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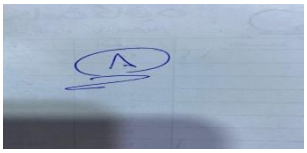

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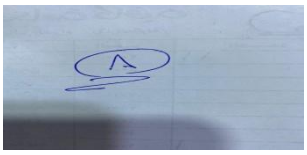
Signature: 

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COMMITTEE DECISION

This Thesis/Dissertation entitled (Prevalence of depression and utilization of antidepressant among cancer patients: a cross-sectional study in Jordan) was successfully defended and approved on the 3rd of June, 2020.

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(Prevalence of depression and utilization of antidepressant among cancer patients: a cross-sectional study in Jordan)

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Abstract

Background

Depression persist in cancer patients and cause an additional burden during treatment course making it more challenging in terms of its management and control. We aimed to explore the prevalence and risk factors of depression among cancer patients in the inpatient and outpatient settings.

Methodology

A total of 1,011 patients (399 inpatients and 612 outpatients) formed the study sample. Patients' depressive status was assessed using the Hospital Anxiety and Depression Scale (HADS) and Patient Health Questionnaire (PHQ-9) scale. Prevalence rate of depression was estimated by dividing the number of patients who exceeded the borderline score (10 or more for each subscale) of the HADS scale and (15 or more). Risk factors were identified using logistic regression.

Results

The prevalence of depression among all patients was 23.4%. Depression was more prevalent across patients who are hospitalized (37.1%) compared to patients in the outpatient setting (14.5%). In the inpatient setting, depression was more prevalent among patients with bladder cancer, while in the outpatient setting, depression was more prevalent among breast and prostate cancer patients. Despite that 24.8% of the patients reported that they feel depressed, 15.5% of them were using medications to manage them.

Conclusions

There is a need to consider depressive disorders as part of the treatment protocol for cancer patients. Enhanced clinical monitoring and treatment of depression among cancer patients are required.

Table of contents

List of Tables

List of Figures

List of Abbreviations

AML	Acute myeloid leukemia
ACEI	Angiotensin converting enzyme inhibitors
BNCT	Boron neutron capture therapy
CEC	Cervical esophageal cancer
CCA	Cholangiocarcinoma
CLL	Chronic lymphocytic leukemia
CML	Chronic myeloid leukemia
CBIs	Cognitive behavioral interventions
CI	Confidence interval
EBRT	External beam radiation therapy
HL	Hodgkin's lymphomas
HADS	Hospital Anxiety and Depression Scale
IGRT	Image guided radiation therapy
HIV	Immunodeficiency virus
IMRT	Intensity-modulated photon therapy
IMPT	Intensity-modulated proton beam therapy
IQR	Interquartile Range
IORT	Intraoperative radiation therapy
KHCC	King Hussein Cancer Center
ALL	Acute Lymphoblastic leukemia
MDD	Major depression disorder
MDD	Major Depressive Disorder
Mixed 5-HT	Mixed Serotonergic Effects
MAOIs	Monoamine oxidase inhibitors
NHL	Non-Hodgkin lymphomas
NDRI	Norepinephrine and Dopamine Reuptake Inhibitor
n	Number
OV	Opisthorchis viverrini
(PHQ)-9	Patient Health Questionnaire
PND	Postnatal depression

SERMs	Selective Estrogen Receptor Modulators
SSRIs	Selective serotonin reuptake inhibitors
SNRIs	Serotonin–Norepinephrine Reuptake Inhibitors
SD	Standard deviation
SABR	Stereotactic ablative radiotherapy
3-D CRT	Three-dimensional conformal radiation therapy
TCAs	Tricyclic antidepressants
WHO	World health organization

Chapter One:

Introduction

1. Introduction

1.1 Overview of cancer

Cancer is an abnormal cell growth that uncontrollably spreads through the body; this process is called metastasis (Su, Yang, Xu, Chen, & Yu, 2015). In 2018, cancer caused as many as 9.6 million deaths worldwide (Bray et al., 2018). It is estimated that around 90.5 million people had cancer in 2015 (Vos et al., 2016). Half of all cancer patients have the metastatic disease (Martin, Ye, Sanders, Lane, & Jiang, 2014). Tobacco is considered one of the most common risk factors that causes cancer and is responsible for about 22% of cancer deaths (World Health Organization, 2018). Other risk factors that are responsible for about 10% of deaths in cancer patients are obesity, low levels of physical activity, poor diet, and excessive alcohol consumption (Jayasekara, MacInnis, Room, & English, 2016; National Cancer Institute, 2017; World Health Organization, 2018). Infections such as hepatitis B, hepatitis C, human immunodeficiency virus (HIV), Helicobacter pylori, human papillomavirus infection and Epstein–Barr virus account for 15% of cancer cases (World Health Organization, 2018). The most common types of cancer in males are lung cancer, prostate cancer, stomach cancer and colorectal cancer, and the most common types of cancer in females are breast cancer, cervical cancer, lung cancer and colorectal cancer. The most common types of cancer in children are brain tumors and lymphoblastic leukaemia. In 2012, 165,000 children below 15 years of age were diagnosed with cancer in the world (Stewart & Wild, 2014).

1.1.1 Epidemiology

Cancer is one of the most common health problems in the world: in 2012, it caused approximately 8.2 million deaths in the world, with 14.1 million people diagnosed with

it in the same year (Torre et al., 2015). The most common types of cancers among females is breast cancer, which accounts for 25.0% among all female cancer patients, and 15.0% deaths among female cancer patients. Lung cancer is the most common cancer in males, accounting for 13.0% of total cancer diagnoses (Torre et al., 2015). In 2012, 14.1 million cancer cases and 8.2 million cancer deaths were recorded in the world. Breast cancer among females and lung cancer among males are currently the most common types of cancer leading to death. However, prostate cancer is the most commonly diagnosed type of cancer in males (Torre et al., 2015). According to the World Health Organization, in 2018, 18.1 million cases of cancer and 9.6 million deaths were recorded in the world ((IARC) & (OMS), 2018). Between 1996-2005 the number of cases of patients with cancer in Jordan was 33,661: 16,981were males and 16,680 were females (Al Tamwneh, Khatib, & Arqub, 2010). The total number of patients diagnosed with cancer between 1996-2009 in Jordan 25,633 (49.7) males and 25,993 (50.3%) females (S. I. Ismail, Soubani, Nimri, & Al-Zeer, 2013). Whereas between 2000-2013, the total number of patients with cancer in Jordan was 58,788: 28,545 (48.6%) were males and 30,243 (51.4%) were females (Khader et al., 2018).

1.1.2 Etiology of cancer

Genetic change is the main cause of abnormal cell growth leading to cancer (Bernstein, Prasad, Nfonsam, & Bernstein, 2013). Mutation in several different genes can cause cancer (Vogelstein et al., 1989). Mutations in gene p53 are found in many types of tumours in patients. Gene p53 is a tumour suppressor: it induces cell cycle arrest and DNA repair. When this gene is inactive, it will lead to uncontrolled cell division and then to tumour growth (Nielsen & Maneval, 1998).

1.1.2.1 Risk factors of cancer

Some of the greatest risk factors of cancer are tobacco, excessive alcohol consumption, infection and dietary habits (Blackadar, 2016). Tobacco remains the major factor, and more than 1 in 3 cancer deaths are brought about by tobacco use (Underwood et al., 2015). Tobacco causes many types of cancers, including lung cancer, mouth cancer, bladder cancer, pancreas cancer, kidney cancer, stomach cancer, oesophageal cancer, colon cancer, acute myeloid leukaemia, larynx cancer and renal pelvis cancer (Henley, 2016). Tobacco smoking creates high oxidative stress and causes the depletion of antioxidants in the body (Gupta, Ganguly, Rozanas, Stuehr, & Panda, 2016). Smokers must ingest more vitamins C and E than non-smokers to achieve the same level in the blood (Shah, Khand, & Khand, 2015). Alcohol is a risk factor of many types of cancer, such as breast cancer, oral cavity, colon, rectal, pharyngeal, laryngeal, oesophogeal and liver cancer (Cao & Giovannucci, 2016). Hepatitis B and C are major chronic infections which can lead to cancer, and they are most commonly found in Africa and Asia (Chan, Wong, Qin, & Chan, 2016). Schistosomiasis infection is common in Egypt and Asia: the eggs of Schistosoma japonicum can cause inflammation and colon cancer or bladder cancer (Adenowo, Oyinloye, Ogunyinka, & Kappo, 2015). Opisthorchis viverrini (Ov) is highly prevalent in southeast Asia and can lead to cholangiocarcinoma (CCA), Ov infection, associated with the production of cytokines and growth factor, may lead to inflammation and, if this persists over time, may turn to cholangiocarcinoma (CCA) (Khoontawad et al., 2017). Chlonorchis sinensis infection can lead to liver and biliary cancer: It is common in Asian countries (Kim, Pak, Kim, & Bahk, 2016). Helicobacter pylori bacteria can cause cancer, gastritis and ulcers in the stomach. In 2018, H.pylori caused 783,000 deaths among stomach cancer patients (Rawla & Barsouk, 2019). Chronic H.pylori infection can cause non- cardia gastric carcinoma (NCGC) (Plummer,

Franceschi, Vignat, Forman, & de Martel, 2015). Human papillomavirus is a common risk factor causing cervical cancer and oropharyngeal cancer: it is spread by sexual contact (Depuydt, Beert, Bosmans, & Salembier, 2016; Taberna et al., 2017). In the epidemiological literature, approximately 200 studies have reviewed cancer incidence related to the inadequate consumption of vegetables and fruit (Block, Patterson, & Subar, 1992). Antioxidants play an important role in limiting cancer incidence: between 64.0 to 81.0% of patient survivors and those diagnosed with cancer use multivitamins (Poljsak & Milisav, 2018). However, a large study in Finland among 30-year-old heavy smokers reported that taking B-carotene supplements led to a slight increase in the risk of lung cancer, total mortality and coronary heart disease. In contrast to this, other findings show that the consumption of fruit and vegetables increases protection (Heinonen et al., 1994). Low folic acid intake can lead to chromosome damage in humans (LeBlanc, Behan, O'Brien, Marchetti, & MacFarlane, 2018). Folic acid is thought to reduce the incidence of colorectal cancer (Burr, Hull, & Subramanian, 2017). Considering other dietary habits, red meat and fat increase the incidence of various cancers, such as colorectal, oesophageal, prostate, lung, pancreas and kidney, as well as non-Hodgkin's lymphoma (Boada, Henríquez-Hernández, & Luzardo, 2016).

Other risk factors

a. **Chemical factors and air pollution**: there are many types of chemicals and chemical mixtures that cause carcinogenicity in humans. This tends to follow exposure among small groups of people in workplaces such as refineries. Air pollution can also be found to carry hazardous carcinogenic toxins, such as carbon tetrachloride, benzene, formaldehyde and acetaldehyde (Zhou, Li, Huijbregts, & Mumtaz, 2015).

b. **Medication:** some medication, such as chemotherapeutic drugs, especially alkylating agents, can lead to second malignancy, leukemia and lymphomas (van Leeuwen & Ng, 2016). Some drugs that are used to reduce fever and relieve pain, such as phenacetin, can increase the risk of cancer (Malmström, 2017). Diethylstilbestrol is another medication which can increase the risk of cancer (Troisi et al., 2017). Immunosuppressive agents, such as cyclosporine, can also increase the risk of cancer (Geissler, 2015). Estrogen replacement therapy can increase the risk of breast cancer (Ettinger, Quesenberry, Schroeder, & Friedman, 2018).

1.1.3 Classifications of cancers

From a histological point of view, there are hundreds of different cancers, which can be classified into six main categories: carcinoma, sarcoma, myeloma, leukaemia, lymphoma, and mixed types.

a. **Carcinoma:**

This type of cancer develops from the epithelial cells (Lowe, 2001). This type of cancer is most common in elderly and can develop into lung, breast, colon, prostate, pancreas, oral, ovarian, skin, hepatocellular cancer and renal cell carcinoma (AIMU, 2016). There are many types of carcinoma: adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, anaplastic carcinoma, large cell carcinoma and small cell carcinoma (Travis, Brambilla, Muller-Hermelink, & Harris, 2004).

Signs and symptoms of carcinoma: these include blood in the stool, persistent cough, unexplained anaemia (low blood count), breast discharge (in the case of breast cancer), changes in urination, such as small amounts of urine, slow urine flow and blood in the urine, swallowing problems, vaginal bleeding, unexpected weight loss, night sweats,

fever, bloating and pelvic pain (emedicine health, 2020).

b. **Sarcoma**:

These types of cancer are formed from transformed cells of the mesenchymal (connective tissues) (J. Yang, Ren, Du, Hao, & Zhou, 2014). The connective tissues include hematopoietic tissues, cartilage, fat, vascular tissues and bone. Sarcomas can be formed from any of these types of tissue (Jeffrey S. Tobias, 2015). They are classified into two types: bone sarcomas and soft tissue sarcomas (Jeffrey S. Tobias, 2015).

Signs and symptoms of sarcoma: the symptoms of bone sarcomas are bone pain - the pain increasing at night - and swelling around the tumour. The symptoms of soft tissue sarcomas are painless lumps or nodules, a feeling of fullness, blood in the stool or vomit, black, tarry stools, abdominal pain and weight loss (Jeffrey S. Tobias, 2015; The American Cancer Society medical and editorial content team, 2018d).

c. **Myeloma:**

This type of cancer forms in plasma cells, especially the white blood cells that form in the bone marrow. White blood cells help the body to defend itself by producing antibodies and attacking germs. The uncontrollable production of plasma cells is called multiple myeloma.

Signs and symptoms of myeloma: bone pain, loss of appetite, fatigue, weight loss, nausea, vomiting, excessive thirst, numbness in the legs and confusion (Mayo Clinic, 2019).

d. Leukemia:

Leukaemia is also a group of blood cancers that are derived from the bone marrow and which are caused by abnormal cell growth (Institute & Health, 2014a). The cause of leukaemia is unknown as a combination of genetic and environmental factors can play a

role in its onset. Other risk factor can increase the incidence of leukaemia, such as chemotherapy, smoking, some chemicals, such as benzene, and Down syndrome (Hutter, 2015; Institute & Health, 213AD). Leukaemia is classified into four types: acute lymphoblastic leukaemia (ALL), chronic myeloid leukaemia (CML), chronic lymphocytic leukaemia (CLL) and acute myeloid leukaemia (AML) (Institute & Health, 213AD).

Signs and Symptoms of Acute Leukaemia: most symptoms are the result of a decrease in the normal level of blood cells: infection, bleeding, feeling weak or tired, pale skin, feeling dizzy, bruises, weight loss, fever, sweating at night and loss of appetite. Sometimes, leukaemia causes joint pain because leukaemia cells build up near the surface of the joints (Appelbaum, 2014; Hoffman et al., 2013; The American Cancer Society medical and editorial content team, 2018a).

e. **Lymphoma**:

This type of cancer is formed from haematopoiesis (blood-forming). Lymphoma is when blood cancer develops from lymphocytes (W A Newman Dorland, 2000). Lymphoma are sub-classified into two categories: Hodgkin's lymphomas (HL)and non-Hodgkin’s lymphomas (NHL) (Walter, 2013). According to the World Health Organization (WHO), there are two other types of lymphoma: multiple myeloma and immunoproliferative diseases. Approximately 90% of patients with lymphoma have non-Hodgkin’s lymphomas (NHL) (Institute & Health, 2014b; Walter, 2013).

Signs and Symptoms of Hodgkin’s Lymphoma: A lump in the neck or under the arm or in the groin is the most common symptom. Other symptoms include **c**hest pain, cough, difficulty in breathing, itching skin, fatigue and loss of appetite. Some people have B symptoms, such as fever, weight loss and sweating at night (The American

Cancer Society medical and editorial content team, 2018b).

Signs and Symptoms of Non-Hodgkin's Lymphoma: these include enlarged lymph nodes (a lump under the skin, on the side of the neck or in the groin or under the arm), easy bruising or bleeding, severe or frequent infections, chills, weight loss, fatigue, swollen abdomen, feeling full after eating a small amount of food, chest pain and shortness of breath or cough. B symptoms such as sweating at night, weight loss and fever. Lymphomas of the brain can cause headache, double vision, facial numbness and trouble with speaking. Lymphoma in the stomach or intestine can cause nausea, vomiting, loss of appetite and abdominal pain. Lymphoma in the chest can cause coughing, trouble with breathing and chest pain or pressure (DeVita et al., 2015; The American Cancer Society medical and editorial content team, 2018d).

f. **Mixed types:**

This is a mixed cancer that can form or develop from two different types of cell, such as adenosquamous carcinoma, teratocarcinoma, mixed mesodermal tumour or carcinosarcoma.

Signs and Symptoms of Mixed Types: these include blood in the urine or stool, sweating, stomach pain, difficulties in chewing and eating, weakness and urination problems (National Cancer Institute, 2019).

1.1.4 Clinical management

Cancer can be treated in various ways: by chemotherapy, hormonal therapy, targeted therapy, synthetic lethality, radiation therapy and or surgery.

1.1.4.1 Therapeutic management of cancer

a. Chemotherapy:

Chemotherapy is used in the treatment of cancer. Surgery or radiation therapy is used to remove cancer cells in certain areas in the body but chemotherapy is used to treat the whole body; it kills the metastasis cancer that spreads throughout the body (Liu, Liu, & Li, 2016). Chemotherapy is the first choice in the treatment of cancer (Airley, 2009). The combination in chemotherapy treatment has advantages, such as a decrease in the resistance to one agent, the reduction of toxicity and the use of lower dosages (Airley, 2009; Wagner et al., 2017). The different types of chemotherapy include: alkylating agents, plant alkaloids, antitumor antibiotics, antimetabolites and topoisomerase inhibitors. Alkylating drugs are used to treat many types of cancer, especially slow-growing cancers. and they are effective during all phases of the cell cycle. They are also used to treat solid tumours and leukaemia. The side effects of alkylating agents include infertility in males through a decrease in sperm production and the cessation of menstruation in females. Alkylating agents can also lead to acute myeloid leukaemia. The different types of alkylating agents include: alkyl sulfonates (busulfan), ethyleneimines and methylmelamines (hexamethylmelamine or altretamine), triazenes (dacarbazine, temozolomide), nitrogen mustards (mechlorethamine, mustine uramustine, cyclophosphamide ifosfamide, uracil mustard) and piperazines, nitrosoureas (carmustine, streptozocin) (Ralhan & Kaur, 2007). Plant alkaloids are used as anticancer treatment, and there are many types of them, such as vinblastine, vincristine, vinorelbine, vindesine, etoposide, taxol, taxotere, teniposide, navelbine, camptothecin, irinotecan and topotecan (Dholwani, Saluja, Gupta, & Shah, 2008). Vinblastine is used to treat Hodgkin’s and non-Hodgkin’s lymphoma, and is also used

in testicular carcinoma, germ cell tumours and breast cancer (Rowinsky & Donehower, 1995). Using vinblastine may lead to toxicity in white blood cells, chest pain, wheezing, constipation, vomiting, nausea, dyspnea and fever (Moudi, Go, Yien, & Nazre, 2013). Vincristine is used in the treatment of acute leukaemia, Wilm's tumour, neuroblastoma, Hodgkin's disease, rhabdomyosarcoma, refractory autoimmune thrombocytopenia, hemolytic uremic syndrome and thrombotic thrombocytopenia purpura. The side effects can include bone marrow suppression, nervous system toxicity, nausea, vomiting and constipation (Moudi et al., 2013; Rowinsky & Donehower, 1995). Taxol (paclitaxel) is also used as anticancer or antitumor treatment (Campbell & DeJong, 2005). It is used in the treatment of breast and ovarian cancer, and also has antifungal properties (J. Y. Li et al., 1998). Podophyllotoxin includes etoposide and teniposide. Etoposide is used in the treatment of acute myeloid leukaemia, lung, ovarian and testicular cancer, lymphoma and choriocarcinoma, Teniposide is used in the treatment of tumours of the central nervous system, bladder cancer and malignant lymphoma (Demain & Vaishnav, 2011). Irinotecan and topotecan are semisynthetic, produced from camptothecin, and they inhibit topoisomerase I, which plays an important role in DNA replication and RNA transcription (Mathijssen, Loos, Verweij, & Sparreboom, 2002), Topotecan is used in the treatment of ovarian cancer as a primary medication. There are other uses for it, which include treating pancreatic cancer, small cell and non-small cell lung carcinoma, retinoblastoma, leukaemia, acute myelogenous, leukaemia, chronic myelomonocytic, multiple myeloma, rhabdomyosarcoma, myelodysplastic syndrome, neuroblastoma and sarcoma (Topotecan, 2016), Irinotecan is used in the treatment of colorectal cancer as a primary medication, along with other uses, which include mesothelioma, cervical cancer, glioma, pancreatic cancer, oesophageal cancer, lung cancer, gastric cancer and mesothelioma (Absorption, 2006). The antitumor antibiotic prevents cell growth by

preventing DNA repair. The disadvantage of these drugs is their high toxicity; the antitumor antibiotics include mitomycins, bleomycins, anthracyclins, actinomycin D (Bhattacharya & Mukherjee, 2015). Daunorubicin, an anthracycline antibiotic, is used in the treatment of leukaemia, breast cancer, ovarian carcinoma and small cell lung cancer (Zhang, Yu, Wang, Wu, & Huang, 2015). Epirubicin, a derivative from doxorubicin, is used in the treatment of gastric, breast, lung and ovarian cancer. Idarubicin is used in the treatment of acute myelogenous leukaemia (Cortés-Funes & Coronado, 2007). Another doxorubicin derivative, valrubicin, is used in the treatment of bladder cancer (Steinberg, Kuznetsov, O'connor, & Alsikafi, 2001). Actinomycin and bleomycin are used in the treatment of squamous cell carcinomas and malignant lymphomas (Madathil et al., 2014).

Antimetabolites include cytarabine, methotrexate, fludarabine, gemcitabine, pemetrexed, fluorouracil, pralatrexate, decitabine, capecitabine and azacytidine (Harvey & Khuri, 2018). Methotrexate is an antifolate which is used in the treatment of lymphoma, sarcoma, graft- versus- host disease, breast, bladder, head and neck cancer and acute leukaemia (Garg et al., 2017; Pouessel et al., 2016; Wiczer, Dotson, Tuten, Phillips, & Maddocks, 2016). Gemcitabine, a pyrimidine antagonist, includes medication such as Floxuridine, Cytarabine, and Gemcitabine, 5-Fluorouracil and Capecitabine. It is used in the treatment of breast, head and neck, ovarian, cervical, bladder and kidney cancer (Noble & Goa, 1997). Topoisomerase inhibitors (I and II) include the topoisomerase I inhibitors topotecan and ironotecan, and topoisomerase II inhibitors include etoposide phosphate, etoposide, teniposide and amsacrine. DNA topoisomerases enzymes are responsible for controlling DNA replication; these drugs are used in various types of cancer that are linked with DNA. The topoisomerase inhibitors, such as irinotecon, inhibit DNA and RNA growth. They are used in breast

cancer, small cell lung cancer, leukaemia and colon cancer treatment. Topotecon is used in the treatment of head and neck cancer, malignant glioma and colorectal cancer (Sinha, 1995). Hormonal therapy is a non-toxic therapy used in the treatment of prostate and breast cancer. Hormonal therapy drugs include Selective Estrogen Receptor Modulators (SERMs) (e.g. tamoxifen) and aromatase inhibitors (Abraham & Staffurth, 2016). Many breast cancer treatments are dependent on estrogen; the use of SERM, such as tamoxifen, is considered the first drug of choice in the treatment of breast cancer in postmenopausal patients (Ito, 2001). Another approach to treating cancer is targeted therapy. This is different from chemotherapy as target therapy aims to reach cancer cells and kill them without affecting any normal cells; that means there will be a less toxic effect (Vasir & Labhasetwar, 2005) Monoclonal antibodies, which are used in targeted therapy, include rituximab, trastuzumab, gemtuzumab-ozogamicin, alemtuzumab, cetuximab, bevacizumab and ibritumomab-tiuxetan. Monoclonal antibodies are used in the treatment of many types of cancer. These antibodies include trastuzumab which is used in metastatic breast cancer treatment; bevacizumab, which is considered the drug of choice in the treatment of metastatic colorectal cancer; ibritumomab-tiuxetan, used for non-Hodgkin's lymphoma, and gemtuzumab-ozogamicin, for acute myeloid leukaemia (Ross, 2004). Synthetic lethality is another way of treating cancer. The principle of this approach is to kill cells by the synthesis of multiple mutations in the cancer cells (Lord, Tutt, & Ashworth, 2014). Poly (ADP-ribose) polymerase (PARP) inhibitors are the first synthetic lethality drugs to have been approved. PARP inhibitors include niraparib, rucaparib, used for ovarian cancer, and olaparib used in the treatment of breast, prostate and ovarian cancer (Lord & Ashworth, 2017; Zimmer, Gillard, Lipkowitz, & Lee, 2018)

b. **Radiation therapy**:

Radiotherapy is another alternative in the treatment of cancer. It is used to kill cancer cells by using ionizing radiation that deposits energy and causes cell death. The high energy leads to defects in the genetic structure of cells and prevents them from dividing (Jackson & Bartek, 2009). Radiation therapy can be used in the treatment of many types of cancers, such as skin cancers (squamous and basal cell), cervical , lung (non-small cell), and prostate carcinomas, Hodgkin's and non-Hodgkin's lymphoma, CNS tumours, and breast s, rectal and anal, and, bladder carcinomas and paediatric tumours (Baskar, Lee, Yeo, & Yeoh, 2012). External beam radiation therapy (EBRT) is one type of radiation therapy which is used for sarcoma. Several studies have reported that EBRT has a positive effect on local tumours (Albertsmeier et al., 2018). Three-dimensional conformal radiation therapy (3-D CRT) is used in the treatment of cervical oesophageal cancer (CEC) and it is considered standard therapeutic strategy for CEC because it protects the function and shape of the oesophagus (H. Yang et al., 2017). Intensity-modulated proton beam therapy (IMPT) and intensity-modulated photon therapy are used in the treatment of oropharyngeal carcinoma; IMPT is also used in the treatment of paediatric tumours. IMPT is less toxic than photon radiotherapy (Blanchard et al., 2016; Mizumoto et al., 2017). Image-guided radiation therapy (IGRT), another type of radiation therapy, is more accurate and precise when focused on a target (Nabavizadeh et al., 2016). Stereotactic ablative radiotherapy (SABR) it is has high local control and a better survival outcome compared to other types of radiotherapy; it is used with various solid tumours, such as non–small-cell lung cancer (Cannon et al., 2015). Intraoperative radiation therapy (IORT) is used during operations and when the tumour is very close to an organ; it is applied directly to the tumour. IORT can deliver high doses of radiation to the tumour and reduce the radiotoxicity of the organ. It is used on such cases as pancreatic cancer (Krempien & Roeder, 2017). Boron neutron capture therapy (BNCT)

is a technique used to treat tumour cells and it is used for the treatment of head and neck cancer. (BNCT) has a low level of intrinsic toxicity (Barth, Mi, & Yang, 2018; Nedunchezhian, Aswath, Thiruppathy, & Thirugnanamurthy, 2016).

c. **Surgical management of cancer**

Surgical management of cancer is one of the most important and promising treatments of many types of tumours. Surgical management has many advantages, such as the removal of tumours without causing damage to other tissue. There are many types of cancer surgeries, depending on the location of the tumour, its size and the stage of the cancer (Paridah et al., 2016). There are many types of surgeries in cancer management, such as: curative surgery, which is done when cancer is located in one part of the body; debulking surgery, which is used to remove a part of a cancer, not all of it, to prevent damage to the surrounding tissue; palliative surgery, which is used to control pain in cancer; supportive surgery, which is used to help patients get other treatment; reconstructive surgery, which is used to improve the appearance of the body after surgery, such as breast reconstruction after a mastectomy, and prophylactic surgery, which is used to remove tissue that may develop into cancer (Dana-Farber Cancer Institute, 2017).

d. Behavioral management of cancer

The ability of psychological management to decrease the stressful effects felt by cancer patient has been confirmed. The various approaches to behavioral management of cancer patients, such as psychoeducational interventions, supportive-expressive group therapy and multimodal intervention, should fit the needs of the patient (Penedo et al., 2004). Cognitive-behavioural interventions (CBIs) are used to improve the symptoms of cancer patients, especially when they have high levels of stress (Baider, Peretz, Hadani,

& Koch, 2001; Trask, Paterson, Griffith, Riba, & Schwartz, 2003). In breast cancer patients, CBIs are used to enhance the immune response after surgery (McGregor et al., 2004) and to improve sleep (Quesnel, Savard, Simard, Ivers, & Morin, 2003). The principle of CBIs is based on how a patient looks at their situation and how that affects their ability to control the situation. This therapy can change the way patients look at their situation by cognitively reframing or changing their perspective, thus improving their ability to control it (Sherwood et al., 2005). Problem-solving therapy is one type of CBIs that helps patients to control their symptoms by teaching them techniques to manage those symptoms and helping them to identify the pain level that they find unacceptable. Problem-solving therapy is used to focus on how to solve problems and manage them to enhance the quality of life (Taeidi, Montazeri, Behroozi, Zadeh, & Deilami, 2018; Visser et al., 2016).

1.1.5 Complications of cancer

Cancer pain is one of the many complications of the condition. Cancer pain is one of the most frightening complications of the disease (LeMay et al., 2011); the pain can be managed through opioids (Berg & Gerlach, 2018). Fatigue is another complication of cancer; it is one of the most common symptoms in cancer patients and can be managed by antidepressants, corticosteroids or psychostimulants (Morrow, Shelke, Roscoe, Hickok, & Mustian, 2005). Pulmonary complications, occurring in patients with cancer such as lung cancer, can lead to pulmonary infections, such as tuberculosis and bacterial pneumonia and can be managed by chemotherapy and inhaled opioid drugs (Abouzgheib & Dellinger, 2016). Nausea and vomiting are two of the symptoms of cancer or a side effect of chemotherapy; this can be controlled by anti-emetics (Lindley & Hirsch, 1992). Constipation and diarrhea are common complications of cancer, and they can lead to dehydration or electrolyte abnormality. A side effect of chemotherapy

can cause constipation such as vinca alkaloid; this can be managed by laxatives. Patients suffering from this condition should be rehydrated and, in severe cases, must be given antidiarrheal drugs, such as octreotide (Solomon & Cherny, 2006). Cachexia is one of the most severe complications of cancer. Weight loss is one of the main complication among cancer patients and it is appearing like anorexia, however, cachexia appears in chronic condition such as cancer. It causes increased morbidity and mortality, and can be managed by enhanced nutritional intake or by pharmacological interventions (C. Cooper, Burden, Cheng, & Molassiotis, 2015). Neurological complications in cancer patients can be divided into metastatic or non-metastatic. The complications of metastatic cancer such as lung, breast, brain and myeloma can be treated with non-enzyme-inducing anticonvulsants, such as pregabalin and by chemotherapy, surgery and radiation therapy (Giglio & Gilbert, 2010). Non-metastatic neurologic complications occur with tumours and can be treated by chemotherapy agents, such as vinca alkaloid, cytosine arabinoside, taxanes and 5-Fluorouracil (Cher, 2004).

1.1.6 Self-management of cancer

Self-management is the ability of a patient to manage the symptoms and difficulties of living with a chronic condition. Treatment involves lifestyle, physical and social adaptations (Barlow, Wright, Sheasby, Turner, & Hainsworth, 2002). High self-efficacy in cancer patients can lead to an enhancement of health care outcomes, such as a decrease in physical and psychological problems (Luszczynska, Sarkar, & Knoll, 2007; Parrott Roxanne, 2001). Self-care management is a broad term; it includes everything that patients do to maintain their health. It is focused on managing the disease or symptoms of the disease over the long term (Foster & Fenlon, 2011). Managing the

cancer can be enhanced by cooperation between patient and health care provider (Zhao, Brettle, & Qiu, 2018). The Health Foundation defines self-management support as health services that help patients or encourage them to live with long-term conditions and to enhance their health (Fenlon & Foster, 2009). With cancer pain, self-reporting is important so that all the dimensions of pain can be identified (Bodenheimer, Lorig, Holman, & Grumbach, 2002). The management of cancer pain is dependent on the patient and caregiver. Symptoms can be controlled by the patient with clinicians; the management can differ from one patient to another, it depends on the patient leading the approach (Luckett et al., 2013). For example, the patient may prefer to not mask the pain by taking drugs but decrease the level of pain (Lovell et al., 2014).

1.1.7 Economic burden of cancer

Cancer treatments causes the loss of economic resources and financial loss, leading to a fall in the quality of life (Yabroff, Lund, Kepka, & Mariotto, 2011). Furthermore, caregiving creates an economic burden for family members (Grbich, Maddocks, & Parker, 2001). The burden of cancer is high in low and middle-income countries. The incidence of cancer has increased in low-income countries because of demographic changes, which have led to greater exposure to risk factors. Around 60.0% of cancer cases are in low and middle-income countries (Farmer et al., 2010); 7%-10% of them will increase the cost of oncology in 2020 (Prager et al., 2018). Cancer also causes indirect economic burdens because it leads to lost workdays (Luengo-Fernandez, Leal, Gray, & Sullivan, 2013), even with an increase in expenditure on cancer treatment in recent decades (between 1960-2004), the share of health spending allocated to it has remained close to 5% (Bosanquet & Sikora, 2004; Mariotto, Robin Yabroff, Shao, Feuer, & Brown, 2011). The cost of one year's cancer drugs in the United States has

increased from $5,000-$10,000 before 2000 to more than $100,000 in 2012 (Kantarjian & Rajkumar, 2015), while in the Middle East, in Lebanon, the price of cancer drugs has increased from $7000 in 2014 to $8,400 in 2016 (Elias et al., 2018), and the median cost of cancer drugs in Jordan, such as for colon cancer, is JD 3,838; for rectal cancer, it is JD 3,623, and for colorectal cancer, it is JD 5,652 (Alefan, Malhees, & Mhaidat, 2017).

1.2 Overview of depression

Depression is one of the most common psychological disorders, characterized by sadness, pessimism and a decrease in one's usual activities. There are many types of depression, and the term is used to refer to a group of mood disorders or clinical conditions. Major Depressive Disorder (MDD) is the most common type of depression and it is characterized by an increased risk of attempted suicide (Lazarou, Kout, Kapsou, & Kaite, 2010). Depression is a state of low mood and involves the numbing of emotions (Semioshkina & Voigt, 2016). According to the WHO, in ten more years, depression will be the second-largest clinical condition in terms of morbidity, and the most common reason for people to visit a psychiatrist. (Kessler et al., 1994; Layer, K.; Khan, 2015).

1.2.1 Epidemiology of depression in the general population

Depression is a serious medical condition. According to the WHO, depression is the fourth leading medical disability, and will be the second by 2020 (Zheng, Wu, Lin, & Lin, 2017). The rate of depression depends on many factors, such as income, sex, age and health behaviour (Hammen, 2018). A previous study on 6,694 participants drawn from the general population in the states of California and New York found the prevalence of depression to be around 5.2% (Ohayon, 2007). The prevalence of

depression is higher in America, south Asia and North Africa (Weinberger et al., 2018; World Health Organization, 2017). Another meta-analysis study of more than 1,112,573 adults in 30 countries, found prevalence of depression were 12.9%, 7.2%, and 10.8%, respectively from 1994 to 2014 (Lim et al., 2018). According to the WHO there is 322 million people living with depression in the world, and the rate of depression increased by 18.4% between 2005 and 2015 (World Health Organization, 2017) .

1.2.2 Epidemiology of depression in patients with cancer

The prevalence of psychological disorder and its stages differs with the type of cancer and its severity, with anxiety shown in the early onset of the disease and major depression and attempted suicide shown in the advanced stages (Caruso et al., 2017). A previous study in the North of Jordan reported that the prevalence rate of depression was 51.9%, with 18.8% of the patients diagnosed with mild depression, 22.1% with moderate depression, and 11.0% with severe depression (Mhaidat, Alzoubi, Al-Sweedan, & Alhusein, 2009). A previous study reported that the prevalence rate of depression differs by type of cancer: 60.6% was recorded for head and neck cancer, 77.2% for lung cancer, 57.9% for breast cancer, 75.8% for oesophageal cancer, 63.4% for stomach cancer, 68.4% for liver cancer, 54.4% for colorectal cancer, and 71.1% for cervical cancer (Hong & Tian, 2014). A systematic review of 15 studies published between 1967-2018 involving 93,805 colorectal cancer patients found that the prevalence of depression was between 1.6% – 57.0% (Peng, Huang, & Kao, 2019). In another systematic review of 47,424 patients between 2000-2019 for the prevalence of depression among breast cancer patients was found to be 32.2% (Pilevarzadeh et al., 2019) In a further systematic review of 20 studies from 2000 to 2018, the prevalence of depression was found to be between 5.4% and 49.0% (Brandenbarg et al., 2019). A

study of 315 Chinese patients who had lung cancer found the prevalence of depression to be 57.1% (Yan, Chen, Li, & Zhang, 2019).

1.2.3 Etiology of depression

There are many factors which cause depression. These include genetic factors, changes in hormone levels, substance abuse and medical conditions (Islam, 2016; Pare & Mack, 1971; Zung, 1965). A further factor that can lead to depression is having suffered a traumatic event; there are many people going through traumatic events in their lives and this can lead to emotional distress (Regier et al., 1993). Childhood difficulties are a higher risk factor and these can increase depression risk. People who have suffered difficulties during their childhood, such as sexual abuse or the death of or separation from a parent, have a higher chance of developing the condition (Pincus et al., 1998; Simon & VonKorff, 1995). Natural and catastrophic disasters such as war, hurricanes and earthquakes, can be the cause of severe depression (Linde, 2008). A low level of serotonin (5-HT) is the major cause of this illness (Carr & Lucki, 2010).

1.2.4 Classifications of depression

a. **Major depression disorder (MDD):** it is the most common type of depression. The symptoms of this type affect eating, sleeping and performing daily activities (Layer, K.; Khan, 2015).
b. **Persistent depression:** it is a mild form of depression which can continue for up to two years or more. It is also called chronic depression (Layer, K.; Khan, 2015).

c. **Prenatal depression:** it occurs during pregnancy (Dollander, 2004).
d. **Postnatal depression (PND):** it occurs in women, but can also affect men. The cause of this type of depression is becoming a parent (P. J. Cooper & Murray, 1998).
e. **Manic depression or bipolar disorder:** it is characterized by symptoms of depression and mania or hypomania (Kilzieh & Akiskal, 1999).
f. **Psychotic depression:** some people with depression have symptoms of psychosis, such as hallucinations or delusion (Keller et al., 2006).
g. **Seasonal depression:** it is also called seasonal affective disorder. It is depression which develops during certain seasons, especially winter (Magnusson & Boivin, 2003).
h. **Situational depression:** it is depression which has developed because of a specific event or situation, such as a medical condition or the death of a loved one (Hirschfeld, 1981).
i. **Atypical depression:** it is one of the types of major depression but it is different because of its atypical features, such as an increase in appetite, weight and sleep (Davidson, Miller, Turnbull, & Sullivan, 1982).

1.2.5 Symptoms of depression

The symptoms include hopelessness, pessimism, crying, social withdrawal, confusion, feelings of guilt, loss of interest in usual activities, weight change (loss or gain), sleep change (insomnia or hypersomnia), loss of interest in sex, psychomotor agitation or retardation, thoughts about death or suicide, headaches, back pain, stomach pain, fatigue, heart palpitations, or hallucination and anxiety (Baethge et al., 2005; Cassano, 2002; Semioshkina & Voigt, 2016).

1.2.6 Diagnosis of depression

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) five or more of the following symptoms need to have been present within the previous two weeks, and nearly every day: a depressed mood, insomnia or hypersomnia, psychomotor agitation or retardation, weight loss or gain, diminished interest in usual activities, fatigue, worthlessness, a feel of guilt, indecisiveness and loss of concentration, and thoughts about death and suicide ideation or attempted suicide (Koukopoulos & Sani, 2014).

1.2.7 Risk factors of depression

There are many psychosocial factors associated with depression, such as alcohol use, drug use during pregnancy, tobacco use, maternal stress, low levels of support, physical inactivity, or low birth weight (Meng et al., 2017). Other risk factors include loneliness, stressful life experiences, a family history of depression or genetic factors, a medical condition or chronic disease, childhood trauma, economic problems or drug abuse (Semioshkina & Voigt, 2016), Divorced and widowed people are at a higher risk (Kebede et al., 2003).

1.2.7.1 Drug use and the occurrence of depression

Some drugs may lead to depression as a side effect, such as the angiotensin-converting enzyme inhibitors (ACE), the calcium channel blockers, and isotretinoin. Several studies have investigated these drugs (Patten & Barbui, 2004). B-blockers are a more common cause of depression (Patten & Love, 1997). Corticosteroids, such as prednisolone, may cause severe psychiatric reactions (Holvey, Connolly, & Taylor,

2010). A cross-sectional study has shown that corticosteroids can cause depression (Scott, Jeanne, & Edgar, 1995). HMG-CoA reductase inhibitors also cause depression; this has been reported in two studies (Harrison & Ashton, 1994; Wardle et al., 1996). Some studies have reported interferon-alpha as causing depression (Bonaccorso et al., 2002; Hosoda et al., 2000), and also interferon-Beta (Feinstein, O'Connor, & Feinstein, 2002; Zephir et al., 2003). Mefloquine is another drug which can cause depression (Corbett, Doherty, & Behrens, 1996; Phillips & Kass, 1996), and some studies have reported that tamoxifen is linked with it (Breuer & Anderson, 2000; Shariff, Cumming, Lees, Handman, & Cumming, 1995).

1.2.8 Complications of depression

Untreated depression affects the quality of life and causes serious emotional and behavioral problems. Some of these complications include alcohol abuse, drug abuse, relationship problems, anxiety, social isolation, suicidal ideation or attempt, and self-mutilation (Bentley, Pagalilauan, & Simpson, 2014).

1.2.9 Management of depression

There are two approaches to managing depression: 1) by medication management, and 2) by behavioural or non-pharmacological management. The goal of depression treatment is to minimize the symptoms, decrease depressive episodes and enhance adherence to medication (Wells BG, Dipiro JT, Dipiro CV, 2009).

1.2.9.1 Therapeutic management of depression

There are many types of antidepressant medications to treat depression. These include:

a. Selective serotonin reuptake inhibitors (SSRIs), including: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline (Ferguson, 2001).
b. Serotonin–Norepinephrine reuptake inhibitors (SNRIs), including: desvenlafaxine, duloxetine and venlafaxine (Machado & Einarson, 2010).
c. Monoamine oxidase inhibitors (MAOIs), including: phenelzine, selegiline and tranylcypromine (Shulman, Herrmann, & Walker, 2013).
d. Alpha2-adrenergic antagonists, including: mirtazapine (Croom, Perry, & Plosker, 2009)
e. Mixed serotonergic effects (mixed 5-HT), including: nefazodone, trazodone and vilazodone (Chen & Marsh, 2013).
f. Tricyclic antidepressants (TCAs), including: amitriptyline, desipramine, doxepin, imipramine and nortriptyline (Diaz et al., 2018).
g. Norepinephrine and dopamine reuptake inhibitors (NDRI), including: bupropion (Dean, Horndasch, Giannopoulos, & McCabe, 2016).
h. Other medications are augmenting and adjunctive medications, including: mood stabilizers (lithium) and antipsychotics (McGirr, Vöhringer, Ghaemi, Lam, & Yatham, 2016).

SSRIs are more effective for treating depression and safer than TCAs (Mendlewicz & Lecrubie, 2000). Fluoxetine is the only SSRI and antidepressant prescribed for children (March et al., 2004). MAOIs are not selective MAO-A and MAO-B. MAOIs have a serious drug-food interaction, especially with food with high levels of tyramine. This interaction can lead to a fatal hypertensive crisis (Mann, 2005). SNRIs are useful in the treatment of chronic pain that is associated with depression (Stahl, Grady, Moret, & Briley, 2005). All antidepressants increase suicidal thinking. Some antidepressants,

those that have a serotonergic effect, can cause serotonin syndrome, neuromuscular abnormities or mental status changes. There are many side effects from taking antidepressants, such as sweating, sexual dysfunction, nausea, vomiting, insomnia, liver toxicity (especially with nefazodon), weight gain, and dry mouth (Wells BG, Dipiro JT, Dipiro CV, 2009). Sometimes, antipsychotics are used with antidepressants to treat psychotic depression. There are two types of antipsychotic drugs: typical antipsychotic drugs (chlorpromazine, fluphenazine, and haloperidol) and atypical ones (olanzapine, aripiprazole, quetiapine, clozapine, ziprasidone, risperidone) (Masand, 2004; Rothschild et al., 2004). Atypical antipsychotics are used in the treatment of bipolar and resistant major depression (Keck Jr, 2005; Kennedy & Lam, 2003). In patients with no response to a single antidepressant, lithium is added (Bauer & Döpfmer, 1999; De Montigny, 1994).

1.2.9.2 Behavioural management of depression

Psychotherapy is considered the first line of treatment for mild depression but is not considered first line in bipolar cases or cases of severe depression (Mann, 2005). The combination of medication and psychotherapy may enhance the treatment, reduce relapse, enhance the quality of life and enhance adherence to medication (Pampallona, Bollini, Tibaldi, Kupelnick, & Munizza, 2004).

1.2.10 Drug-drug interaction of antidepressants with anticancer medication

Antidepressants are commonly used in the treatment of depression in cancer patients. There may be a drug-drug interaction between the second generation of antidepressants and the anticancer drugs (Hemeryck & Belpaire, 2002; Spina, Santoro, & D'Arrigo,

2008),. SSRIs and Hypericum extract have the ability to inhibit the cytochrome P450 isoenzymes and CYP2D6. The use of these drugs will decrease the benefits of anticancer medication such as tamoxifen by decreasing the active metabolites. The combination of paroxetine and tamoxifen in breast cancer patients will increase the risk of death (Kelly et al., 2010). Citalopram, escitalopram, mirtazapine and venlafaxine are weak inhibitors of CYP iso-form and have a weak interaction with anticancer medication (Caraci, Crupi, Drago, & Spina, 2011). Extracts of Hypericum perforatum are used in the treatment of mild to moderate depression (Kasper, Caraci, Forti, Drago, & Aguglia, 2010), Hypericum extract can change the pharmacokinetics of anticancer drugs and increase the expression of P-glycoprotein (P-gp), which transports the anticancer drugs (Blower, De Wit, Goodin, & Aapro, 2005; Izzo, 2004; Kober, Pohl, & Efferth, 2008). Many antineoplastic agents have drug interactions with antidepressants such as fluvoxamine, sertraline, paroxetine and fluoxetine because they both share the same metabolic pathway and that will lead to a decrease in the efficacy of antineoplastic or an increase in its toxicity (Rodin et al., 2007).

1.2.11 The use of antidepressant medications in the management of depression among patients with cancer

Previous studies have shown that the poor psychological status of a patient may influence the duration of their illness and the power of their immune status (Greer, 1983; Miller, 1998). In addition, untreated depression can lead to increased morbidity and mortality in cancer patients (Newport & Nemeroff, 1998). Previous studies have reported the role of antidepressants in alleviating their symptoms and improving their quality of life (G. et al., 2007; M. Li, Fitzgerald, & Rodin, 2012). Antidepressants medications can also be used for non-psychiatric cancer-linked symptoms, such as hot

flashes, neuropathic pain, nausea and vomiting, fatigue, and pruritus (Luigi Grassi, Caruso, Hammelef, Nanni, & Riba, 2014). There are many classes of antidepressant, such as monoamine oxidase inhibitors (MAOIs), which are used in patients who are depressant resistant but they are not used in cancer patients because of drug interaction with a wide range of cancer medication Tricyclic antidepressants are also not used because of their anticholinergic profile that may be a problem for cancer patients. SSRIs have the fewest drug-drug interactions, especially sertraline, citalopram and escitalopram. These are considered the first-line treatment of depression in cancer patients, with bupropion, duloxetine and mirtazapine also being used in this capacity (L Grassi, Nanni, Rodin, Li, & Caruso, 2017). Selective SNRIs, such as reboxetine, are used in the treatment of depression in cancer patients (Luigi Grassi, Biancosino, Marmai, & Righi, 2004). A study of 1,538 cancer patients with depression showed that 1,130 (73.0%) were not receiving antidepressants (Walker et al., 2014).

Chapter Two: Literature review on the prevalence of depression among patients with cancer

The prevalence rate of depression in patients with cancer is not easy to predict. The reported prevalence rate of depression varies from 1.0% among patients with acute leukaemia to over 40% of patients with other malignant diseases (Bukberg, Penman, & Holland, 1984; Colón, Callies, Popkin, & McGlave, 1991). A study by McDaniel investigated the prevalence rate of depression among cancer patients and reported that the prevalence of major depression disorders ranged between 4.8% - 9.2%. Another study by Derogatis investigated the prevalence of the rate of depression among adults treated for three different types of cancer; of which 53.0% were classified as having no psychiatric diagnosis and the remaining 47.0% being diagnosed with different psychological problems (Derogatis et al., 1983). In a study of 1,217 Chinese cancer patients, the prevalence rates of depression were 77.2% for lung cancer, 75.8% for oesophageal, 71.1% for cervix, 68.4% for liver, 63.4% for stomach, 60.6% for head and neck, 57.9% for breast and 54.4% for colorectal cancer. The risk factors influencing depression in patients were age, pain, educational level, gender and performance status (Hong & Tian, 2014). In a cross-sectional study of 96 patients in Rwanda, the results reported that 67.7% of the study population had depression (Uwayezu, Gishoma, Sego, Mukeshimana, & Collins, 2019). In a cross-sectional analysis study of 39,223 metastatic cancer patients using hospital discharge data from the National Inpatient Sample between 2008 and 2013, the results reported that the prevalence of depression among

metastatic cancer patients was 7.3% (Boakye et al., 2020). In another study, in south Korea among 1,248,914 patients with cancer, the prevalence rate of depression was reported as 3.6%, and the highest percentage of sufferers was among patients with lung cancer (11.0%), followed by non-Hodgkin's lymphoma (9.2%), prostate (9.1%), bladder (8.8%), breast (7.8%), cervical (7.8%), colorectal (7.7%), stomach (6.9%) and liver cancer (6.5%) (Park et al., 2017). In a meta-analysis of 14 studies, among a total number of 2,831 patients, the prevalence of depression among patients with cancer was 35.0% (Aryankhesal et al., 2019). In a study in India among 120 cancer inpatients, the prevalence of depression was 64.2% (Kumar, Singh, Rae, Singh, & Singh, 2016). In another study in India, but among 534 cancer outpatients, the results reported 46.4% of patients had depression (Shankar, Dracham, Ghoshal, & Grover, 2016). A study in Portugal of 270 cancer inpatients showed 34.1% had depression (Cardoso, Graca, Klut, Trancas, & Papoila, 2016). Among 108 outpatients with cancer in Thailand, 29.6% were diagnosed with a depressive disorder (Maneeton, Maneeton, & Mahathep, 2012). A study in India among 401 inpatients reported 43.0% of patients had depression and needed pharmacological intervention (Tiwari, 2019). In Germany, a study among 4,705 outpatients with cancer reported the rate of depression as 11.1% (Grapp, Terhoeven, Nikendei, Friederich, & Maatouk, 2019). A study in Singapore among 315 cancer inpatients presented results showing 16.8% of them had depression (Tan, Beck, Li, Lim, & Krishna, 2014). A study in Pakistan of 116 cancer inpatients reported the prevalence rate of depression as being 58.0% (Mushtaq et al., 2017). In another study in India of 234 cancer outpatients, the prevalence of depression was reported to be 70.0% (Sudarisan, Abraham, & George, 2019). A study in Europe among 935 inpatients and outpatients reported 134 patients (14.3%) had depression, of which 92 (11.5%) were non-depressed patients using antidepressants, and 32 (23.9%) depressed patients were

using antidepressants (Grotmol et al., 2019). A study in Turkey of 170 elderly cancer patients reported 19.2% had depression, and 18.2% had already been diagnosed with depression and were using antidepressants (Atag et al., 2018).

3. Chapter Three: Methods

3.1 Aim

This study aims to investigate the prevalence rate of depression and the utilization of antidepressants among cancer patients in King Hussein Cancer Center (KHCC) in Jordan.

3.2 Study design

This was a prospective cross-sectional study conducted at KHCC in Amman, Jordan, between October 2019 and February 2020.

3.3 Sample size calculation

The minimum required sample size for this study was 384 participants. The sample size for this study was calculated using the following formula, which is used for prevalence studies (Taherdoost, 2017):

$$\text{Sample size} = \frac{Z_{1-a/2}{}^2 P(1-P)}{d^2}$$

$Z_{1-a/2} =$ Is standard normal variate (at 5% type 1 error ($p<0.05$) it is 1.96 and at 1% type 1 error ($p<0.01$) it is 2.58). As in majority of studies P value are considered significant below 0.05 hence 1.96 is used in formula.

P = Expected proportion in population based on previous studies or pilot studies.

d = Absolute error or precision

Sample size = (1.962 * 0.52 (1-0.52))/ 0.052 = 3.84 * (0.52*0.48) = (3.84 *0.25)/0.0025 = 384 participants

3.4 Sampling strategy

Cancer patients who had any type of cancer, at any stage, and who were willing to participate in the study formed the study population.

3.5 Sampling procedure

A convenience sampling technique was used to recruit eligible participants. This sampling technique is a type of non-probability sampling in which participants from the target population who met the inclusion criteria of the study and who were easily accessible through geographical proximity, available at a given time, or who were willing to take part in the study were included. Patient recruitment was done by trained pharmacists (including the researcher). The questionnaire was completed with eligible participants in a consistent manner to reduce the risk of assessment bias.

3.6 Inclusion and exclusion criteria

Patient recruitment in this study was carried out based on the following inclusion and exclusion criteria:

Inclusion criteria: a) have any type of cancer, b) from any stage of the disease, c) in the inpatients and outpatient's settings, d) above 18 years old, e) whether male or females, and f) are stable and conscious patients.

Exclusion criteria: a) patients who are unconscious, b) patients who refused to sign consent form, c) patients who do not speak Arabic , and d) patients under 18 years old.

3.7 Participant recruitment

Cancer patients in KHCC were approached and invited to participate in the study. When a patient agreed to participate, the aim and objectives of the study were explained further. Participant information sheets were provided for further clarification. In addition, the participants were asked for written consent to participate.

The participants were informed that there was no right or wrong answer to the questions they were being asked. In addition, they were notified about how long answering the study questions might take. Their contribution was appreciated, and they were thanked for their help towards improving healthcare. Furthermore, they were assured that the study information was completely anonymous and the researcher(s) would not be able to identify them from the responses provided. Furthermore, they would not be asked to put their name anywhere on the data collection form and their information would not be used for any purpose other than this research. They were provided with the researcher's contact details if they needed any further clarification. Finally, they were notified that participation was voluntary and they were free to withdraw from the study at any time, without giving any reason.

3.8 The questionnaire tool

Previously validated scales, the Patient Health Questionnaire (PHQ)-9 scale (Arabic version) and the Hospital Anxiety and Depression Scale (HADS) (Arabic version) (Fitzpatrick, Gibbons, & Mackintosh, 2009), were used in this study to explore the prevalence and use of antidepressant medication among cancer patients, and the degree of depression severity. The PHQ-9 scale is a 9-question instrument given to patients in a primary care setting to screen for the presence and severity of depression. The HADS is

a 14-question instrument given to patients in a secondary care setting to screen for the presence and severity of depression.

The use of a pre-existing instrument has the advantage of it being a validated and tested instrument, which increases the reliability of its measurements. The HADS questionnaire is a 14-question instrument that asks the patients about the degree of applicability of each item (question) using a 4-point Likert scale. It contains two subscales: one for depression and one for anxiety. Each one was comprised of seven questions. We were interested in the first subscale, which was about depression. The patients' responses ranged from 0 to 3, where 0 meant "Often" and 3 meant "Very seldom" or from "Not at all" to "Most of the time". Similarly, in the PHQ-9 questionnaire, the patients were asked about the degree of applicability of each item (question) using a 4-point Likert scale. Their responses ranged from 0 to 3, where 0 meant "Not at all" and 3 meant "Nearly every day".

3.8.1 Estimation of depression prevalence and classification of depression.

The prevalence rate of depression was determined using a cut-off point of the PHQ-9 and HADS scales. In the inpatient department, using the HADS instrument, depression was defined as a total score of (10 or more) on the "depression subscale". In the outpatient department, depression was defined as a total score of (15 and above) in the PHQ-9 instrument, indicating a case of severe depression.

The prevalence rate of depression was estimated by dividing the number of patients who exceeded the borderline score by the total number of patients.

In the inpatient department

The depression subscale of the HADS instrument includes seven items. Items are scored from 0 to 3, generating a total score ranging from 0 to 21. A total score of 0–7 indicates a normal case, 8–10 a borderline case, and 11– 21 an abnormal case of depression.

In the outpatient department

The PHQ-9 instrument includes nine items, which are scored from 0 to 3, generating a total score ranging from 0 to 27. A total score of 0 – 4 indicates minimal depression, 5 – 9 mild depression, 10 – 14 moderate depression, 15 - 19 moderately severe depression, and 20 – 27 severe depression.

3.9 Ethical considerations

Approval for this study was obtained from the Institutional Review Board committee at King Hussein Cancer Center in Jordan (No. 19 KHCC 94).

3.10 Statistical analysis

Descriptive statistics were used to describe patient demographics, medication use and comorbidities. Continuous data were reported as the mean ± SD for normally distributed variables and the median (interquartile range (IQR)) for non-normally distributed variables. Categorical data were reported as percentages (frequencies). Logistic regression was used to estimate odd ratios (ORs), with 95% confidence intervals (CIs) for anxiety or depression. Logistic regression models were carried out using anxiety or depression scores above the cut-off points highlighted above. A two-sided $p<0.05$ was considered as statistically significant. The statistical analyses were carried out using SPSS for Windows (version 25; Chicago, IL, USA).

4.Chapter Four: Results

4.1 Prevalence of depression among cancer patients in the inpatient settings

The total number of participants from the inpatient department was 399, of which 225 (56.4%) were males with a mean age 55.6 (SD: 15.6). Cancer metastasis in the inpatient department can be described as follows: 80 (20.1%) patients reported that they were diagnosed with metastatic cancer, 146 (36.6%) non-metastatic, and 173 (43.4%) didn't know the stage of their disease. The most prevalent stage of metastasis was stage 4, which was reported among 65 (81.3%) patients. In term of types of cancer therapy being received by the patients, around 190 (47.6%) patients reported that they were being treated by chemotherapy, 119 (29.8%) by a combination of surgery and chemotherapy, 116 (29.1%) patients by radiotherapy, and 40 (10.0%) had undergone surgery. The median duration of the disease was 12.00 years (IQR: 4:00 – 36:00). The results showed that 149 (37.3%) patients had first-degree relatives who had had cancer, of which 28 (18.8%) had relatives with the same type that they had. The majority of the patients were married (n= 331; 83.2%). Around 43.1% (n= 172) of the patients were unemployed, and 82.0% (n= 327) of them reported that their income was lower than 500 JD. For further details on patient demographics in the inpatient settings, refer to **Table 1**.

Table 1: Patient demographics inpatients setting; n= 399.

Variable	Frequency (%)
Gender	
Males	225 (56.4%)
Female	174 (43.6%)
Marital status (n= 398)	
Single	37 (9.3%)
Married	331 (83.2%)
Divorced	8 (2.0%)
Widowed	22 (5.5%)
Employment status	
Employed	103 (25.8%)
Unemployed	172 (43.1%)
Retired	124 (31.1%)
Monthly income	
Lower than 500 JD	327 (82.0%)
500 to 1000 JD	54 (13.5%)
1000 to 1500 JD	7 (1.8%)
1500 JD or above	11 (2.8%)
Area of residence	
Amman (the capital)	229 (57.4%)
Other cities	126 (31.6%)

Outside Jordan	44 (11.0%)
Nationality	
Jordanian	344 (86.2%)
Non-Jordanian	55 (13.8%)
Cancer metastasis	
Metastatic	80 (20.05%)
Non-metastatic	146 (36.6%)
I don't know	173 (43.4%)
Stage of metastasis (n= 80)	
1	2 (2.5%)
2	5 (6.3%)
3	8 (10.0%)
4	65 (81.3%)
Cancer therapy	
Surgery	40 (10.0%)
Chemotherapy	190 (47.6%)
Combination of surgery and chemotherapy	119 (29.8%)
Radiotherapy	116 (29.1%)
Was not receiving treatment	36 (9.0%)

The most common types of cancer among the patients from the inpatient department were: lymphoma at 60 (15.0%); breast 47 (11.8%); lung 44 (11.0%) and colon 44 (11.0%). For more information, please refer to **Table 2**.

Table 2: Types of cancer among the study participants in the inpatient department.

Type of cancer	Frequency (%)
Lymphoma	60 (15.0%)
Breast	47 (11.8%)
Lung	44 (11.0%)
Colon	44 (11.0%)
Bone marrow	18 (4.5%)

Bladder	18 (4.5%)
Ovarian	17 (4.3%)
Pancreatic	15 (3.8%)
Brain	14 (3.5%)
Stomach	14 (3.5%)
Liver	13 (3.3%)
Prostate	13 (3.3%)
Cervical	10 (2.5%)
Kidney	10 (2.5%)
Pharyngeal	9 (2.3%)
thyroid	9 (2.3%)
Sarcoma	8 (2%)
Multiple myeloma	6 (1.5%)
Testicular	6 (1.5%)
Laryngeal	6 (1.5%)
Mouth	4 (1.0%)
Colorectal	3 (0.8%)
Rectal	3 (0.8%)
Jaw	2 (0.5%)
Oesophageal	2 (0.5%)
Bone	1 (0.3%)
Leukaemia	1 (0.3%)
Thymus gland	1 (0.3%)
Adrenal gland	1 (0.3%)

Around 37.1% (n= 148) of the patients reported that they felt depressed; however, only 14.1% (n= 21) reported that they were receiving antidepressant medication. A majority of the patients who received antidepressant medication (n=19; 90.5%) had received instructions on how to use them: 18 (94.7%) from physicians and one (5.3%) from a nurse. A total of 15 out of 19 (78.9%) considered these instructions important.

Only two out of 21 patients (9.52%) who have received antidepressant treatment had questions about it, two of them asked about side effect and one patient asked about treatment time, and another patient asked about interaction with other drugs. When patients were asked about the duration of time it takes for the antidepressant effects be observed, eight out of 19 patients (42.1%) said that they didn't know, while five (26.3%) thought the antidepressant effect should be observed after 12 hours of drug administration (see **Figure 1**).

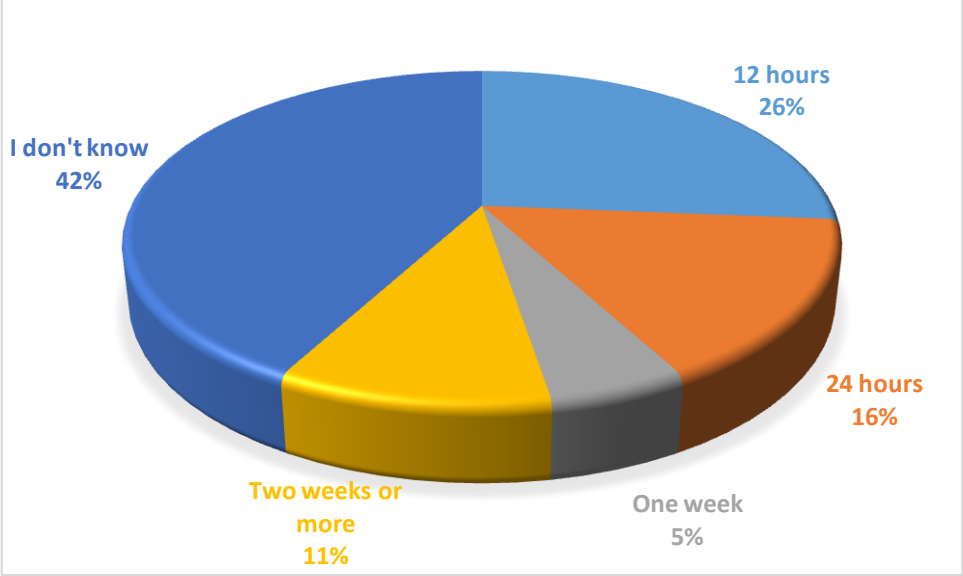

Figure 1: Patients' answers when they were asked About anticipated onset of antidepressant drug action (n= 19).

Only two (10.0%) out of 20 patients increased their dose of antidepressants without consulting their doctor and 18 (90%) patients said they had not increased the dosage. The results show that nine (45.0%) out of 20 patient said they had experienced side effects from taking antidepressants and eight (40.0%) patients said they had not. Eight (88.9%) out of the nine complained of dizziness and six (66.7%) complained of nausea (see **Table 3** for more information).

Table 3: Patient reported side effects from the use of antidepressants (n= 20).

Variable	Frequency (%)
Yes	9 (45.0%)

No	8 (40.0%)
I don’t know	3 (15.0%)
Side effect (n=9)	
Dizziness	8 (88.9%)
Nausea	6 (66.7%)
Vomiting	4 (44.4%)
Diarrhea	2 (22.2%)
Anxiety	2 (22.2%)

Around 50.0% of the patients, didn’t know whether or not antidepressants were addictive, whereas 35.0% of the patients thought antidepressants cause addiction. Nine patients (45.0%) did not know whether or not antidepressants can cause tolerance, whereas five patients (25.0%) thought antidepressants could cause tolerance.

Around 50.0% of the patients, 10 out of 20, thought they should stop taking antidepressant drugs gradually, and five (25.0%) of patients stopped taking the drug without consulting their doctor. All patients who stopped the antidepressant therapy reported that low tolerance to side effects was one of the main causes (see **Table 4** for more information).

Table 4: Knowledge of patients about treatment withdrawal (n=20).

Variable	**Frequency (%)**
Should the drug be withdrawn at the end of the treatment gradually?	
Yes	10 (50.0%)
No	5 (25.0%)
I don’t know	5 (25.0%)
Did you stop treatment without consulting the doctor (n=5)	Yes 5 (25.0%)
Reasons for antidepressants withdrawal (n = 5)	

Low tolerance to side effects.	5 (100%)
Improvement of depression symptoms.	1 (20.0%)
Interactions with other medications.	1 (20.0%)

The results reported seven (35.0%) out of 20 patients took other medication besides their antidepressant drugs, three (43.0%) out of the seven took propranolol with their antidepressant drugs, the same percentage took lorazepam, one patient reported the use of warfarin, and one patient reported the use of carbamazepine.

The results showed five (25.0%) out of 20 used citalopram (see **Table 5** for more information). The mean age of first use of an antidepressant was 50.4 years (SD: 18.7). 10 (50.0%) out of 20 patients used the antidepressant drug last year, 12 (24.0%) out of 20 currently use antidepressant drug and 14 (70.0%) out of 20 are under medical monitoring. The results showed that 15 (75.0%) out of 20 patients used antidepressant drugs for depression, while five (25.0%) out of 20 patients used antidepressant drugs for anxiety.

Table 5: The antidepressant that patients used (n= 20).

Medication	**Frequency (%)**
Citalopram	5 (25.0%)
Mirtazapine	2 (10.0%)
Sertraline	2 (10.0%)
Fluoxetine	1 (5.0%)
Amitriptyline	1 (5.0%)
Indication (n= 20)	
Depression	15 (75.0%)

Anxiety	5 (25.0%)

Depression states among patients

The state of depression was evaluated using HADS: 0-7= normal, 8-10 = borderline abnormal (borderline case), 11-21 = abnormal (case). Based on patients' scores, from HADS scale the results showed 195 (48.9%) out of 399 patients were normal, 148 (37.1%) were abnormal and 56 (14.0%) were abnormal borderline cases (see **Figure 2**).

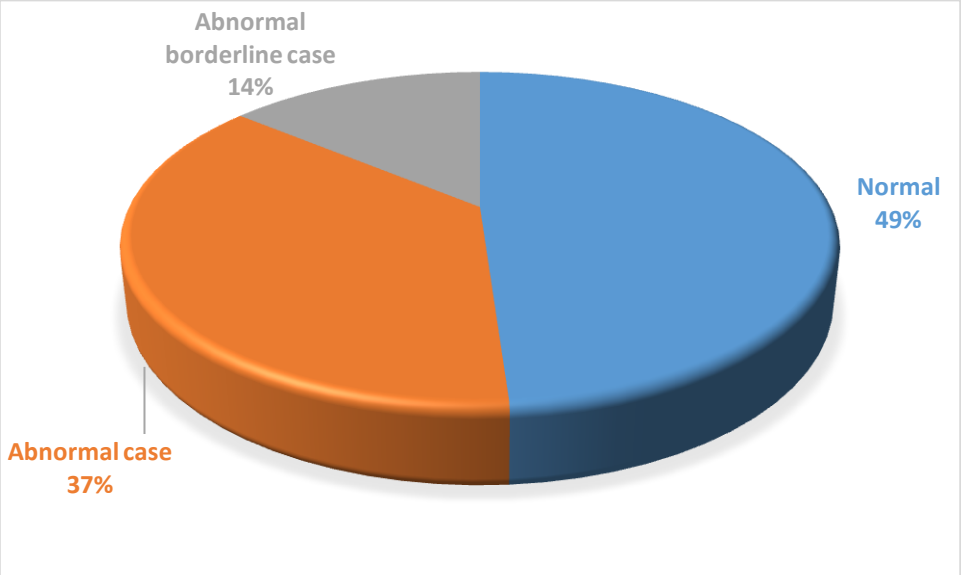

Figure 2: Depression states among patients based on scores from the HADS scale: (n=399).

After examining the risk factor for depression among patients in the inpatient department, the results showed that the patients who had metastatic cancer were more likely to be depressed, and that there was statistical significance between having metastatic cancer and depression [OR: 2.62 (1.61 – 4.28)]; the results showed stage three as [OR: 5.26 (1.05 – 26.41)] and stage four as [OR: 2.73 (1.61 – 4.62)] (for more information see **Table 6**).

Table 6: Risk factors of depression according to patient demographics.

Variable	Odds ratio (95%CI) for depression according to HADS	P-value
Gender		
Male (Reference)	1.00	
Female	1.12 (0.75 – 1.68)	0.575
Age		
Less than 50 years	1.00	
50 years and above	0.76 (0.50 – 1.18)	0.221
Marital status		
Single (Reference)	1.00	
Married	1.15 (0.66 – 1.99)	0.628
Divorced	1.73 (0.43 – 7.01)	0.445
Widowed	0.63 (0.24 – 1.63)	0.338
Occupational status		
Employed (Reference)	1.00	
Unemployed	1.15 (0.76 – 1.73)	0.503
Retired	1.16 (0.75 – 1.80)	0.501
Monthly income		
Below 500 JD (Reference)	1.00	
500 to 1000 JD	0.68 (0.36 – 1.27)	0.224
1000 to 1500 JD	1.28 (0.28 – 5.79)	0.751
More than 1500 JD	0.97 (0.28 – 3.37)	0.960
Duration of disease		

Less than 12 years (Reference)	1.00	

Type of cancer	Odds ratio (95%CI) for depression according to HADS score	P-value
12 years and above	1.10 (0.72 – 1.67)	0.656
Metastasis		
No (Reference)	1.00	
Yes	2.62 (1.61 – 4.28)***	0.000***
Stage of cancer		
1 (Reference)	1:00	
2	0.42 (0.05 – 3.79)	0.440
3	5.26 (1.05 – 26.41)*	0.044*
4	2.73 (1.61 – 4.62)***	0.000***
Cancer therapy		
Not receiving treatment (Reference)	1.00	
Chemotherapy	1.12 (0.74 – 1.67)	0.601
Combination of surgery and chemotherapy	0.77 (0.49 – 1.20)	0.245
Radiotherapy	1.51 (0.97 – 2.34)	0.070
Surgery	1.02 (0.52 – 2.00)	0.955

After examining the risk factors for depression, according to the type of cancer experienced by patients in the inpatient department, the results showed that there was no statistically significant association between specific types of cancer and depression (for more information see **Table 7**).

Table 7: Risk factors of depression according to type of cancer.

Bladder	1.74 (0.68 – 4.49)	0.251
Prostate	0.75 (0.23 – 2.47)	0.632
Lung	1.64 (0.87 – 3.08)	0.124
Testicular	1.71 (0.34 – 8.59)	0.514
Breast	0.86 (0.45 – 1.63)	0.645
Cervical	0.18 (0.02 – 1.46)	0.109
Colon	1.20 (0.63 – 2.27)	0.579
Rectal	0.85 (0.08 – 9.42)	0.892
Ovarian	1.19 (0.45 – 3.21)	0.722
Pancreatic	1.14 (0.40 – 3.26)	0.812
Brain	0.67 (0.21 – 2.17)	0.504
Stomach	0.45 (0.12 – 1.65)	0.228
Bone	-	-
Pharyngeal	2.16 (0.57 – 8.17)	0.257
Mouth	1.71 (0.24 – 12.24)	0.595
Liver	1.06 (0.34 – 3.31)	0.917
Leukaemia	-	-
Kidney	0.42 (0.09 – 1.99)	0.272
Sarcoma	1.72 (0.42 – 6.96)	0.450
Myeloma	0.85 (0.15 – 4.68)	0.848
Oesophageal	-	-
Lymphoma	0.90 (0.51 – 1.60)	0.716
Bone marrow	0.84 (0.31 – 2.29)	0.736
Thymus	-	-
Thyroid	1.37 (0.36 – 5.17)	0.645
Throat or larynx	0.85 (0.15 – 4.68)	0.848
Colorectal	-	-
Jaw	1.70 (0.11 – 27.39)	0.708
Adrenal	-	-

4.2 Prevalence of depression among cancer patients in the outpatient settings

The total number of participants in the outpatient department was 612, of which 335 (54.7%) were males and the mean age was 54.4 (SD: 15.0). Cancer metastasis in the outpatient department can be described as follows: 299 (48.9%) patients reported that they were diagnosed with non-metastatic cancer, 207 (33.8%) said they did not know about the disease stage, and 106 (17.3%) had metastatic cancer. The most prevalent stage of metastasis was stage 4, which was reported by 68 (11.1%) patients. In terms of types of cancer therapy received by the patients, around 376 (61.6%) patients reported that they were being treated by chemotherapy, 233 (38.2%) by a combination of surgery and chemotherapy, and 182 (29.8%) by radiotherapy. The median duration of the disease was 12:00 years (IQR: 5:00 – 24:00). The results showed that 228 (37.3%) patients had a first-degree relative who had had cancer, of which 63 (28.0%) patients had relatives who had had the same type of cancer as them. The marital status results showed that the majority of patients were married 502 (82.0%). Most patients were unemployed 299 (48.9%), and 410 (67.0%) reported that they had an income lower than 500 JD. For further details on patient demographics in the outpatient setting, refer to **Table 8**.

Table 8: Patient demographics in the outpatient department (n= 612).

Variable	**Frequency (%)**
Gender	
Males	335 (54.7%)

Female	277 (45.3%)
Marital status (n= 398)	
Single	62 (10.1%)
Married	502 (82.0%)
Divorced	15 (2.5%)
Widowed	33 (5.4%)
Employment status	
Employed	173 (28.3%)
Unemployed	299 (48.9%)
Retired	140 (22.9%)
Income	
Lower than 500 JD	410 (67.0%)
500 to 1000 JD	143 (23.4%)
1000 to 1500 JD	28 (4.6%)
1500 JD or above	31 (5.1%)
Area of residence	
Amman (the capital)	373 (60.9%)
Other cities	158 (25.8%)
Outside Jordan	81 (13.2%)
Nationality	
Jordanian	522 (85.3%)
Non-Jordanian	90 (14.7%)
Cancer metastasis	
Metastatic	106 (17.3%)
Non-metastatic	299 (48.9%)
I don’t know	207 (33.8%)
Stage of metastasis (n= 106)	
1	8 (7.5%)
2	13 (12.3%)
3	17 (16.03%)
4	68 (64.2%)
Cancer therapy	
Surgery	0

Chemotherapy	376 (61.6%)
Combination of surgery and chemotherapy	233 (38.2%)
Radiotherapy	182 (29.8%)
Was not receiving treatment	0

The most common types of cancer among patients in the outpatient department were: colon 100 (16.3%); lymphoma 88 (14.4%); lung 76 (12.4%); cervical 36 (5.9%) and Breast 35 (5.7%). For more data, see **Table 9**.

Table 9: Types of cancer among study participants (n= 612).

Type of cancer	**Frequency (%)**
Colon	100 (16.3%)
Lymphoma	88 (14.4%)
Lung	76 (12.4%)
Cervical	36 (5.9%)
Breast	35 (5.7%)
Stomach	24 (3.9%)
Bladder	23 (3.8%)
Ovarian	23 (3.8%)
Leukaemia	23 (3.8%)
Pancreatic	19 (3.1%)
Multiple myeloma	18 (2.9%)
Bone marrow	17 (2.8%)
Prostate	15 (2.5%)
Colorectal	15 (2.5%)
Liver	15 (2.5%)
Rectal	13 (2.1%)
Brain	12 (2.0%)
Oesophageal	10 (1.6%)
Kidney	9 (1.5%)
Sarcoma	9 (1.5%)

Larynx	6 (1.0%)
Testicular	4 (0.7%)
Pharyngeal	4 (0.7%)
Thyroid	3 (0.5%)
Bone	3 (0.5%)
Mouth	2 (0.3%)
Thymus	1 (0.2%)

The results showed 16.8% (n=103) of patients felt depressed and only 15.1% (n=18) reported that they were receiving antidepressant medication. The majority of patients 94.4% (n=17) have received instructions on how to use the antidepressant therapy; most patients, 88.9% (n= 16), have received instructions from their physician and only one (5.5%) from a pharmacist. Most patients, 12 (70.5%) out of 17, considered these instructions to be important, 3 (42.9%) out of 7 patients think it is important because increases confidence of therapy, 2 (28.6%) patients think it is reducing problems such as side effects and drug interactions associated with therapy, 1 (14.3%) think it is increase confidence in therapy and also 14.3% patients think it is increase safety of therapy. four (23.5%) didn't know, and one (5.9%) considered these instructions not important.

Only four (23.5%) out 18 of patients who have received antidepressant treatment had queries about the medication, 2 (50.0%) patients asked about mechanism of actions, 1patient (25.0%) asked about side effects, duration of treatment, medication dependency and onset of drug action. A total of six (35.3%) out of 17 patients thought the antidepressant effects should be observed at 12 hours, five (29.4%) thought the effect should be observed at two weeks or more, a further five (29.4%) said they didn't know the duration of time it takes for the antidepressant effects be observed, and one patient thought that it should be observed within 24 hours.

Three out of 17 (17.6%) patients increased their dosage of antidepressants without consulting their doctor and 14 (82.4%) said they had not increased their dosage. The results reported that eight out of 17 (47.1%) patients stated that they had not complained of side effects from their antidepressants, but six (35.3%) had. All the patients complained of suffering insomnia, five (83.3%) of headache, and five (83.3%) of nausea (see **Table 10** for more information).

Table 10: Patient reported side effects from the use of antidepressants (n= 17).

Variable	**Frequency (%)**
No	8 (47.1%)
Yes	6 (35.3%)
I don't know	3 (17.6%)
Side effect (n=6)	
Vomiting	6 (100%)
Nausea	5 (83.3%)
Dizziness	5 (83.3%)
Diarrhea	2 (33.3%)
Anxiety	1 (16.7%)

The results showed that 11 (64.7%) out of 17 patients didn't know if antidepressants were addictive or not, and four (23.5%) patients think antidepressant can cause addiction. Eleven (64.7%) patients didn't know if antidepressants had a tolerance level or not (see **Table 11** for more information).

Table 11: Patients 'Knowledge about antidepressant-associated addiction and tolerance (n=17).

Variable	**Frequency (%)**

Can antidepressants cause addiction?	
I don't know	11 (64.7%)
Yes	4 (23.5%)
No	2 (11.8%)
Can antidepressants cause tolerance?	
I don't know	11 (64.7%)
Yes	3 (17.6%)
No	3 (17.6%)

When patients who took antidepressants were asked about drug withdrawal, 12 (70.6%) out of 17 patients thought antidepressants should be stopped gradually at the end of treatment, and five (29.4%) said they didn't know. The results reported that seven out of 17 (41.2%) patients stopped take antidepressant drugs without consulting their doctor. A total of five out of seven (71.4%) patients stopped because of improvements in their depressive symptoms (see **Table 12** for more information).

Table 12: Knowledge of patients about end of treatment (n=17).

Variable	**Frequency (%)**
Should the drug be withdrawn at the end of the treatment gradually?	
Yes	12 (70.6%)
No	0 (%)
I don't know	5 (29.4%)
Did you stop treatment without consulting the doctor?	Yes 7 (41.2%)
For what reason stop the drug?	
Improvement of depressive symptoms	5 (71.4%)
Low tolerance to side effects	0 (%)
Cost of treatment	0 (%)
Interactions with other medicines	1 (14.3%)

The results reported that six out of 17 (35.3%) patients took other medication besides the antidepressants. Three (50.0%) out of the six took propranolol with their antidepressant drugs and two (33.3%) out of 6 patients take carbamazepine with

antidepressant drug and the same percentage as those who took lorazepam, and one patient reported the use of warfarin. The results reported that the mean age of first consumption of antidepressants was 54.6 years (SD: 15.9). Seven (63.6%) out of 11 patients took sertraline, six (54.5%) of them having used the antidepressant over the previous year. Nine out of 11 (81.8%) patients were currently using the antidepressant drug and all eleven were undergoing medical monitoring. The results reported that all 11 patients were taking their antidepressants for depression, while six (54.5%) were taking them for anxiety (see **Table 13**).

Table 13: The antidepressant that patients used (n= 11).

Medication	**Frequency (%)**
Sertraline	7 (63.6%)
Fluvoxamine	1 (9.1%)
Fluoxetine	1 (9.1%)
Paroxetine	1 (9.1%)
Escitalopram	1 (9.1%)
Patient Reported-consumption reason: (n= 11) *****Patients could choose more than one option	
Depression	11 (100%)
Anxiety	6 (54.5%)

Depression states among the patients

The mean PHQ-9 score: Depression 5.00 (IQR 2:00 – 10:00) out of 27. The score of depression state was based on the PHQ-9 scale: 0-4 for minimal depression, 5-9 mild depression, 10-14 moderate depression, 15-9 moderately severe depression and 20-27 severe depression. The results reported, based on the PHQ-9 scale, were 282 (46.1%) out of 612 patients had minimal depression, 165 (27.0%) mild depression, 76 (12.4%)

moderate depression, 56 (9.2%) moderately severe depression, and 33 (5.4%) patients' severe depression (see **Figure 3**).

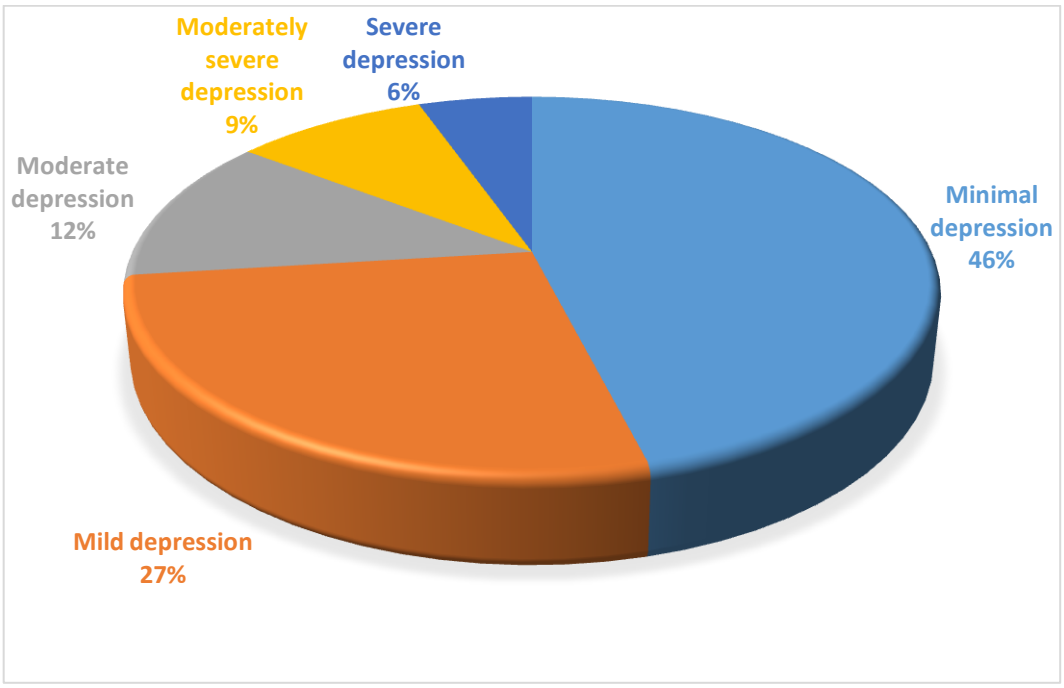

Figure 3: Depression states among patients based on the PHQ-9 scale (n=612).

After examining the risk factors for outpatients, the result reported that there was statistical significance between metastatic cancer and depression of 3.36 (1.33 – 8.50), while there was no significance between other demographic risk factors (see **Table 14** for more information). And after examining the risk factors according to the type of cancer experienced by patients in the outpatient department, the results showed there was statistical significance between prostate cancer and depression of 4.73 (1.27 – 17.64), breast cancer and depression of 3.27 (1.18 – 9.06) and in leukaemia and depression of 4.07 (1.30 – 12.72) (see **Table 15** for more information).

Table 14: Risk factors of depression according to patients' demographics.

Variable	**Odds ratio (95%CI) for severe depression according to PHQ-9**	**P-value**

Gender		
Male (Reference)	1.00	
Female	1.29 (0.64 – 2.59)	0.474
Age		
Less than 50 years	1.00	
50 years and above	0.81 (0.39 – 1.65)	0.556
Marital status		
Single (Reference)	1.00	
Married	0.80 (0.34 – 1.90)	0.619
Divorced	-	-
Widowed	1.14 (0.26 – 4.99)	0.861
Occupational status		
Employed (Reference)	1.00	
Unemployed	1.45 (0.71 – 2.95)	0.305
Retired	0.74 (0.30 – 1.83)	0.511
Income		
Below 500 JD (Reference)	1.00	
500 to 1000 JD	1.05 (0.46 – 2.39)	0.903
1000 to 1500 JD	1.37 (0.31 – 6.05)	0.676
More than 1500 JD	0.57 (0.08 – 4.33)	0.588
Duration of disease		
Less than 12 years (Reference)	1.00	
12 years and above	1.42 (0.68 – 2.95)	0.354
Metastasis		
No (Reference)	1.00	
Yes	3.36 (1.33 – 8.50)*	0.011*
Stage of cancer		
1 (Reference)	1:00	
2	3.33 (0.71 – 15.69)	0.128
3	1.10 (0.14 – 8.55)	0.928
4	2.29 (0.95 – 5.49)	0.064
Cancer therapy		

Isn't receiving treatment (Reference)	1.00	
Chemotherapy	0.79 (0.39 – 1.62)	0.520
Combination of surgery and chemotherapy	1.28 (0.62 – 2.62)	0.507
Radiotherapy	1.90 (0.92 – 3.90)	0.082
Surgery	-	-

Table 15: Risk factors of depression according to type of cancer.

Type of cancer	**Odds ratio (95%CI) for severe depression according to PHQ-9 score**	**P-value**
Bladder	-	-
Prostate	4.73 (1.27 – 17.64)*	0.021*
Lung	0.97 (0.33 – 2.84)	0.958
Testicular	-	-
Breast	3.27 (1.18 – 9.06)*	0.023*
Cervical	0.49 (0.06 – 3.66)	0.483
Colon	0.69 (0.24 – 2.02)	0.503
Rectal	-	-
Ovarian	-	-
Pancreatic	-	-
Brain	1.61 (0.20 – 12.89)	0.652
Stomach	2.66 (0.75 – 9.41)	0.130
Bone	-	-
Pharyngeal	-	-
Mouth	-	-
Liver	1.26 (0.16 – 9.89)	0.825
Leukaemia	4.07 (1.30 – 12.72)*	0.016*
Kidney	2.23 (0.27 – 18.38)	0.456
Sarcoma	-	-
Myeloma	-	-
Oesophagus	-	-

Lymphoma	0.81 (0.28 – 2.37)	0.704
Bone marrow	-	-
Thymus	-	-
Thyroid	-	-
Throat or larynx	3.59 (0.41 – 31.62)	0.250
Colorectal	-	-
Jaw	-	-
Adrenal	-	-

Chapter Five: Discussion

In this study, we have assessed the prevalence of depression and the utilization of antidepressants among cancer patients for both inpatient and outpatient settings. In our study, we found that the prevalence of depression among cancer patients was high (37.1% for inpatients and 14.6% for outpatients) (defined as the presence of severe depression and moderately severe depression). The results reported there was

association between metastatic cancer and depression for patients within the inpatient and outpatient settings. The risk factor of depression may be different according to the type of cancer; Some studies have suggested that there is an association between patients with breast and lung cancers and depression (Massie, 2004). In our study, the results reported that prostate and breast cancer and leukaemia patients were the high-risk groups for depression in the outpatient settings. Despite the high percentage of depression among cancer patients, the utilization of antidepressants medications was low: only 21 (14.1%) patients used antidepressants among inpatients and 18 (15.1%) among outpatients. Only one study in Jordan has assessed the prevalence of depression, and only for an inpatient setting (Mhaidat et al., 2009). The prevalence of depression in that study was 51.9% for inpatients, distributed as mild, moderate and severe depression among more than 400 participants. In our study, the prevalence of depression for inpatients in total was 37.1% for moderate and severe depression among 399 participants. On the other hand, the results reported for 612 outpatient participants in total showed a prevalence of depression of 14.6% (9.2% moderately severe depression and 5.4% severe depression) and, according to the PHQ-9 survey, no treatment was offered in cases of minimal depression (total score 0-4) do not need psychological intervention but, in cases of mild depression (total score 5-9) and moderate depression (total score 10-14), the treatment was based on the patient's duration of symptoms and the functional impairment, and in cases of moderately severe depression (total score 15-19) and severe depression (total score 20-27), the treatment plan used antidepressants, psychotherapy and/or a combination of treatments. Previous studies have reported that the prevalence of depression is between 10.0% - 25.0% (Pirl, 2004). A previous meta-analysis in Iran with a total number of 2,831 cancer patients (Aryankhesal et al., 2019) reported a relationship between the stage of the disease and

depression. In our study, the results for the inpatient (stage 3 and 4) and outpatient groups reported there was a relationship between metastasis cancer and depression. Also, in this meta-analysis study, there was a relationship between depression and breast cancer, and the level of depression identified in the patients with breast cancer was higher than in other patients. In our study, the results in the outpatients group reported there was a relationship between patients with breast cancer, prostate cancer and leukaemia. In another study among 2,059 cancer outpatients, the results reported 11.3% moderate depression and 3.7% severe depression (Hinz et al., 2016). In our study, the results showed a higher percentage of severe depression among cancer outpatients cancer (5.4%). A meta-analysis study reviewed the risk factors for depression according to the type of cancer and the stage, and reported that patients with lung cancer, pancreatic cancer, breast cancer and head and neck cancer, and also patients with advanced-stage and patients with low socio-economic status, were more likely to be depressed (Caruso et al., 2017). In our study, there was no relationship between low socio-economic status and depression, but there was a relationship between patients with advanced-stage cancer and depression. Our study also reported in the outpatients group that there was a relationship between patients with prostate and breast cancer and leukaemia and depression. Another study in Iran among 150 cancer inpatients showed 21.3% of them had symptomatic depression. In this study, there was a relationship between older aged patients and depression, and also those who have been diagnosed with breast and stomach cancer and who had received chemotherapy as the sole treatment (Nikbakhsh, Moudi, Abbasian, & Khafri, 2014). In our study, there was no relationship between the type of treatment and depression. The prevalence of depression was higher in the inpatients group (37.1% for moderate and severe depression) and, also, there was no relationships between age and depression.

Clinical implications

Our study investigated the use of antidepressants among cancer patients stratified by type, where the rate of using antidepressants medications among patients diagnosed with depression was (15.5%). The majority of patients used selective serotonin reuptake inhibitors (SSRIs) antidepressants (sertraline, citalopram, fluoxetine, fluvoxamine, and paroxetine), while tetracyclic antidepressants (mirtazapine) and tricyclic antidepressants (amitriptyline) were used to a lesser extent. The selection of antidepressant medicine needs to be guided by clear guidelines that consider interactions with chemotherapeutic and other concurrently administered medication as well as side effects to enable identification of specific contraindications. Sertraline and citalopram are usually recommended, as they have less interactions and are usually well tolerated (Chochinov, 2001; M. F. Ismail, Lavelle, & Cassidy, 2017; Nead, Sinha, Yang, & Nguyen, 2017; Niedzwiedz, Knifton, Robb, Katikireddi, & Smith, 2019; Rao & Faso, 2012; Smith, 2015). Despite the fact that the use of medications for depression among cancer patients in this study was low, the selection of pharmacological agents is in line with the above recommendations. However, patient-centred approach and customised treatment plans need to be considered, as studies reported that the SSRIs need to be avoided in elderly patients due to the risk of hyponatraemia. Fluoxetine and paroxetine are contraindicated in patients being treated with tamoxifen. Mirtazapine should be avoided where white blood cells are compromised and SSRIs should be avoided where platelets are compromised (Pitman, Suleman, Hyde, & Hodgkiss, 2018). Finally, almost 70.0% of the patients reported that they experienced nausea. In this case SSRIs need to be avoided as this will augment chemotherapy-induced nausea and vomiting.

5.1 Strengths and limitations

This study has numerous strengths. The large sample size (1,011 patients) with no restrictions on the type of cancer or settings made our results more generalizable. We used validated assessment tools (PHQ-9 and HADS) for the assessment of depression. There are only a limited number of studies that estimate the prevalence of depression among cancer patients in the Middle East However, our study did have some limitations. Chemotherapy and other medication and treatment used in cancer therapy, such as steroids, induce the symptoms of depression and emotional disturbance. Therefore, our results should be interpreted with care. Another limitation is that drug utilization data were patient reported and were not confirmed using patient health records. In the inpatient setting, the type and stage of cancer and the name of antidepressant used were confirmed using patient health records, however, this was not possible for outpatients. In addition, we failed to investigate drug utilization history of the patients. Therefore, whether or not depressive symptoms were drug-induced is not known. Recall bias is another limitation in this study as patients could more or less likely be able to recall information regarding their exposure and their outcome.

5.2 Conclusion

Depression is a serious condition among cancer patients because, if left untreated, it can lead to increased morbidity and mortality, as well as suicidal thinking. Thus, it may cause additional suffering to the patient. Our results have reported a high prevalence of depression among cancer patients, and very low utilization of antidepressant therapy. Therefore, clinical physicians should consider focusing more on their patients' psychological state and pay greater attention to their mental health.

References:

(IARC), I. A. for R. on C., & (OMS), W. H. O. (2018). *GLOBOCAN 2018: Latest global cancer data. Press release No 263.* (September), 13–15. Retrieved from http://gco.iarc.fr/,

Abouzgheib, W., & Dellinger, R. P. (2016). Pulmonary complications in cancer patients. *Oncologic Emergency Medicine: Principles and Practice*, *46*(5), 191–202. https://doi.org/10.1007/978-3-319-26387-8_16

Abraham, J., & Staffurth, J. (2016). Hormonal therapy for cancer. *Medicine (United Kingdom)*, *44*(1), 30–33. https://doi.org/10.1016/j.mpmed.2015.10.014

Absorption, O. (2006). Drug Name : Irinotecan. *Etc*, *2018*(April 2005), 1–9.

Adenowo, A. F., Oyinloye, B. E., Ogunyinka, B. I., & Kappo, A. P. (2015). Impact of human schistosomiasis in sub-Saharan Africa. *Brazilian Journal of Infectious Diseases*, *19*(2), 196–205.

AIMU. (2016). Cancer : Symptoms, Causes, Diagnosis, Classification and Management. Retrieved July 17, 2019, from aimu.us website: https://www.aimu.us/2016/10/20/cancer-symptoms-causes-diagnosis-classification-and-management/

Airley, R. (2009). *Cancer chemotherapy: basic science to the clinic*. John Wiley & Sons.

Al Tamwneh, M., Khatib, S., & Arqub, K. (2010). *Cancer incidence in Jordan, 1996-2005*.

Albertsmeier, M., Rauch, A., Roeder, F., Hasenhütl, S., Pratschke, S., Kirschneck, M., … Sargos, P. (2018). External beam radiation therapy for resectable soft tissue sarcoma: a systematic review and meta-analysis. *Annals of Surgical Oncology*, *25*(3), 754–767.

Alefan, Q., Malhees, R., & Mhaidat, N. (2017). Direct medical cost associated with colorectal cancer in north of Jordan. *Current Problems in Cancer*, *41*(5), 371–381.

Appelbaum, F. R. (2014). Acute leukemias in adults. In *Abeloff's Clinical Oncology. 5th ed. Philadelphia, Pa. Elsevier*.

Aryankhesal, A., Ghashghaee, A., Sardari, E., Mahmoudi, S., Alihosseini, S., Dehnad, A., … Gharagozlou, D. (2019). Prevalence of depression in patients with cancer in Iran: a systematic review and meta-analysis. *BMJ Supportive & Palliative Care*, *0*, 1–8.

Atag, E., Mutlay, F., Soysal, P., Semiz, H. S., Kazaz, S. N., Keser, M., … Karaoglu, A. (2018). Prevalence of depressive symptoms in elderly cancer patients receiving chemotherapy and influencing factors. *Psychogeriatrics*, *18*(5), 365–370.

Baethge, C., Baldessarini, R. J., Freudenthal, K., Streeruwitz, A., Bauer, M., & Bschor, T. (2005). Hallucinations in bipolar disorder: Characteristics and comparison to unipolar depression and schizophrenia. *Bipolar Disorders*, *7*(2), 136–145. https://doi.org/10.1111/j.1399-5618.2004.00175.x

Baider, L., Peretz, T., Hadani, P. E., & Koch, U. (2001). Psychological intervention in cancer patients: a randomized study. *General Hospital Psychiatry*, *23*(5), 272–277.

Barlow, J., Wright, C., Sheasby, J., Turner, A., & Hainsworth, J. (2002). Self-management approaches for people with chronic conditions: a review. *Patient Education and Counseling*, *48*(2), 177–187.

Barth, R. F., Mi, P., & Yang, W. (2018). Boron delivery agents for neutron capture

therapy of cancer. *Cancer Communications*, *38*(1), 35.

Baskar, R., Lee, K. A., Yeo, R., & Yeoh, K. W. (2012). Cancer and radiation therapy: Current advances and future directions. *International Journal of Medical Sciences*, *9*(3), 193–199. https://doi.org/10.7150/ijms.3635

Bauer, M., & Döpfmer, S. (1999). Lithium augmentation in treatment-resistant depression: meta-analysis of placebo-controlled studies. *Journal of Clinical Psychopharmacology*, *19*(5), 427–434.

Bentley, S. M., Pagalilauan, G. L., & Simpson, S. A. (2014). Major Depression. *Medical Clinics of North America*, *98*(5), 981–1005. https://doi.org/10.1016/j.mcna.2014.06.013

Berg, D., & Gerlach, H. (2018). Recent advances in understanding and managing sepsis. *F1000Research*, *7*(0), 1–10. https://doi.org/10.12688/f1000research.15758.1

Bernstein, C., Prasad, A. R., Nfonsam, V., & Bernstein, H. (2013). DNA damage, DNA repair and cancer. In *New Research Directions in DNA Repair*. IntechOpen.

Bhattacharya, B., & Mukherjee, S. (2015). Cancer Therapy Using Antibiotics. *Journal of Cancer Therapy*, *06*(10), 849–858. https://doi.org/10.4236/jct.2015.610093

Blackadar, C. B. (2016). Historical review of the causes of cancer. *World Journal of Clinical Oncology*, *7*(1), 54–86. https://doi.org/10.5306/wjco.v7.i1.54

Blanchard, P., Garden, A. S., Gunn, G. B., Rosenthal, D. I., Morrison, W. H., Hernandez, M., … Fuller, C. D. (2016). Intensity-modulated proton beam therapy (IMPT) versus intensity-modulated photon therapy (IMRT) for patients with oropharynx cancer–a case matched analysis. *Radiotherapy and Oncology*, *120*(1), 48–55.

Block, G., Patterson, B., & Subar, A. (1992). Fruit, vegetables, and cancer prevention: a review of the epidemiological evidence. *Nutrition and Cancer*, *18*(1), 1–29.

Blower, P., De Wit, R., Goodin, S., & Aapro, M. (2005). Drug–drug interactions in oncology: why are they important and can they be minimized? *Critical Reviews in Oncology/Hematology*, *55*(2), 117–142.

Boada, L. D., Henríquez-Hernández, L. A., & Luzardo, O. P. (2016). The impact of red and processed meat consumption on cancer and other health outcomes: Epidemiological evidences. *Food and Chemical Toxicology*, *92*, 236–244.

Boakye, E. A., Osazuwa-Peters, N., Mohammed, K. A., Challapalli, S., Buchanan, P., Burroughs, T. E., & Varvares, M. A. (2020). Prevalence and factors associated with diagnosed depression among hospitalized cancer patients with metastatic disease. *Social Psychiatry and Psychiatric Epidemiology*, *55*(1), 15–23.

Bodenheimer, T., Lorig, K., Holman, H., & Grumbach, K. (2002). Patient self-management of chronic disease in primary care. *Jama*, *288*(19), 2469–2475.

Bonaccorso, S., Marino, V., Biondi, M., Grimaldi, F., Ippoliti, F., & Maes, M. (2002). Depression induced by treatment with interferon-alpha in patients affected by hepatitis C virus. *Journal of Affective Disorders*, *72*(3), 237–241.

Bosanquet, N., & Sikora, K. (2004). The economics of cancer care in the UK. *The Lancet Oncology*, *5*(9), 568–574.

Brandenbarg, D., Maass, S. W. M. C., Geerse, O. P., Stegmann, M. E., Handberg, C., Schroevers, M. J., & Duijts, S. F. A. (2019). A systematic review on the prevalence of symptoms of depression, anxiety and distress in long- term cancer survivors: Implications for primary care. *European Journal of Cancer Care*, e13086.

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*, *68*(6), 394–424.

Breuer, B., & Anderson, R. (2000). The relationship of tamoxifen with dementia, depression, and dependence in activities of daily living in elderly nursing home residents. *Women & Health*, *31*(1), 71–85.

Bukberg, J., Penman, D., & Holland, J. C. (1984). Depression in hospitalized cancer patients. *Psychosomatic Medicine*. https://doi.org/10.1097/00006842-198405000-00002

Burr, N. E., Hull, M. A., & Subramanian, V. (2017). Folic acid supplementation may reduce colorectal cancer risk in patients with inflammatory bowel disease. *Journal of Clinical Gastroenterology*, *51*(3), 247–253.

Campbell, W. W., & DeJong, R. N. (2005). *DeJong's the neurologic examination*. Lippincott Williams & Wilkins.

Cannon, N. A., Meyer, J., Iyengar, P., Ahn, C., Westover, K. D., Choy, H., & Timmerman, R. (2015). Neutrophil–lymphocyte and platelet–lymphocyte ratios as prognostic factors after stereotactic radiation therapy for early-stage non–small-cell lung cancer. *Journal of Thoracic Oncology*, *10*(2), 280–285.

Cao, Y., & Giovannucci, E. L. (2016). Alcohol as a risk factor for cancer. *Seminars in Oncology Nursing*, *32*(3), 325–331. Elsevier.

Caraci, F., Crupi, R., Drago, F., & Spina, E. (2011). Metabolic drug interactions between antidepressants and anticancer drugs: focus on selective serotonin reuptake inhibitors and hypericum extract. *Current Drug Metabolism*, *12*(6), 570–577.

Cardoso, G., Graca, J., Klut, C., Trancas, B., & Papoila, A. (2016). Depression and anxiety symptoms following cancer diagnosis: a cross-sectional study. *Psychology, Health & Medicine*, *21*(5), 562–570.

Carr, G. V., & Lucki, I. (2010). The Role of Serotonin in Depression. In *Handbook of Behavioral Neuroscience* (Vol. 21). https://doi.org/10.1016/S1569-7339(10)70098-9

Caruso, R., Nanni, M. G., Riba, M., Sabato, S., Mitchell, A. J., Croce, E., & Grassi, L. (2017). Depressive spectrum disorders in cancer: prevalence, risk factors and screening for depression: a critical review. *Acta Oncologica*, *56*(2), 146–155.

Cassano, F. M. (2002). *Depression and public health, an overview. Journal of Psychosomatic Research*. *53*, 849–857.

Chan, S. L., Wong, V. W., Qin, S., & Chan, H. L. (2016). Infection and cancer: the case of hepatitis B. *J Clin Oncol*, *34*(1), 83–90.

Chen, J. J., & Marsh, L. (2013). Depression in Parkinson's disease: identification and management. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, *33*(9), 972–983.

Cher, L. (2004). Neurologic complications of cancer chemotherapy. *Cancer Forum*, *28*(1), 12–14. https://doi.org/10.1002/9781119000822.hfcm127

Chochinov, H. M. (2001). Depression in cancer patients. *The Lancet Oncology*, *2*(8), 499–505.

Colón, E. A., Callies, A. L., Popkin, M. K., & McGlave, P. B. (1991). Depressed Mood and Other Variables Related to Bone Marrow Transplantation Survival in Acute Leukemia. *Psychosomatics*. https://doi.org/10.1016/S0033-3182(91)72045-8

Cooper, C., Burden, S. T., Cheng, H., & Molassiotis, A. (2015). Understanding and managing cancer-related weight loss and anorexia: Insights from a systematic review of qualitative research. *Journal of Cachexia, Sarcopenia and Muscle*, *6*(1), 99–111. https://doi.org/10.1002/jcsm.12010

Cooper, P. J., & Murray, L. (1998). Postnatal depression. *Bmj*, *316*(7148), 1884–1886.

Corbett, E. L., Doherty, J. P., & Behrens, R. H. (1996). Adverse events associated with mefloquine. Study in returned travellers confirms authors' findings. *BMJ: British Medical Journal*, *313*(7071), 1552.

Cortés-Funes, H., & Coronado, C. (2007). Role of anthracyclines in the era of targeted therapy. *Cardiovascular Toxicology*, *7*(2), 56–60.

Croom, K. F., Perry, C. M., & Plosker, G. L. (2009). Mirtazapine. *CNS Drugs*, *23*(5), 427–452.

Dana-Farber Cancer Institute. (2017). What Are the Different Types of Cancer Surgery? Retrieved December 24, 2019, from dana-farber.org website: https://blog.dana-farber.org/insight/2017/02/what-are-the-different-types-of-cancer-surgery/

Davidson, J. R. T., Miller, R. D., Turnbull, C. D., & Sullivan, J. L. (1982). Atypical Depression. *Archives of General Psychiatry*, *39*(5), 527–534. https://doi.org/10.1001/archpsyc.1982.04290050015005

De Montigny, C. (1994). Lithium addition in treatment-resistant depression. *International Clinical Psychopharmacology*.

Dean, Z., Horndasch, S., Giannopoulos, P., & McCabe, C. (2016). Enhanced neural response to anticipation, effort and consummation of reward and aversion during bupropion treatment. *Psychological Medicine*, *46*(11), 2263–2274.

Demain, A. L., & Vaishnav, P. (2011). Natural products for cancer chemotherapy. *Microbial Biotechnology*, *4*(6), 687–699. https://doi.org/10.1111/j.1751-7915.2010.00221.x

Depuydt, C. E., Beert, J., Bosmans, E., & Salembier, G. (2016). Human Papillomavirus (HPV) virion induced cancer and subfertility, two sides of the same coin. *Facts, Views & Vision in ObGyn*, *8*(4), 211.

Derogatis, L. R., Morrow, G. R., Fetting, J., Penman, D., Piasetsky, S., Schmale, A. M., … Carnicke, C. L. M. (1983). The Prevalence of Psychiatric Disorders Among Cancer Patients. *JAMA: The Journal of the American Medical Association*.

https://doi.org/10.1001/jama.1983.03330300035030

DeVita, V. T., Lawrence, T. S., & Rosenberg, S. A. (2015). *DeVita, Hellman, and Rosenberg's cancer: principles & practice of oncology* (10th ed.). Lippincott Williams & Wilkins.

Dholwani, K. K., Saluja, A. K., Gupta, A. R., & Shah, D. R. (2008). A review on plant-derived natural products and their analogs with anti-tumor activity. *Indian Journal of Pharmacology*, *40*(2), 49.

Diaz, D., Vallejos, Á., Torres, S., Hernández, W., Calvache, J., Merchán, J., … Maldonado, L. (2018). Detection of potential risks in the prescription of tricyclic antidepressants through an online clinical alert system. *Revista Colombiana de Psiquiatría*, *49*(1), 9–14.

Dollander, M. (2004). Perinatal paternal depression. *Neuropsychiatrie de l'Enfance et de l'Adolescence*, *52*(5), 274–278. https://doi.org/10.1016/j.neurenf.2004.05.003

Elias, F., Bou-Orm, I. R., Adib, S. M., Gebran, S., Gebran, A., & Ammar, W. (2018). Cost of Oncology Drugs in the Middle-Eastern Country of Lebanon: An Update (2014-2016). *Journal of Global Oncology*, *4*, 1–7.

emedicine health. (2020). Common Cancer Symptoms and Signs. Retrieved August 4, 2020, from emedicinehealth.com website: https://www.emedicinehealth.com/cancer_symptoms/article_em.htm#what_should_i_know_about_cancer

Ettinger, B., Quesenberry, C., Schroeder, D. A., & Friedman, G. (2018). Long-term postmenopausal estrogen therapy may be associated with increased risk of breast cancer: A cohort study. *Menopause*, *25*(11), 1191–1194.

Farmer, P., Frenk, J., Knaul, F. M., Shulman, L. N., Alleyne, G., Armstrong, L., … Feachem, R. (2010). Expansion of cancer care and control in countries of low and middle income: a call to action. *The Lancet*, *376*(9747), 1186–1193.

Feinstein, A., O'Connor, P., & Feinstein, K. (2002). Multiple Sclerosis, interferon beta-1b and depression. *Journal of Neurology*, *249*(7), 815–820.

Fenlon, D., & Foster, C. (2009). Self-management support: a review of the evidence. *Southhampton: Macmillan Research Unit: University of Southhampton*.

Ferguson, J. M. (2001). SSRI antidepressant medications: adverse effects and tolerability. *Primary Care Companion to the Journal of Clinical Psychiatry*, *3*(1), 22.

Fitzpatrick, R., Gibbons, E., & Mackintosh, A. (2009). An overview of patient-reported outcome measures for people with anxiety and depression. *Report to the Department of Health*.

Foster, C., & Fenlon, D. (2011). Recovery and self-management support following primary cancer treatment. *British Journal of Cancer*, *105*(S1), S21–S28. https://doi.org/10.1038/bjc.2011.419

G., R., N., L., M., K., E., G., J.A., M., & R.K.S., W. (2007). The treatment of depression in cancer patients: A systematic review. *Supportive Care in Cancer*.

Garg, N. K., Tyagi, R. K., Sharma, G., Jain, A., Singh, B., Jain, S., & Katare, O. P.

(2017). Functionalized lipid–polymer hybrid nanoparticles mediated codelivery of methotrexate and aceclofenac: a synergistic effect in breast cancer with improved pharmacokinetics attributes. *Molecular Pharmaceutics*, *14*(6), 1883–1897.

Geissler, E. K. (2015). Skin cancer in solid organ transplant recipients: are mTOR inhibitors a game changer? *Transplantation Research*, *4*(1), 1.

Giglio, P., & Gilbert, M. R. (2010). Neurologic complications of cancer and its treatment. *Current Oncology Reports*, *12*(1), 50–59. https://doi.org/10.1007/s11912-009-0071-x

Grapp, M., Terhoeven, V., Nikendei, C., Friederich, H.-C., & Maatouk, I. (2019). Screening for depression in cancer patients using the PHQ-9: The accuracy of somatic compared to non-somatic items. *Journal of Affective Disorders*, *254*, 74–81.

Grassi, L, Nanni, M. G., Rodin, G., Li, M., & Caruso, R. (2017). The use of antidepressants in oncology: a review and practical tips for oncologists. *Annals of Oncology*, *29*(1), 101–111.

Grassi, Luigi, Biancosino, B., Marmai, L., & Righi, R. (2004). Effect of reboxetine on major depressive disorder in breast cancer patients: an open-label study. *The Journal of Clinical Psychiatry*, *65*(4), 515–520.

Grassi, Luigi, Caruso, R., Hammelef, K., Nanni, M. G., & Riba, M. (2014). Efficacy and safety of pharmacotherapy in cancer-related psychiatric disorders across the trajectory of cancer care: A review. *International Review of Psychiatry*. https://doi.org/10.3109/09540261.2013.842542

Grbich, C. F., Maddocks, I., & Parker, D. (2001). Family caregivers, their needs, and home-based palliative cancer services. *Journal of Family Studies*, *7*(2), 171–188.

Greer, S. (1983). Cancer and the mind. *British Journal of Psychiatry*.

Grotmol, K. S., Lie, H. C., Loge, J. H., Aass, N., Haugen, D. F., Stone, P. C., … Hjermstad, M. J. (2019). Patients with advanced cancer and depression report a significantly higher symptom burden than non-depressed patients. *Palliative & Supportive Care*, *17*(2), 143–149.

Gupta, I., Ganguly, S., Rozanas, C. R., Stuehr, D. J., & Panda, K. (2016). Ascorbate attenuates pulmonary emphysema by inhibiting tobacco smoke and Rtp801-triggered lung protein modification and proteolysis. *Proceedings of the National Academy of Sciences*, *113*(29), E4208–E4217.

Hammen, C. (2018). Risk factors for depression: An autobiographical review. *Annual Review of Clinical Psychology*, *14*, 1–28.

Harrison, R. W., & Ashton, C. H. (1994). Do cholesterol- lowering agents affect brain activity? A comparison of simvastatin, pravastatin, and placebo in healthy volunteers. *British Journal of Clinical Pharmacology*, *37*(3), 231–236.

Harvey, R. D., & Khuri, F. R. (2018). *Cytotoxic Chemotherapy - he Scientific Basis for Cytotoxic Chemotherapy Use in Cancer*. 220–235.

Heinonen, O. P., Huttunen, J. K., Albanes, D., Haapakoski, J., Palmgren, J., Pietinen, P., … Edwards, B. K. (1994). Effect of vitamin-E and beta-carotene on the incidence

of lung-cancer and other cancers in male smokers. *New England Journal of Medicine*, *330*(15), 1029–1035.

Hemeryck, A., & Belpaire, F. M. (2002). Selective serotonin reuptake inhibitors and cytochrome P-450 mediated drug-drug interactions: an update. *Current Drug Metabolism*, *3*(1), 13–37.

Henley, S. J. (2016). Vital signs: disparities in tobacco-related cancer incidence and mortality—United States, 2004–2013. *MMWR. Morbidity and Mortality Weekly Report*, *65*(44), 1212–1218.

Hinz, A., Mehnert, A., Kocalevent, R.-D., Brähler, E., Forkmann, T., Singer, S., & Schulte, T. (2016). Assessment of depression severity with the PHQ-9 in cancer patients and in the general population. *BMC Psychiatry*, *16*(1), 22.

Hirschfeld, R. M. A. (1981). Situational depression: Validity of the concept. *British Journal of Psychiatry*, *139*(4), 297–305. https://doi.org/10.1192/bjp.139.4.297

Hoffman, R., Benz Jr, E. J., Silberstein, L. E., Heslop, H., Anastasi, J., & Weitz, J. (2013). *Hematology: basic principles and practice*. Elsevier Health Sciences.

Holvey, C., Connolly, A., & Taylor, D. (2010). Psychiatric side effects of non-psychiatric drugs. *British Journal of Hospital Medicine (2005)*, *71*(8), 432–436.

Hong, J. S., & Tian, J. (2014). Prevalence of anxiety and depression and their risk factors in Chinese cancer patients. *Supportive Care in Cancer*, *22*(2), 453–459. https://doi.org/10.1007/s00520-013-1997-y

Hosoda, S., Takimura, H., Shibayama, M., Kanamura, H., Ikeda, K., & Kumada, H. (2000). Psychiatric symptoms related to interferon therapy for chronic hepatitis C: clinical features and prognosis. *Psychiatry and Clinical Neurosciences*, *54*(5), 565–572.

Hutter, J. J. (2015). Childhood Leukemia Abbreviations : *Pediatrics in Review*, *31*(6), 234–241.

Institute, N. C., & Health, at the N. I. of. (213AD). A Snapshot of Leukemia. Retrieved July 18, 2019, from archive.org website: https://web.archive.org/web/20140704183430/http://www.cancer.gov/researchandfunding/snapshots/leukemia

Institute, N. C., & Health, at the N. I. of. (2014a). Leukemia. Retrieved July 18, 2019, from cancer.gov website: https://www.cancer.gov/types/leukemia

Institute, N. C., & Health, at the N. I. of. (2014b). lymphoma. Retrieved July 18, 2019, from cancer.gov website: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/lymphoma?redirect=true

Islam, F. (2016). Mini Review: Depression during Adolescence: The Rage Within. *Clin Depress*, *2*, 107.

Ismail, M. F., Lavelle, C., & Cassidy, E. M. (2017). Steroid-induced mental disorders in cancer patients: a systematic review. *Future Oncology*, *13*(29), 2719–2731.

Ismail, S. I., Soubani, M., Nimri, J. M., & Al-Zeer, A. H. (2013). Cancer Incidence in Jordan from 1996 to 2009 - A Comprehensive Study. *Asian Pacific Journal of Cancer Prevention*. https://doi.org/10.7314/apjcp.2013.14.6.3527

Ito, Y. (2001). Chemotherapy and Hormone Therapy for Breast Cancer: Current Status and Perspective. *Journal of the Japan Medical Association*, *125*(11), 1713–1720. Retrieved from http://www.med.or.jp/english/pdf/2002_10/424_433.pdf

Izzo, A. A. (2004). Drug interactions with St. John's Wort (Hypericum perforatum): a review of the clinical evidence. *International Journal of Clinical Pharmacology and Therapeutics*, *42*(3), 139–148.

Jackson, S. P., & Bartek, J. (2009). The DNA-damage response in human biology and disease. *Nature*, *461*(7267), 1071.

Jayasekara, H., MacInnis, R. J., Room, R., & English, D. R. (2016). Long-term alcohol consumption and breast, upper aero-digestive tract and colorectal cancer risk: A systematic review and meta-analysis. *Alcohol and Alcoholism*. https://doi.org/10.1093/alcalc/agv110

Jeffrey S. Tobias, D. H. (2015). Cancer and its Management. In *Cancer and its Management* (7th ed.).

Kantarjian, H., & Rajkumar, S. V. (2015). Why are cancer drugs so expensive in the United States, and what are the solutions? *Mayo Clinic Proceedings*, *90*(4), 500–504. Elsevier.

Kasper, S., Caraci, F., Forti, B., Drago, F., & Aguglia, E. (2010). Efficacy and tolerability of Hypericum extract for the treatment of mild to moderate depression. *European Neuropsychopharmacology*, *20*(11), 747–765.

Kebede, D., Alem, A., Deyassa, N., Shibre, T., Negash, A., & Beyero, T. (2003). Socio-demographic correlates of depressive disorder in Butajira, rural Ethiopia. *The Central African Journal of Medicine*, *49*(7–8), 78–83.

Keck Jr, P. E. (2005). Bipolar depression: a new role for atypical antipsychotics? *Bipolar Disorders*, *7*, 34–40.

Keller, J., Gomez, R. G., Kenna, H. A., Poesner, J., Debattista, C., Flores, B., & Schatzberg, A. F. (2006). Detecting psychotic major depression using psychiatric rating scales. *Journal of Psychiatric Research*, *40*(1), 22–29. https://doi.org/10.1016/j.jpsychires.2005.07.003

Kelly, C. M., Juurlink, D. N., Gomes, T., Duong-Hua, M., Pritchard, K. I., Austin, P. C., & Paszat, L. F. (2010). Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: a population based cohort study. *Bmj*, *340*, c693.

Kennedy, S. H., & Lam, R. W. (2003). Enhancing outcomes in the management of treatment resistant depression: a focus on atypical antipsychotics. *Bipolar Disorders*, *5*, 36–47.

Kessler, R. C., McGonagle, K. A., Zhao, S., Nelson, C. B., Hughes, M., Eshleman, S., … Kendler, K. S. (1994). Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. *Archives of General Psychiatry*, *51*(1), 8–19.

Khader, Y. S., Sharkas, G. F., Arkoub, K. H., Alfaqih, M. A., Nimri, O. F., & Khader, A. M. (2018). The epidemiology and trend of cancer in Jordan, 2000–2013. *Journal of Cancer Epidemiology*. https://doi.org/10.1155/2018/2937067

Khoontawad, J., Pairojkul, C., Rucksaken, R., Pinlaor, P., Wongkham, C., Yongvanit, P., … Potriquet, J. (2017). Differential protein expression marks the transition from infection with Opisthorchis viverrini to cholangiocarcinoma. *Molecular & Cellular Proteomics*, *16*(5), 911–923.

Kilzieh, N., & Akiskal, H. S. (1999). Rapid-cycling bipolar disorder: An overview of research and clinical experience. *Psychiatric Clinics of North America*, *22*(3), 585–607. https://doi.org/10.1016/S0193-953X(05)70097-6

Kim, T.-S., Pak, J. H., Kim, J.-B., & Bahk, Y. Y. (2016). Clonorchis sinensis, an oriental liver fluke, as a human biological agent of cholangiocarcinoma: a brief review. *BMB Reports*, *49*(11), 590.

Kober, M., Pohl, K., & Efferth, T. (2008). Molecular mechanisms underlying St. John's wort drug interactions. *Current Drug Metabolism*, *9*(10), 1027–1037.

Koukopoulos, A., & Sani, G. (2014). DSM- 5 criteria for depression with mixed features: a farewell to mixed depression. *Acta Psychiatrica Scandinavica*, *129*(1), 4–16.

Krempien, R., & Roeder, F. (2017). Intraoperative radiation therapy (IORT) in pancreatic cancer. *Radiation Oncology*, *12*(1), 8.

Kumar, R., Singh, K. K., Rae, A. A., Singh, R. K., & Singh, G. R. (2016). Prevalence of anxiety and depression among cancer patients. *Journal of Medical Science and Clinical Research*, *4*(11), 13696–13699.

Layer, K.; Khan, Z. (2015). Depression – A Review Review Paper Depression – A Review. *Research Journal and Recent Sciences*, *1*(4), 79–87.

Lazarou, C., Kout, C., Kapsou, M., & Kaite, C. (2010). Review of epidemiology of depression and implications for community nursing practice. *East African Journal of Public Health*, *7*(3), 246–249.

LeBlanc, D. P., Behan, N. A., O'Brien, J. M., Marchetti, F., & MacFarlane, A. J. (2018). Folate deficiency increases chromosomal damage and mutations in hematopoietic cells in the transgenic mutamouse model. *Environmental and Molecular Mutagenesis*, *59*(5), 366–374.

LeMay, K., Wilson, K. G., Buenger, U., Jarvis, V., Fitzgibbon, E., Bhimji, K., & Dobkin, P. L. (2011). Fear of pain in patients with advanced cancer or in patients with chronic noncancer pain. *The Clinical Journal of Pain*, *27*(2), 116–124.

Li, J. Y., Sidhu, R. S., Ford, E. J., Long, D. M., Hess, W. M., & Strobel, G. A. (1998). The induction of taxol production in the endophytic fungus—Periconia sp from Torreya grandifolia. *Journal of Industrial Microbiology and Biotechnology*, *20*(5), 259–264.

Li, M., Fitzgerald, P., & Rodin, G. (2012). Evidence-based treatment of depression in patients with cancer. *Journal of Clinical Oncology*. https://doi.org/10.1200/JCO.2011.39.7372

Lim, G. Y., Tam, W. W., Lu, Y., Ho, C. S., Zhang, M. W., & Ho, R. C. (2018). Prevalence of depression in the community from 30 countries between 1994 and 2014. *Scientific Reports*, *8*(1), 1–10.

Linde, K. (2008). St. John's wort for depression–development of a Cochrane review from 1993 to 1996. *Zeitschrift Für Evidenz, Fortbildung Und Qualität Im Gesundheitswesen*, *102*(8), 487–492.

Lindley, C. M., & Hirsch, J. D. (1992). *Nausea and vomiting and cancer patients ' quality of life : a discussion of Professor Selby ' s paper*. *29*, 26–29.

Liu, T., Liu, X., & Li, W. (2016). Tetrandrine, a Chinese plant-derived alkaloid, is a potential candidate for cancer chemotherapy. *Oncotarget*, *7*(26). https://doi.org/10.18632/oncotarget.8315

Lord, C. J., & Ashworth, A. (2017). PARP inhibitors: Synthetic lethality in the clinic. *Science*, *355*(6330), 1152–1158.

Lord, C. J., Tutt, A. N. J., & Ashworth, A. (2014). Synthetic Lethality and Cancer Therapy: Lessons Learned from the Development of PARP Inhibitors. *Annual Review of Medicine*, *66*(1), 455–470. https://doi.org/10.1146/annurev-med-050913-022545

Lovell, M. R., Luckett, T., Boyle, F. M., Phillips, J., Agar, M., & Davidson, P. M. (2014). Patient education, coaching, and self-management for cancer pain. *Journal of Clinical Oncology*, *32*(16), 1712–1720. https://doi.org/10.1200/JCO.2013.52.4850

Lowe, D. (2001). Carcinoma. In *Progress in pathology* (p. 52).

Luckett, T., Davidson, P. M., Green, A., Boyle, F., Stubbs, J., & Lovell, M. (2013). Assessment and management of adult cancer pain: a systematic review and synthesis of recent qualitative studies aimed at developing insights for managing barriers and optimizing facilitators within a comprehensive framework of patient care. *Journal of Pain and Symptom Management*, *46*(2), 229–253.

Luengo-Fernandez, R., Leal, J., Gray, A., & Sullivan, R. (2013). Economic burden of cancer across the European Union: a population-based cost analysis. *The Lancet Oncology*, *14*(12), 1165–1174.

Luszczynska, A., Sarkar, Y., & Knoll, N. (2007). Received social support, self-efficacy, and finding benefits in disease as predictors of physical functioning and adherence to antiretroviral therapy. *Patient Education and Counseling*, *66*(1), 37–42.

Machado, M., & Einarson, T. R. (2010). Comparison of SSRIs and SNRIs in major depressive disorder: a meta- analysis of head- to- head randomized clinical trials. *Journal of Clinical Pharmacy and Therapeutics*, *35*(2), 177–188.

Madathil, M. M., Bhattacharya, C., Yu, Z., Paul, R., Rishel, M. J., & Hecht, S. M. (2014). Modified bleomycin disaccharides exhibiting improved tumor cell targeting. *Biochemistry*, *53*(43), 6800–6810.

Magnusson, A., & Boivin, D. (2003). Seasonal Affective Disorder: An overview. *Chronobiology International*, *20*(2), 189–207. https://doi.org/10.1081/CBI-120019310

Malmström, P.-U. (2017). Drugs and risk of cancer. *Scandinavian Journal of Urology*, *51*(3), 212–218.

Maneeton, B., Maneeton, N., & Mahathep, P. (2012). Prevalence of depression and its

correlations: a cross-sectional study in Thai cancer patients. *Asian Pacific Journal of Cancer Prevention*, *13*(5), 2039–2043.

Mann, J. J. (2005). The medical management of depression. *New England Journal of Medicine*, *353*(17), 1819–1834.

March, J., Silva, S., Petrycki, S., Curry, J., Wells, K., Fairbank, J., … Vitiello, B. (2004). Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *Jama*, *292*(7), 807–820.

Mariotto, A. B., Robin Yabroff, K., Shao, Y., Feuer, E. J., & Brown, M. L. (2011). Projections of the cost of cancer care in the United States: 2010–2020. *Journal of the National Cancer Institute*, *103*(2), 117–128.

Martin, T., Ye, L., Sanders, A., Lane, J., & Jiang, W. (2014). Cancer Invasion and Metastasis: Molecular and Cellular Perspective. In *Cancer Invasion and Metastasis: Molecular and Cellular Perspective*.

Masand, P. S. (2004). Atypical antipsychotics in the treatment of affective symptoms: a review. *Annals of Clinical Psychiatry*, *16*(1), 3–13.

Massie, M. J. (2004). Prevalence of depression in patients with cancer. *Journal of the National Cancer Institute. Monographs*, *32*, 57–71. https://doi.org/10.1093/jncimonographs/lgh014

Mathijssen, R. H. J., Loos, W. J., Verweij, J., & Sparreboom, A. (2002). Pharmacology of topoisomerase I inhibitors irinotecan (CPT-11) and topotecan. *Current Cancer Drug Targets*, *2*(2), 103–123.

Mayo Clinic. (2019). Multiple myeloma. Retrieved August 4, 2020, from mayoclinic.org website: https://www.mayoclinic.org/diseases-conditions/multiple-myeloma/symptoms-causes/syc-20353378

McGirr, A., Vöhringer, P. A., Ghaemi, S. N., Lam, R. W., & Yatham, L. N. (2016). Safety and efficacy of adjunctive second-generation antidepressant therapy with a mood stabiliser or an atypical antipsychotic in acute bipolar depression: a systematic review and meta-analysis of randomised placebo-controlled trials. *The Lancet Psychiatry*, *3*(12), 1138–1146.

McGregor, B. A., Antoni, M. H., Boyers, A., Alferi, S. M., Blomberg, B. B., & Carver, C. S. (2004). Cognitive–behavioral stress management increases benefit finding and immune function among women with early-stage breast cancer. *Journal of Psychosomatic Research*, *56*(1), 1–8.

Mendlewicz, J., & Lecrubie, Y. (2000). Antidepressant selection: proceedings from a TCA/SSRI consensus conference. *Acta Psychiatrica Scandinavica*, *101*, 5–8.

Meng, X., Brunet, A., Turecki, G., Liu, A., D'Arcy, C., & Caron, J. (2017). Risk factor modifications and depression incidence: A 4-year longitudinal Canadian cohort of the Montreal Catchment Area Study. *BMJ Open*, *7*(6). https://doi.org/10.1136/bmjopen-2016-015156

Mhaidat, N. M., Alzoubi, K. H., Al-Sweedan, S., & Alhusein, B. A. (2009). Prevalence of depression among cancer patients in Jordan: A national survey. *Supportive Care in Cancer*, *17*(11), 1403–1407. https://doi.org/10.1007/s00520-009-0600-z

Miller, A. H. (1998). Neuroendocrine and immune system interactions in stress and depression. *Psychiatric Clinics of North America*. https://doi.org/10.1016/S0193-953X(05)70015-0

Mizumoto, M., Murayama, S., Akimoto, T., Demizu, Y., Fukushima, T., Ishida, Y., … Okumura, T. (2017). Long- term follow- up after proton beam therapy for pediatric tumors: a Japanese national survey. *Cancer Science*, *108*(3), 444–447.

Morrow, G. R., Shelke, A. R., Roscoe, J. A., Hickok, J. T., & Mustian, K. (2005). Management of Cancer-Related Fatigue. *Cancer Investigation*, *23*(3), 229–239. https://doi.org/10.1081/CNV-200055960

Moudi, M., Go, R., Yien, C. Y. S., & Nazre, M. (2013). Vinca alkaloids. *International Journal of Preventive Medicine*, *4*(11), 1231.

Mushtaq, R., Ansar, A., Anwar Bibi, H. K., Ali, J., Islam, A., Saleem, F., … Tariq, I. (2017). Frequency of Depression Among Cancer Patients. *Annals of PIMS ISSN*, *13*(1), 83–87.

Nabavizadeh, N., Elliott, D. A., Chen, Y., Kusano, A. S., Mitin, T., Thomas Jr, C. R., & Holland, J. M. (2016). Image guided radiation therapy (IGRT) practice patterns and IGRT's impact on workflow and treatment planning: results from a National Survey of American Society for Radiation Oncology members. *International Journal of Radiation Oncology* Biology* Physics*, *94*(4), 850–857.

National Cancer Institute. (2017). Obesity and Cancer. Retrieved July 13, 2019, from cancer.gov website: https://www.cancer.gov/about-cancer/causes-prevention/risk/obesity/obesity-fact-sheet#q3

National Cancer Institute. (2019). Cancer Classification. Retrieved August 4, 2020, from training.seer.cancer.gov website: https://training.seer.cancer.gov/disease/categories/classification.html#mixed_types

Nead, K. T., Sinha, S., Yang, D. D., & Nguyen, P. L. (2017). Association of androgen deprivation therapy and depression in the treatment of prostate cancer: a systematic review and meta-analysis. *Urologic Oncology: Seminars and Original Investigations*, *35*(11), 664-e1. Elsevier.

Nedunchezhian, K., Aswath, N., Thiruppathy, M., & Thirugnanamurthy, S. (2016). Boron neutron capture therapy-a literature review. *Journal of Clinical and Diagnostic Research: JCDR*, *10*(12), ZE01.

Newport, D. J., & Nemeroff, C. B. (1998). Assessment and treatment of depression in the cancer patient. *Journal of Psychosomatic Research*. https://doi.org/10.1016/S0022-3999(98)00011-7

Niedzwiedz, C. L., Knifton, L., Robb, K. A., Katikireddi, S. V., & Smith, D. J. (2019). Depression and anxiety among people living with and beyond cancer: a growing clinical and research priority. *BMC Cancer*, *19*(1), 1–8.

Nielsen, L. L., & Maneval, D. C. (1998). P53 tumor suppressor gene therapy for cancer. *Cancer Gene Therapy*, *5*(1), 52–63.

Nikbakhsh, N., Moudi, S., Abbasian, S., & Khafri, S. (2014). Prevalence of depression and anxiety among cancer patients. *Caspian Journal of Internal Medicine*, *5*(3), 167.

Noble, S., & Goa, K. L. (1997). Gemcitabine. A review of its pharmacology and clinical potential in non-small cell lung cancer and pancreatic cancer. *Drugs*, *54*(3), 447–472. https://doi.org/10.2165/00003495-199754030-00009

Ohayon, M. M. (2007). Epidemiology of depression and its treatment in the general population. *Journal of Psychiatric Research*, *41*(3–4), 207–213. https://doi.org/10.1016/j.jpsychires.2006.10.006

Pampallona, S., Bollini, P., Tibaldi, G., Kupelnick, B., & Munizza, C. (2004). Combined pharmacotherapy and psychological treatment for depression: a systematic review. *Archives of General Psychiatry*, *61*(7), 714–719.

Pare, C. M., & Mack, J. W. (1971). Differentiation of two genetically specific types of depression by the response to antidepressant drugs. *Journal of Medical Genetics*, *8*(3), 306.

Paridah, M. ., Moradbak, A., Mohamed, A. ., Owolabi, F. abdulwahab taiwo, Asniza, M., & Abdul Khalid, S. H. . (2016). An Overview of Cancer Treatment Modalities. *Intech*, *i*(tourism), 13. https://doi.org/http://dx.doi.org/10.5772/57353

Park, B., Youn, S., Yi, K.-K., Lee, S., Lee, J.-S., & Chung, S. (2017). The prevalence of depression among patients with the top ten most common cancers in South Korea. *Psychiatry Investigation*, *14*(5), 618.

Parrott Roxanne, N. E. (2001). Self-efficacy and rural women's performance of breast and cervical cancer detection practices. *Journal of Health Communication*, *6*(3), 219–233.

Patten, S. B., & Barbui, C. (2004). Drug-induced depression: A systematic review to inform clinical practice. *Psychotherapy and Psychosomatics*, *73*(4), 207–215. https://doi.org/10.1159/000077739

Patten, S. B., & Love, E. J. (1997). Drug-induced depression. *Psychotherapy and Psychosomatics*, *66*(2), 63–73.

Penedo, F. J., Dahn, J. R., Molton, I., Gonzalez, J. S., Kinsinger, D., Roos, B. A., … Antoni, M. H. (2004). Cognitive-Behavioral Stress Management Improves Stress-Management Skills and Quality of Life in Men Recovering from Treatment of Prostate Carcinoma. *Cancer*, *100*(1), 192–200. https://doi.org/10.1002/cncr.11894

Peng, Y.-N., Huang, M.-L., & Kao, C.-H. (2019). Prevalence of Depression and Anxiety in Colorectal Cancer Patients: A Literature Review. *International Journal of Environmental Research and Public Health*, *16*(3), 411.

Phillips, M. A., & Kass, R. B. (1996). User acceptability patterns for mefloquine and doxycycline malaria chemoprophylaxis. *Journal of Travel Medicine*, *3*(1), 40–45.

Pilevarzadeh, M., Amirshahi, M., Afsargharehbagh, R., Rafiemanesh, H., Hashemi, S.-M., & Balouchi, A. (2019). Global prevalence of depression among breast cancer patients: a systematic review and meta-analysis. *Breast Cancer Research and Treatment*, *176*, 519–533.

Pincus, H. A., Tanielian, T. L., Marcus, S. C., Olfson, M., Zarin, D. A., Thompson, J., & Zito, J. M. (1998). Prescribing trends in psychotropic medications: primary care, psychiatry, and other medical specialties. *Jama*, *279*(7), 526–531.

Pirl, W. F. (2004). Evidence report on the occurrence, assessment, and treatment of depression in cancer patients. *JNCI Monographs*, *2004*(32), 32–39.

Pitman, A., Suleman, S., Hyde, N., & Hodgkiss, A. (2018). Exploring low mood in a person with cancer. *BMJ*, *361*, k1488.

Plummer, M., Franceschi, S., Vignat, J., Forman, D., & de Martel, C. (2015). Global burden of gastric cancer attributable to Helicobacter pylori. *International Journal of Cancer*, *136*(2), 487–490.

Poljsak, B., & Milisav, I. (2018). The Role of Antioxidants in Cancer, Friends or Foes? *Current Pharmaceutical Design*, *24*(44), 5234–5244.

Pouessel, D., Chevret, S., Rolland, F., Gravis, G., Geoffrois, L., Roubaud, G., … Dauba, J. (2016). Standard or accelerated methotrexate, vinblastine, doxorubicin and cisplatin as neoadjuvant chemotherapy for locally advanced urothelial bladder cancer: Does dose intensity matter? *European Journal of Cancer*, *54*, 69–74.

Prager, G. W., Braga, S., Bystricky, B., Qvortrup, C., Criscitiello, C., Esin, E., … Ilbawi, A. (2018). Global cancer control: Responding to the growing burden, rising costs and inequalities in access. *ESMO Open*, *3*(2), 1–10. https://doi.org/10.1136/esmoopen-2017-000285

Quesnel, C., Savard, J., Simard, S., Ivers, H., & Morin, C. M. (2003). Efficacy of cognitive-behavioral therapy for insomnia in women treated for nonmetastic breast cancer. *Journal of Consulting and Clinical Psychology*, *71*(1), 189.

Ralhan, R., & Kaur, J. (2007). Alkylating agents and cancer therapy. *Expert Opinion on Therapeutic Patents*, *17*(9), 1061–1075. https://doi.org/10.1517/13543776.17.9.1061

Rao, K. V, & Faso, A. (2012). Chemotherapy-induced nausea and vomiting: optimizing prevention and management. *American Health & Drug Benefits*, *5*(4), 232.

Rawla, P., & Barsouk, A. (2019). Epidemiology of gastric cancer: global trends, risk factors and prevention. *Przeglad Gastroenterologiczny*, *14*(1), 26.

Regier, D. A., Narrow, W. E., Rae, D. S., Manderscheid, R. W., Locke, B. Z., & Goodwin, F. K. (1993). The de facto US mental and addictive disorders service system: Epidemiologic Catchment Area prospective 1-year prevalence rates of disorders and services. *Archives of General Psychiatry*, *50*(2), 85–94.

Rodin, G., Lloyd, N., Katz, M., Green, E., Mackay, J. A., Wong, R. K. S., & Care, S. C. G. G. of C. C. O. P. in E.-B. (2007). The treatment of depression in cancer patients: a systematic review. *Supportive Care in Cancer*, *15*(2), 123–136.

Ross, J. S. (2004). Targeted Therapy for Cancer. *American Journal of Cancer*, *3*(4), 205–214. https://doi.org/10.2165/00024669-200403040-00001

Rothschild, A. J., Williamson, D. J., Tohen, M. F., Schatzberg, A., Andersen, S. W., Van Campen, L. E., … Tollefson, G. D. (2004). A double-blind, randomized study of olanzapine and olanzapine/fluoxetine combination for major depression with psychotic features. *Journal of Clinical Psychopharmacology*, *24*(4), 365–373.

Rowinsky, E. K., & Donehower, R. C. (1995). Paclitaxel (taxol). *New England Journal of Medicine*, *332*(15), 1004–1014.

Scott, B. P., Jeanne, V. A. W., & Edgar, J. L. (1995). Self-reported depressive symptoms in association with medication exposures among medical inpatients: a cross-sectional study. *The Canadian Journal of Psychiatry*, *40*(5), 264–269.

Semioshkina, N., & Voigt, G. (2016). An overview on depression. *Journal Of Pharmacology and Toxicological Studies*, *47*(2), 95–100. https://doi.org/10.1016/j.steroids.2009.10.005

Shah, A. A., Khand, F., & Khand, T. U. (2015). Effect of smoking on serum xanthine oxidase, malondialdehyde, ascorbic acid and α-tocopherol levels in healthy male subjects. *Pakistan Journal of Medical Sciences*, *31*(1), 146.

Shankar, A., Dracham, C., Ghoshal, S., & Grover, S. (2016). Prevalence of depression and anxiety disorder in cancer patients: An institutional experience. *Indian Journal of Cancer*, *53*(3), 432.

Shariff, S., Cumming, C. E., Lees, A., Handman, M., & Cumming, D. C. (1995). Mood disorder in women with early breast cancer taking tamoxifen, an estradiol receptor antagonist: An expected or unexpected effect? *Annals of the New York Academy of Sciences*, *761*(1), 365–368.

Sherwood, P., Given, B. A., Given, C. W., Champion, V. L., Doorenbos, A. Z., Azzouz, F., … Monahan, P. O. (2005). A cognitive behavioral intervention for symptom management in patients with advanced cancer. *Oncology Nursing Forum*, *32*(6), 1190–1198. https://doi.org/10.1188/05.ONF.1190-1198

Shulman, K. I., Herrmann, N., & Walker, S. E. (2013). Current place of monoamine oxidase inhibitors in the treatment of depression. *CNS Drugs*, *27*(10), 789–797.

Simon, G. E., & VonKorff, M. (1995). Recognition, management, and outcomes of depression in primary care. *Archives of Family Medicine*, *4*(2), 99–105.

Sinha, B. K. (1995). Topoisomerase Inhibitors: A Review of their Therapeutic Potential in Cancer. *Drugs*, *49*(1), 11–19. https://doi.org/10.2165/00003495-199549010-00002

Smith, H. R. (2015). Depression in cancer patients: Pathogenesis, implications and treatment. *Oncology Letters*, *9*(4), 1509–1514.

Solomon, R., & Cherny, N. I. (2006). *Constipation and Diarrhea in Patients with Cancer*. 355–364.

Spina, E., Santoro, V., & D'Arrigo, C. (2008). Clinically relevant pharmacokinetic drug interactions with second-generation antidepressants: an update. *Clinical Therapeutics*, *30*(7), 1206–1227.

Stahl, S. M., Grady, M. M., Moret, C., & Briley, M. (2005). SNRIs: the pharmacology, clinical efficacy, and tolerability in comparison with other classes of antidepressants. *CNS Spectrums*, *10*(9), 732–747.

Steinberg, G. D., Kuznetsov, D. D., O'connor, R. C., & Alsikafi, N. F. (2001). Intravesical valrubicin in the treatment of carcinoma in situ of the bladder. *Expert Opinion on Pharmacotherapy*, *2*(6), 1009–1013.

Stewart, B., & Wild, C. (2014). World Cancer Report 2014. *International Agency for Research on Cancer*.

Su, Z., Yang, Z., Xu, Y., Chen, Y., & Yu, Q. (2015). Apoptosis, autophagy, necroptosis, and cancer metastasis. *Molecular Cancer*, *14*(1), 48.

Sudarisan, S. S. P., Abraham, B., & George, C. (2019). Prevalence, correlates of depression, and its impact on quality of life of cancer patients attending a palliative care setting in South India. *Psycho‐ oncology*, *28*(6), 1308–1313.

Taberna, M., Mena, M., Pavón, M. A., Alemany, L., Gillison, M. L., & Mesía, R. (2017). Human papillomavirus-related oropharyngeal cancer. *Annals of Oncology*, *28*(10), 2386–2398.

Taeidi, E., Montazeri, S., Behroozi, N., Zadeh, M. H. H., & Deilami, A. A. (2018). The Effect of Problem Solving Therapy on Breast Cancer Women. *International Journal of Cancer Management*, *11*(9), e69336.

Taherdoost, H. (2017). Determining Sample Size; How to Calculate Survey Sample Size. *International Journal of Economics and Management Systems*, *2*(2), 237–239.

Tan, S. M., Beck, K. R., Li, H., Lim, E. C. L., & Krishna, L. K. R. (2014). Depression and anxiety in cancer patients in a Tertiary General Hospital in Singapore. *Asian Journal of Psychiatry*, *8*, 33–37.

The American Cancer Society medical and editorial content team. (2018a). Signs and Symptoms of Acute Lymphocytic Leukemia (ALL). Retrieved July 18, 2019, from cancer.org website: https://www.cancer.org/cancer/acute-lymphocytic-leukemia/detection-diagnosis-staging/signs-symptoms.html#written_by

The American Cancer Society medical and editorial content team. (2018b). Signs and Symptoms of Hodgkin Lymphoma. Retrieved July 18, 2019, from cancer.org website: https://www.cancer.org/cancer/hodgkin-lymphoma/detection-diagnosis-staging/signs-and-symptoms.html

The American Cancer Society medical and editorial content team. (2018c). Signs and Symptoms of Non-Hodgkin Lymphoma. Retrieved July 18, 2019, from cancer.org website: https://www.cancer.org/cancer/non-hodgkin-lymphoma/detection-diagnosis-staging/signs-symptoms.html#written_by

The American Cancer Society medical and editorial content team. (2018d). Signs and Symptoms of Soft Tissue Sarcomas. Retrieved July 18, 2019, from cancer.org website: https://www.cancer.org/cancer/soft-tissue-sarcoma/detection-diagnosis-staging/signs-symptoms.html

Tiwari, A. (2019). Prevalence of depression and anxiety among cancer patients in small town in India: Single Centre study. *International Journal of Radiation Oncology• Biology• Physics*, *103*(4), 1018.

Topotecan, S. S. (2016). Topotecan Monograph. *BC Cancer Agency Cancer Drug Manual*, (February), 7. Retrieved from http://www.bccancer.bc.ca/drug-database-site/Drug Index/Topotecan monograph_1Feb2016.pdf

Torre, L. A., Bray, F., Siegel, R. L., Ferlay, J., Lortet-Tieulent, J., & Jemal, A. (2015). Global cancer statistics, 2012. *CA: A Cancer Journal for Clinicians*, *65*(2), 87–108. https://doi.org/10.3322/caac.21262

Trask, P. C., Paterson, A. G., Griffith, K. A., Riba, M. B., & Schwartz, J. L. (2003).

Cognitive- behavioral intervention for distress in patients with melanoma: Comparison with standard medical care and impact on quality of life. *Cancer: Interdisciplinary International Journal of the American Cancer Society*, *98*(4), 854–864.

Travis, W. D., Brambilla, E., Muller-Hermelink, H. K., & Harris, C. C. (2004). World Health Organization classification of tumours. *Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart*, *10*, 179–184.

Troisi, R., Hatch, E. E., Titus, L., Strohsnitter, W., Gail, M. H., Huo, D., … Hoover, R. N. (2017). Prenatal diethylstilbestrol exposure and cancer risk in women. *Environmental and Molecular Mutagenesis*, *60*(5), 395–403.

Underwood, J. M., Richards, T. B., Henley, S. J., Momin, B., Houston, K., Rolle, I., … Stewart, S. L. (2015). Decreasing trend in tobacco-related cancer incidence, United States 2005–2009. *Journal of Community Health*, *40*(3), 414–418.

Uwayezu, M. G., Gishoma, D., Sego, R., Mukeshimana, M., & Collins, A. (2019). Anxiety and depression among cancer patients: prevalence and associated factors at a Rwandan referral hospital. *Rwanda Journal of Medicine and Health Sciences*, *2*(2), 118–125.

van Leeuwen, F. E., & Ng, A. K. (2016). Long-term risk of second malignancy and cardiovascular disease after Hodgkin lymphoma treatment. *Hematology 2014, the American Society of Hematology Education Program Book*, *2016*(1), 323–330.

Vasir, J. K., & Labhasetwar, V. (2005). Targeted drug delivery in cancer therapy. *Technology in Cancer Research and Treatment*, *4*(4), 363–374. https://doi.org/10.1177/153303460500400405

Visser, M. M., Heijenbrok-Kal, M. H., van 't Spijker, A., Lannoo, E., Busschbach, J. J. V, & Ribbers, G. M. (2016). Problem-solving therapy during outpatient stroke rehabilitation improves coping and health-related quality of life: randomized controlled trial. *Stroke*, *47*(1), 135–142.

Vogelstein, B., Fearon, E. R., Kern, S. E., Preisinger, A. C., Nakamura, Y., & White, R. (1989). Allelotype of colorectal carcinomas. *Science*, *244*(4901), 207–211.

Vos, T., Allen, C., Arora, M., Barber, R. M., Brown, A., Carter, A., … Zuhlke, L. J. (2016). Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet*. https://doi.org/10.1016/S0140-6736(16)31678-6

W A Newman Dorland. (2000). *Dorland's Illustrated medical dictionary* (29th ed.).

Wagner, A. D., Syn, N. L. X., Moehler, M., Grothe, W., Yong, W. P., Tai, B., … Unverzagt, S. (2017). Chemotherapy for advanced gastric cancer. *Cochrane Database of Systematic Reviews*, (8).

Walker, J., Hansen, C. H., Martin, P., Symeonides, S., Ramessur, R., Murray, G., & Sharpe, M. (2014). Prevalence, associations, and adequacy of treatment of major depression in patients with cancer: a cross-sectional analysis of routinely collected clinical data. *The Lancet Psychiatry*, *1*(5), 343–350.

Walter, J. (2013). The Lymphoma Guide. *The Leukemia & Lymphoma Society*, 1–48.

Wardle, J., Armitage, J., Collins, R., Wallendszus, K., Keech, A., & Lawson, A. (1996). Randomised placebo controlled trial of effect on mood of lowering cholesterol concentration. *BMJ*, *313*(7049), 75–78.

Weinberger, A. H., Gbedemah, M., Martinez, A. M., Nash, D., Galea, S., & Goodwin, R. D. (2018). Trends in depression prevalence in the USA from 2005 to 2015: widening disparities in vulnerable groups. *Psychological Medicine*, *48*(8), 1308–1315.

Wells BG, Dipiro JT, Dipiro CV, S. T. (2009). *Pharmacotherapy Handbook* (Vol. 7).

Wiczer, T., Dotson, E., Tuten, A., Phillips, G., & Maddocks, K. (2016). Evaluation of incidence and risk factors for high-dose methotrexate-induced nephrotoxicity. *Journal of Oncology Pharmacy Practice*, *22*(3), 430–436.

World Health Organization. (2017). Depression and other common mental disorders: global health estimates. *Geneva: World Health Organization*, Licence: CC BY-NC-SA 3.0 IGO.

World Health Organization. (2018). Cancer. Retrieved July 13, 2019, from who.int website: https://www.who.int/en/news-room/fact-sheets/detail/cancer

Yabroff, K. R., Lund, J., Kepka, D., & Mariotto, A. (2011). Economic burden of cancer in the United States: Estimates, projections, and future research. *Cancer Epidemiology Biomarkers and Prevention*, *20*(10), 2006–2014. https://doi.org/10.1158/1055-9965.EPI-11-0650

Yan, X., Chen, X., Li, M., & Zhang, P. (2019). Prevalence and risk factors of anxiety and depression in Chinese patients with lung cancer: a cross-sectional study. *Cancer Management and Research*, *11*, 4347.

Yang, H., Feng, C., Cai, B.-N., Yang, J., Liu, H.-X., & Ma, L. (2017). Comparison of three-dimensional conformal radiation therapy, intensity-modulated radiation therapy, and volumetric-modulated arc therapy in the treatment of cervical esophageal carcinoma. *Diseases of the Esophagus: Official Journal of the International Society for Diseases of the Esophagus*, *30*(2), 1–8.

Yang, J., Ren, Z., Du, X., Hao, M., & Zhou, W. (2014). The role of mesenchymal stem/progenitor cells in sarcoma: update and dispute. *Stem Cell Investigation*, *1*.

Zephir, H., De Seze, J., Stojkovic, T., Delisse, B., Ferriby, D., Cabaret, M., & Vermersch, P. (2003). Multiple sclerosis and depression: influence of interferon b therapy. *Multiple Sclerosis Journal*, *9*(3), 284–288.

Zhang, Z., Yu, X., Wang, Z., Wu, P., & Huang, J. (2015). Anthracyclines potentiate anti-tumor immunity: A new opportunity for chemoimmunotherapy. *Cancer Letters*, *369*(2), 331–335.

Zhao, Y., Brettle, A., & Qiu, L. (2018). The Effectiveness of Shared Care in Cancer Survivors—A Systematic Review. *International Journal of Integrated Care*, *18*(4), 2.

Zheng, Y., Wu, X., Lin, X., & Lin, H. (2017). The prevalence of depression and depressive symptoms among eye disease patients: a systematic review and meta-analysis. *Scientific Reports*, *7*, 46453.

Zhou, Y., Li, C., Huijbregts, M. A. J., & Mumtaz, M. M. (2015). Carcinogenic air toxics exposure and their cancer-related health impacts in the United States. *PloS One*, *10*(10), e0140013.

Zimmer, A. S., Gillard, M., Lipkowitz, S., & Lee, J.-M. (2018). Update on PARP inhibitors in breast cancer. *Current Treatment Options in Oncology*, *19*(5), 21.

Zung, W. W. K. (1965). A self-rating depression scale. *Archives of General Psychiatry*, *12*(1), 63–70.