) was 19%.[5] Depressive disorder was more common among women, younger adults, and Caucasians. The point prevalence of major depression in that study (past 12 months) was 7%, of which approximately 30% were considered severe.[6] Depression is also found in KSA. Although population-based studies of depressive disorder in the general population are lacking, a study is now in the field that will provide rates among Saudi nationals.[7] Most of what we know about depression in KSA comes from studies of primary care medical patients.

Impact of depression. Based on a joint study conducted by the Harvard School of Public Health and the World Health Organization in 1990, depression was the leading cause of disability in the world (measured by years of life lived with disability).[8] In 2020, depression is expected to be the world's second leading cause of disability, surpassed only by cardiovascular disease.[9] Depressive disorder is one of the strongest predictor of suicide,[10] which ends the life of nearly one million people worldwide each year.[11] For those with depression, nearly 10% will end their lives by committing suicide.[12] Besides increasing the risk of suicide, depressive disorder also affects physiological functions vital for the preservation of physical health and recovery from disease. Depression has been associated with a host of immune,[13] endocrine,[14] and pro-inflammatory dysfunctions[15] that could affect patients' susceptibility to disease and ability to respond to medical treatments. Depression is associated with an altered balance in the T helper 1/T helper 2 (Th1/Th2) ratio, that is, higher pro-inflammatory Th1 cytokines (interleukin [IL]-1, IL-12, interferon-γ), higher pro-inflammatory monocytic cytokines (IL-6, tumor necrosis factor [TNF]-α),[16-18] and lower anti-inflammatory Th2 cytokines (IL-4, IL-10).[19] Depressed patients also have reduced natural killer cell cytotoxicity,[20] and diminished lymphocyte responses to phytohemagglutinin and concanavalin A.[21] Importantly, impaired immune functions associated with depression have been shown to normalize in response to treatment with antidepressant drug therapy (serum TNF-α and C-reactive protein),[22] and psychological interventions.[23] Finally, there is evidence that the alterations in immune and endocrine function associated with depression increase medical morbidity by increasing risk of infection,[24] inflammatory disorders,[25] and possibly malignancy.[26-28]

Diagnosis, treatment, and course. The diagnosis of major depressive disorder requires the presence of depressed mood or loss of interest for at least 2 weeks, plus significant difficulty functioning in work, play, or interpersonal relationships. At least 4 of the following 8 symptoms must also be present: guilt (or feeling like a burden), loss of energy, decreased concentration, loss of appetite with significant weight loss (or increase in appetite with significant weight gain), psychomotor retardation (or agitation), difficulty sleeping (or sleeping too much), loss of interest (if not already included), and suicidal thoughts.[29] Depressive disorder is treatable in approximately 85% of cases (often after several antidepressant trials), particularly if antidepressant drug therapy is combined with psychotherapy.[30] Without treatment, however, an episode of major depression can last up to 24 months with a mean duration of 8 months, and more severe forms of depression can last even longer.[31]

Depression in patients with medical illness. While the point prevalence of major depression worldwide is 6%, this figure increases dramatically among patients with medical illness. The point prevalence ranges from 10% to 45% depending on setting.[32,33] As noted above, depressive disorder is already a potent risk factor for disease morbidity in those with physical illness, and medical patients with depression have double the mortality of non-depressed patients.[34]

Depressive disorders are also common among medical patients in KSA. The largest study to date was a 1995 national survey of 7,970 patients age 60 or over (identified from medical records at primary care clinics).[35] The prevalence of depressive symptoms (scores of 10 or higher on the Geriatric Depression Scale[36]) was 39%, and the prevalence of severe depression was 8.4% (scores of 20 or higher). Correlates of depression were poor education, unemployment, divorced or widowed status, older age, and being female.

Other studies among medical patients in KSA have reported similar results. Becker et al in 2002[37] studied a younger population of 431 medical outpatients at King Khalid University Hospital in Riyadh in 2000-2001 (75% under age 50), reporting a prevalence of depressive disorder of 20% using the Patient Health Questionnaire (PHQ). Likewise, Al-Kathami and Ogbeide in 2002[38]

surveyed 609 primary care patients (mean age 34) in central Saudi Arabia using the Rahim Anxiety-Depression Scale. Researchers reported that 18.2% had "mental illness," and if sub-threshold disorders were included, then the rate increased to 30.2%. Women, younger adults, divorcees or widows, and patients with asthma had the highest rates.

The rates of depression in primary care outpatient settings in KSA range from 8-39%, depending on the severity of the symptoms (with 20% representing an average for depressive symptoms that reach the "disorder" level of severity). In addition, at least two studies of primary care patients in KSA indicate that about two-thirds of emotional disorders are not detected or treated.[39,40] When depressive disorders go unrecognized by primary care physicians, this has implications for patient treatment, outcomes of the medical illness, and provider satisfaction.[41]

Depression in patients with cancer. The point prevalence of major depression in cancer patients ranges from 0-38%, and for all types of depression, ranges from is 0-58% (average 25%).[42] An early study in the U.S. by the Psychosocial Collaborative Oncology Group of 215 randomly selected inpatients and outpatients at 3 major cancer centers found that 47% had a recognizable psychiatric disorder using Diagnostic and Statistical Manual, 3rd edition (DSM-III) criteria. Of those, 68% had an adjustment disorder mood, and 13% had major depression, with an overall prevalence of 38% for mood disorders.[43] Cancer patients at higher risk of depression are those in poor physical condition, those with inadequately controlled pain, advanced stages of illness, or pre-existing mood disorders.[44]

Depression in Saudi patients with cancer. Very little research has examined the prevalence and correlates of depression among cancer patients in KSA. In a study of non-pain symptoms, Al-Shahri et al[45] in 2012 at the King Faisal Specialist Hospital in Riyadh examined the prevalence of depression in 124 patients with advanced incurable cancer in the hospital's palliative care outpatient clinic. Female breast cancer (27%), head and neck cancer (15%), genitourinary cancer (13%), and gastrointestinal cancer (10%) were the most frequent diagnoses. Depression was one of 10 non-pain symptoms asked about. Patients were asked whether the symptom was present (yes versus no), and then self-rated it on a 0-10 scale of severity. Results indicated that more than half (51%) of patients admitted they felt depressed, which was rated on average 4.2 in severity. Characteristics of those with depression were not mentioned.

In another report from the same sample of cancer patients, Al-Shahri et al[46] examined the presence and extent to which patients were "suffering" (mu'aanah), again assessing the severity of the symptom on a 0 to 10 scale. More than 60% of patients indicated a 5 or higher on the 0-10 scale. Not surprisingly, suffering was strongly correlated with depression (r=0.47, p<0.0001). In fact, of the 11 symptoms examined (pain, tiredness, depression, nausea, anxiety, shortness of breath, drowsiness, insomnia, dry mouth, loss of appetite, confusion), other than pain, depression was the strongest predictor of suffering in a multiple regression analysis.

Depression in patients with colorectal cancer. The diagnosis of colon cancer not only brings with it the threat of mortality (stage IV with only a 6% 5-year survival[47]), but both the disease and its treatment can cause much suffering. Bowel obstruction, metastatic disease, colostomy from surgery, and side effects from chemotherapy or radiation therapy can overwhelm many patients. Little wonder that psychiatric illness, particularly depression is widely prevalent. The point prevalence of depression in Western countries ranges from 13-57% (**Table 1**).

Table 1 - Studies examining depression in colorectal cancer in a study conducted in Jeddah, Kingdom of Saudi Arabia.

Authors	Year	n	Colorectal cancer	Location	Measure	Prevalence %
Fras et al[59]	1967	110	64	Rochester, USA	MMPI	13
Koenig et al[60]	1967	50	50	Detroit, USA	MMPI	25
Matsushita et al[48]	2005	85	38	Tokyo, Japan	HADS	28
Sherif et al[51]	2001	30	10	Jeddah, KSA	DSM-IV criteria	40
Pasquini et al[49]	2006	165	58	Rome, Italy	HADS/SCID-I	20
Tavoli et al[50]	2007	142	54	Tehran, Iran	HADS	57

MMPI - Minnesota Multiphasic Personality Inventory, HADS - Hospital Anxiety and Depression Scale,
DSM-IV - Diagnostic and Statistical Manual, 4th edition, SCID-I - Structure Clinical Interview for DSM-V Axis I Disorders

In 2005, researchers published a study on depression in 85 inpatients with digestive cancers living in Tokyo, Japan, of which 38 had CRCs (patients awaiting surgery).[48] The Hospital Anxiety and Depression Scale (HADS) was used to screen patients for depressive symptoms. The HADS is a 14-item symptom rating scale that includes a 7-item depression subscale. Each item in the depression scale is self-rated on severity from 0 to 3, with a total subscale score range from 0 to 21. Investigators found that 28% of these patients had depressive symptoms of at least moderate severity. However, only 7 patients (8%) were being treated for depressive disorder at the time of the study.

In 2006, researchers in Italy examined mental disorders in 165 cancer patients from the oncology division of a major medical center; 35% of patients had colon cancer, the most common cancer.[49] Patients were again screened using the HADS. Of those, 45 who screened positive also received the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). Of those patients, 31 had a depressive disorder (5 with major depression and 26 with dysthymia), giving a prevalence of approximately 20%.

Finally, in 2007 (the latest study available), researchers at Shahed University in Tehran, Iran, surveyed 142 patients with gastrointestinal cancer (38% with CRC) diagnosed within the previous year.[50] The average age of participants was 54, 56% were men, and the average time since diagnosis was 4.4 months. Again, the HADS was used to assess depressive symptoms. Scores of 11 or higher are considered significant depression. Results indicated that 57% of patients scored "high" on depressive symptoms. Regression analysis examined correlates of depressive symptoms. There was no correlation between depression and gender, education, marital status, cancer site, age, time since diagnosis, or initial treatment (surgery, chemotherapy, and so forth). Patients who were told they had a diagnosis of cancer, however, were significantly more depressed.

Depression in Saudi patients with colorectal cancer. One small study has examined depressive disorders in cancer patients in KSA.[51] This study surveyed 30 cancer patients at King Khalid National Guard Hospital in Jeddah. One third of all cancers were of the gastrointestinal tract (the second most common cancer, after breast cancer). Of the 30 patients, 12 had a depressive disorder (9 with adjustment disorder and 3 with major depression). This would make the point prevalence approximately 40% (although no information was provided on rates of depression specifically in gastrointestinal or CRC specifically). The Hamilton Depression Rating Scale (HDRS) measured depressive symptoms, and DSM-IV clinical criteria were used to make diagnoses (although no structured psychiatric interview was used). Interestingly, depressive symptoms were significantly higher among cancer patients than among a control group of 30 patients with chronic medical illness (difference was significant at $p<0.01$ on HDRS). Overall, then, 13-40% of colon cancer patients experience a depressive disorder (25% on average, based on studies of cancer worldwide and in KSA). No information exists on the prevalence of depression in Saudi CRC patients, on the demographic or psychosocial characteristics of those with depression, on what proportion are treated for depression, or on the course of depression, with or without treatment. Thus, there is a huge gap in knowledge regarding the prevalence, characteristics, diagnosis, treatment, and course of depressive disorder in CRC patients in KSA (and in the rest of the world, for that matter).

Implications for future research. The findings of this review have many implications for future research. First, we need to know the prevalence of major and dysthymic disorder among patients with CRC in KSA. Depressive disorder should be diagnosed using a structured psychiatric interview[52] administered to a random or systematic sample of CRC patients so results can be generalized to other settings. Structured psychiatric interviews used to diagnose depressive disorders include the Diagnostic Interview Schedule (DIS),[53] the SCID,[54] the MINI-International Neuropsychiatric Diagnostic Interview (MINI),[55] and the CIDI.[56]

Second, research is needed on when depressive disorder is most likely to develop during the course of illness in patients with CRC and its natural history over time. For example, is depression most likely to develop during the first few months after diagnosis, during treatment, when it recurs after remission, or only during the final stages of the disease prior to death? Likewise, do these depressive disorders persist over time or do they resolve spontaneously in a short time without treatment? This information is needed in order to determine when patients are at highest risk for developing depression and whether it is persistent enough to warrant treatment.

Third, we need to know how often physicians diagnose and treat depressive disorders in CRC patients. We also need to know the types of treatments for depression that are instituted, that is, antidepressant drug therapy, psychotherapy, electroconvulsive therapy, or other biological therapies. For example, nothing is known regarding what types of antidepressants are being prescribed or how compliant Saudi patients are with taking them. The same applies to psychological

therapies. What types of psychotherapy are depressed colorectal patients referred for and most receptive.

Fourth, research is needed on characteristics of CRC patients that increase their risk of having a depressive disorder, and more importantly, influence the course of depression over time. This includes demographic (age, gender, race, education, nationality), social (marital status, family size, living situation, social support), psychological (personality style, coping resources), and physical (cancer stage at diagnosis, other co-morbid medical problems, physical disability) characteristics. Such information will allow the development of a profile of CRC patients in Saudi Arabia who are at greater risk for persistent depression and may warrant screening for depression by their physicians.

Finally, what is the impact of depressive disorder on the course of CRC over time and its response to medical treatments? Although depression has been shown to predict greater mortality among patients with cancer,[57,58] there is no research yet showing that treatment of depression increases survival in these patients. Studies in KSA are needed to determine the effects of depressive disorder on physical functioning and longevity, and on how depression modifies the response of the cancer to chemotherapy, radiation, and surgical therapies. Furthermore, research is needed to explain the mechanism by which such effects occur, particularly the impact of depression on immune and endocrine functions necessary to contain the cancer or enhance its response to treatment.

In conclusion, millions of Saudis have CRCs, and we estimate that as many as one-quarter to one-third experience depressive disorder. Depression not only destroys quality of life, but it also adversely affects motivation for self care, can lead to premature death due to suicide, neglect of treatment, and adverse physiological changes (cardiovascular, endocrine, and immune) that worsen CRC outcomes. This, in turn, may lead to multiple hospitalizations and increase health expenditures, both for exacerbations of disease and for medically unexplained symptoms due to increased somatization brought on by the depression. As far as we know, nearly two-thirds of such depressions are undiagnosed and untreated by medical physicians. Knowing how common depression is, its natural course over time (with and without treatment), and factors that increase risk of depression or worsen its prognosis will provide important information for medical physicians and CRC specialists. This will increase the likelihood that depression will be diagnosed and treated, ultimately reducing suffering, increasing quality of life, and lowering the cost of health care.

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