Kurdistan Region of Iraq

Ministry of higher education & scientific research

Salahaddin University – Erbil

College of Science

Chemistry Department

APITHERAPY AND NANO CHEMOTHERAPY FOR THE TREATMENT OF BREAST CANCER

A Project Submitted to the Scientific Committee in the Chemistry Department in Partial Fulfillment of the Requirement for the Degree of Bachelor Science in Chemistry.

Prepared by:

Diman Arshad

Supervisor:

Dedication

Acknowledgement

Table of Contents

Dedication 2

Acknowledgement 3

List of Figures 6

List of Tables 7

Summary 8

1. Introduction 9

1.2 types of Cancer 11

1.2.1 Bone Cancer 11

1.2.2 Breast Cancer 12

1.2.3 Kidney Cancer 13

1.2.4 Anal Cancer 14

1.2.5 Prostate Cancer 15

1.2.6 Skin Cancer 16

1.2.7 Testicular Cancer 17

1.2.8 Thyroid Cancer 18

1.2.9 Bladder cancer 19

1.2.10 Brain cancer 19

2.0 Breast Cancer 20

2.1 Risk Factors of Breast Cancer 21

2.1.1 Aging 21

2.1.2 Family history 21

2.1.3 Reproductive factors 21

2.1.4 Estrogen 22

2.1.5 Life style 22

Types of breast cancer 23
Non-invasive breast cancer 23
Invasive breast cancer 23
Stages of breast cancer 25
Stage 0 25
Stage 1 25
Stage 2 25
Stage 3 25
Stage 4 26
Diagnosis of breast cancer 26
References 32

List of Figures

List of Tables

Summary

1. Introduction

Cancer is a large group of diseases that can start in almost any organ or tissue of the body when abnormal cells grow uncontrollably, go beyond their usual boundaries to invade adjoining parts of the body and/or spread to other organs. The latter process is called metastasizing and is a major cause of death from cancer. A neoplasm and malignant tumor are other common names for cancer.

Cancer is the second leading cause of death globally, accounting for an estimated 9.6 million deaths, or 1 in 6 deaths, in 2018. Lung, prostate, colorectal, stomach and liver cancer are the most common types of cancer in men, while breast, colorectal, lung, cervical and thyroid cancer are the most common among women.

The cancer burden continues to grow globally, exerting tremendous physical, emotional and financial strain on individuals, families, communities and health systems. Many health systems in low- and middle-income countries are least prepared to manage this burden, and large numbers of cancer patients globally do not have access to timely quality diagnosis and treatment. In countries where health systems are strong, survival rates of many types of cancers are improving thanks to accessible early detection, quality treatment and survivorship care.

Between 30% and 50% of cancer deaths could be prevented by modifying or avoiding key risk factors and implementing existing evidence-based prevention strategies. The cancer burden can also be reduced through early detection of cancer and management of patients who develop cancer. Prevention also offers the most cost-effective long-term strategy for the control of cancer.

Cancer is more likely to respond to effective treatment when identified early, resulting in a greater probability of surviving as well as less morbidity and less expensive treatment.

There are two distinct strategies that promote early detection:

1. Early diagnosis identifies symptomatic cancer cases at the earliest possible stage.
2. Screening aims to identify individuals with abnormalities suggestive of a specific cancer or pre-cancer who have not developed any symptoms and refer them promptly for diagnosis and treatment.

Treatment options include surgery, cancer medicines and/or radiotherapy, administered alone or in combination. A multidisciplinary team of cancer professionals recommends the best possible treatment plan based on tumor type, cancer stage, clinical and other factors. The choice of treatment should be informed by patients' preferences and consider the capacity of the health system.

Palliative care, which focuses on improving the quality of life of patients and their families, is an essential component of cancer care. Survivorship care includes a detailed plan for monitoring cancer recurrence and detection of new cancers, assessing and managing long-term effects associated with cancer and/or its treatment, and services to ensure that cancer survivor needs are met.

1.2 types of Cancer

1.2.1 Bone Cancer

Bone cancer can refer to primary bone cancer or secondary bone cancer and the two types are quite different. Primary bone cancer is cancer that begins in the bones. Secondary (metastatic) bone cancer refers to a cancer that started elsewhere in the body and has spread to the bones.

The most common symptom of bone cancer is pain in the bones and joints, which may be worse at night or during activity.

Some factors that can increase risks of bone cancer include:

- previous radiotherapy, particularly for people who received high doses at a young age
- other bone conditions, such as Paget's disease of the bone
- genetic factors, such as inherited conditions like Li-Fraumeni syndrome, and a strong family history of certain cancers.

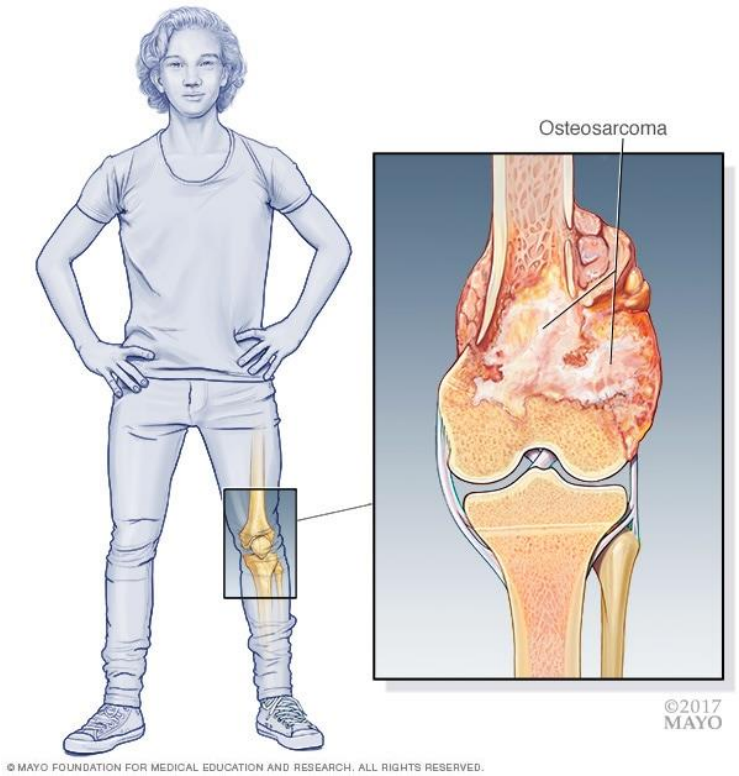

Figure 1. Bone Cancer

1.2.2 Breast Cancer

Breast cancer is the abnormal growth of the cells lining the breast lobules or ducts. These cells grow uncontrollably and have the potential to spread to other parts of the body. Both men and women can develop breast cancer, although it is uncommon in men. Transwomen, non-binary people can also get breast cancer.

Signs and symptoms of breast cancer include the following:

- new lumps or thickening in the breast, especially if in only one breast
- nipple sores, change in shape of the nipple
- nipple discharge or turning in
- changes in the size or shape of the breast
- skin of the breast dimpling
- discomfort or swelling in the armpit

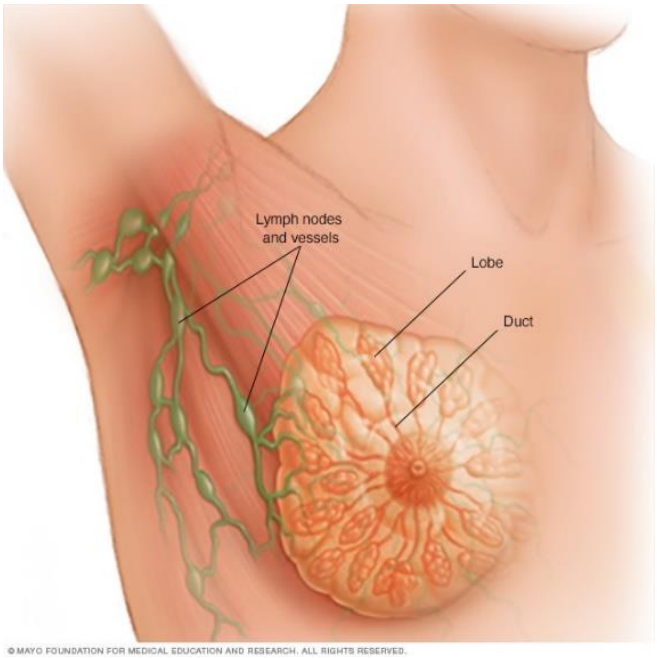

Figure 2. Breast Cancer

1.2.3 Kidney Cancer

Kidney cancer is cancer that starts in the cells of the kidney. The most common type of kidney cancer is renal cell carcinoma (RCC), accounting for about 90% of all cases. Usually only one kidney is affected, but in rare cases the cancer may develop in both kidneys.

Sign and symptoms include the following:

- blood in the urine or passing urine frequently or during the night, change in urine colour – dark, rusty or brown
- pain or a dull ache in the side or lower back that is not due to an injury
- a lump in the abdomen
- constant tiredness
- rapid, unexplained weight loss
- fever not caused by a cold or flu.

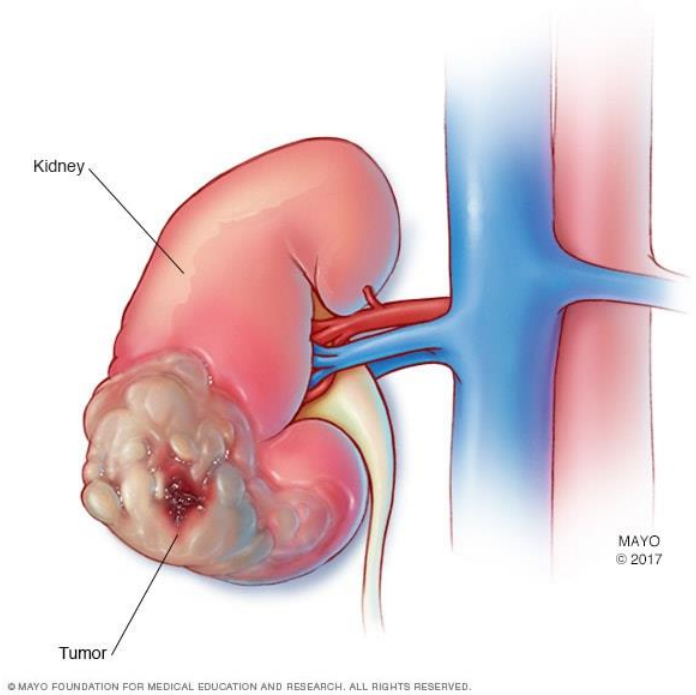

Figure 3. Kidney Cancer

1.2.4 Anal Cancer

Anal cancer is a rare tumor with an incidence that has been rising over the last 25 years. The disease was once thought to develop as a result of chronic irritation, but it is now known that this is not the case. Multiple risk factors, including human papillomavirus (HPV) infection, anoreceptive intercourse, cigarette smoking, and immunosuppression, have been identified. HIV infection is also associated with anal cancer; there is a higher incidence in HIV-positive patients but the direct relationship between HIV and anal cancer has been difficult to separate from the prevalence of HPV in this population. (Uronis and Bendell, 2007)

Sign and symptoms include the following:

- lumps around the anus or in the groin
- ulcers around the anus
- pain, discomfort, or itching around the anus
- blood or mucus in stools (faces) from the anus
- difficulty controlling your bowel movements
- a feeling of fullness, pain, or discomfort in the rectum.

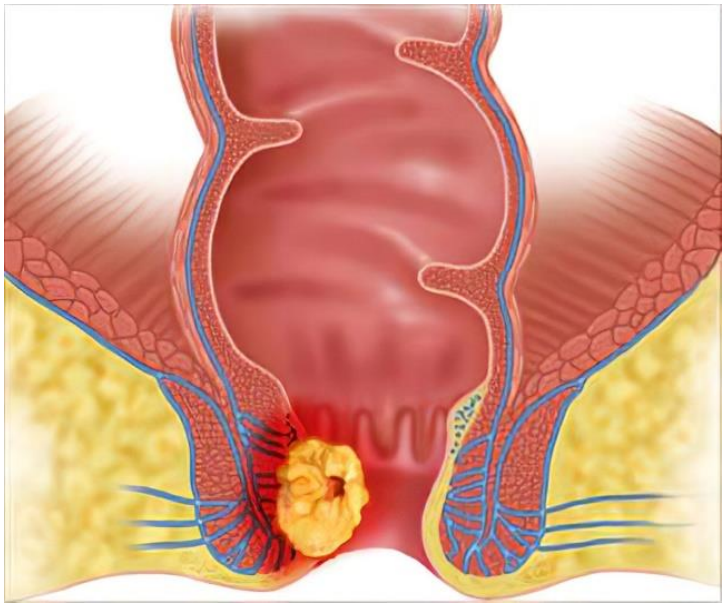

Figure 4. Anal Cancer

1.2.5 Prostate Cancer

Prostate cancer is the second most frequent cancer diagnosis made in men and the fifth leading cause of death worldwide. It develops when abnormal cells in the prostate gland grow in an uncontrolled way, forming a malignant tumor. it may be asymptomatic at the early stage and often has an indolent course that may require only active surveillance. Based on GLOBOCAN 2018 estimates, 1,276,106 new cases of prostate cancer were reported worldwide in 2018, with higher prevalence in the developed countries. (Rawla, 2019)

Sign and symptoms include the following:

- frequent urination
- pain while urinating
- blood in the urine or semen
- a weak stream
- pain in the back or pelvis

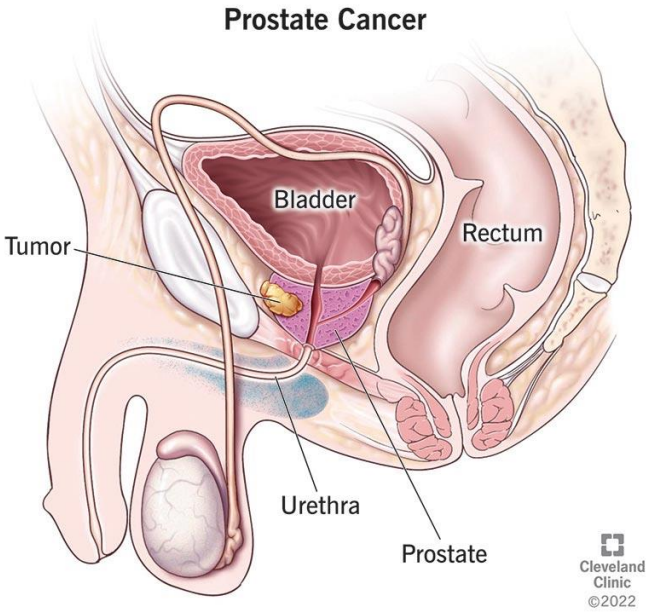

Figure 5. Prostate Cancer

1.2.6 Skin Cancer

Cutaneous carcinoma, or skin cancer, is a pre-eminent global public health problem. Skin cancer encompasses every ethnicity, socioeconomic and demographic cohort, geographic region, and covers the entire lifespan. 1 Skin cancer represents the most common worldwide malignancy and its incidence shows no signs of plateauing. 2,3 The American Cancer Society estimated in excess of 1.6 million new reported cases of cutaneous malignancy in 2012, and 12,190 deaths from skin cancer. 4 Most new cases were non-melanoma skin cancer (NMSC); however, among new cases, 76,250 were malignant melanoma and most of the 9,180-skin cancer-related deaths were from malignant melanoma. (Gordon, 2013

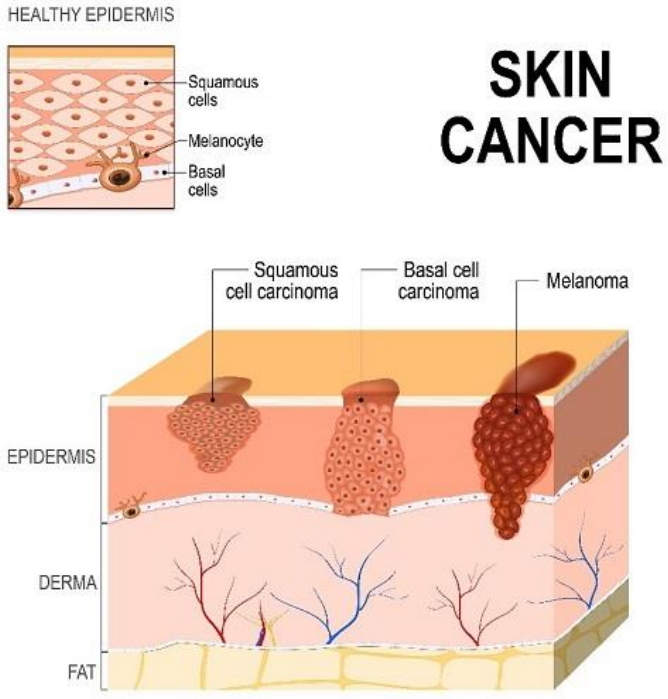

Figure 6. Skin Cancer

1.2.7 Testicular Cancer

Testicular cancer is the most common malignancy among men between 14 and 44 years of age, and its incidence has risen over the past two decades in Western countries. Both genetic and environmental factors contribute to the development of testicular cancer, for which cryptorchidism is the most common risk factor. (Cheng et al., 2018) Testicular cancer may cause no symptoms. The most common symptom is a painless swelling or a lump in a testicle or a change in size or shape.

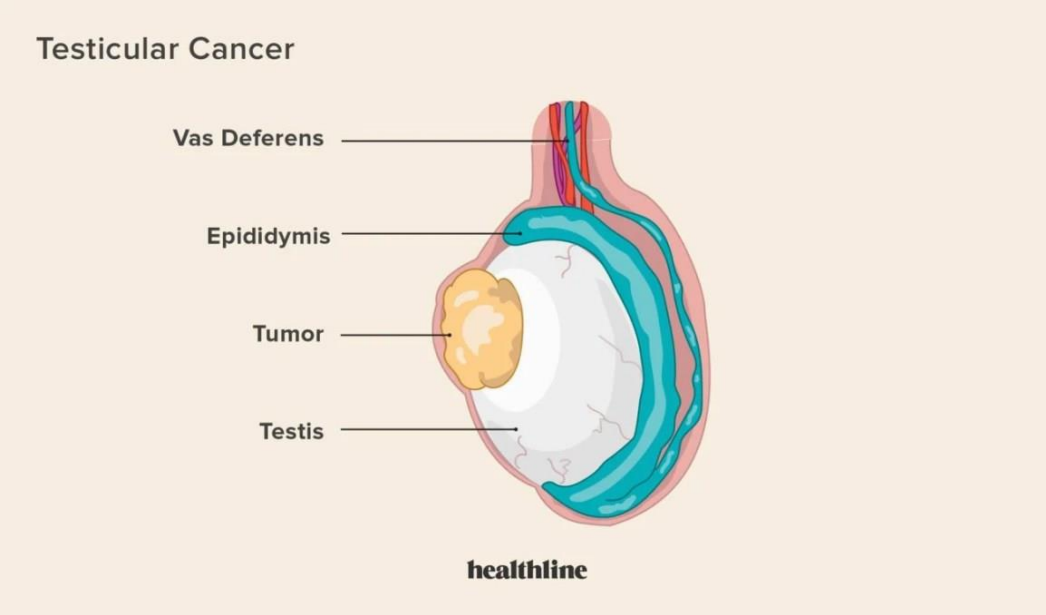

Figure 7. Testicular Cancer

1.2.8 Thyroid Cancer

Thyroid cancer is the most common endocrine malignancy, accounting for ~2.1% of all cancer diagnoses worldwide, with ~77% of these diagnoses occurring in women. During the past few decades, the incidence of thyroid cancer has increased substantially in many countries. The rise in incidence seems to be attributable both to the growing use of diagnostic imaging and fine-needle aspiration biopsy, which has led to enhanced detection and diagnosis of subclinical thyroid cancers, and environmental factors. (Kitahara and Sosa, 2016)

Signs and symptoms include the following:

- a lump in the neck or throat that may get bigger over time
- difficulty breathing or swallowing
- swollen lymph glands in the neck
- a hoarse voice

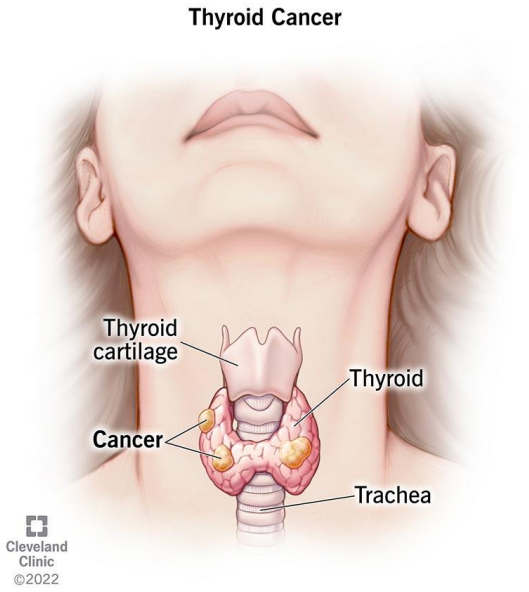

Figure 8. Thyroid Cancer

1.2.9 Bladder cancer

Bladder cancer is a complex disease associated with high morbidity and mortality rates if not treated optimally. Each year, bladder cancer is diagnosed in about more than 430 000 patients worldwide, making it the fourth most common cancer in men and the 11th most common cancer in women. (Kamat et al., 2016)

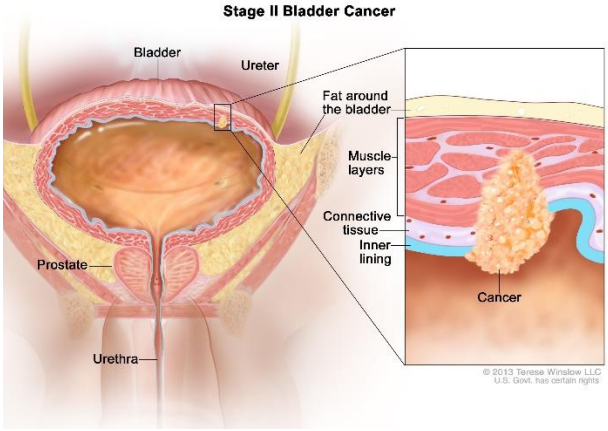

Figure 9. Bladder Cancer

1.2.10 Brain cancer

Brain tumors constitute a profound and unsolved clinical problem although significant strides have been made in the treatment of many other cancer types. The incidence of primary brain tumors in the United States has been estimated at approximately 43,800 per year and 18,500 of these are expected to be malignant. Currently brain tumors account for at least 12,690 deaths in the United States yearly and are the most common cause of cancer-related death for children 0–14 years of age.

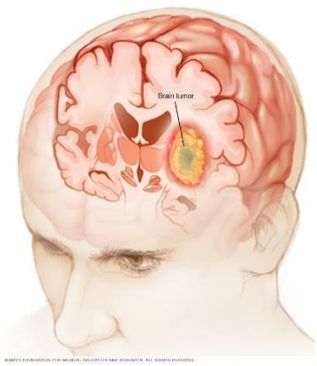

Figure 10. Brain Cancer

2.0 Breast Cancer

Breast cancer is the most common cancer and also the primary cause of mortality due to cancer in female around the World. About 1.38 million new breast cancer cases were diagnosed in 2008 with almost 50% of all breast cancer patients and approximately 60% of deaths occurring in developing countries. There is a huge difference in breast cancer survival rates worldwide, with an estimated 5-year survival of 80% in developed countries to below 40% for developing countries (Coleman et al., 2008).

Developing countries face resource and infrastructure constraints that challenge the objective of improving breast cancer outcomes by timely recognition, diagnosis and management (Anderson et al., 2008). In developed countries like the United States, about 232,340 females will be diagnosed and death of 39,620 female will occur due to breast cancer in 2013. (Siegel et al., 2013) The lifetime risk of developing breast cancer in an American female is 12.38% [3]. The significant decline in morality due to breast cancer in the United States from 1975 to 2000 is attributed to constant enhancement in both screening mammography and management (Berry et al., 2005).

According to the World Health Organization (WHO), enhancing breast cancer outcome and survival by early detection remains the foundation of breast cancer regulations. Different modern medicines are prescribed to treat breast cancer. Medical therapy of breast cancer with antiestrogens such as raloxifene or tamoxifen might avoid breast cancer in individuals who are at increased possibility of developing it (Peng et al., 2009). Surgery of both breasts is an added preventative measure in some increased probability of developing cancer in female. In patients who have been identified with breast tumor, different strategies of management are used such as targeted therapy, hormonal therapy, radiation therapy, surgery and chemotherapy. In individuals with distant metastasis, managements are typically aimed at enhancing life quality and survival rate (Reeder & Vogel, 2008). The unpleasant side effects of breast cancer treatment are one of the most motivating factors to find some alternative methods. The use of herbs for treating the patients having breast cancer is considered a natural alternative, because some plants may contain properties that naturally have the ability to treat breast cancer. (Abdull Razis and Noor, 2013; Mary et al., 2012)

2.1 Risk Factors of Breast Cancer

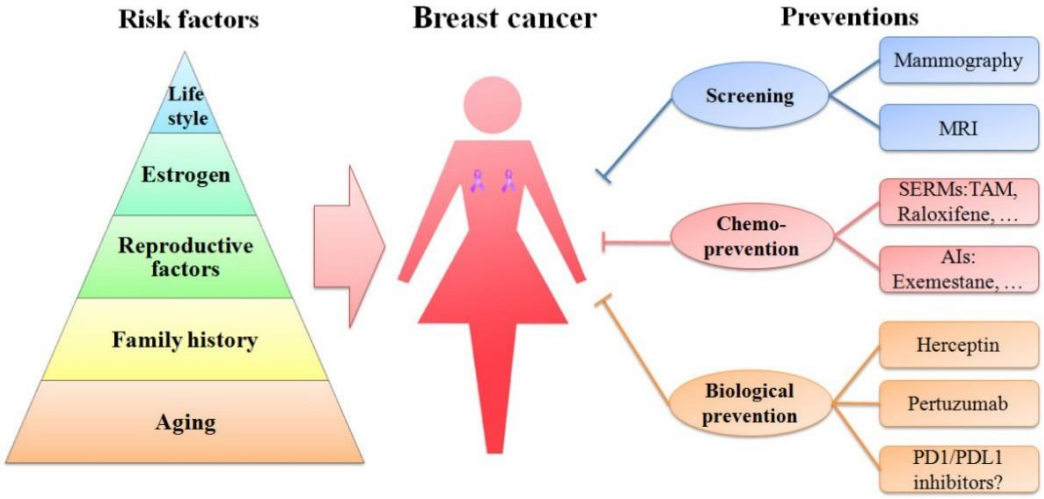

Figure 11. Risk Factors

2.1.1 Aging

Besides sex, aging is one of the most important risk factors of breast cancer, because the incidence of breast cancer is highly related to the increasing age. In 2016, approximately 99.3% and 71.2% of all breast cancer-associated deaths in America were reported in women over the age of 40 and 60, respectively [3]. Therefore, it is necessary to have a mammography screening ahead of time in women aged 40 or older.

2.1.2 Family history

Nearly a quarter of all breast cancer cases are related to family history [65]. Women, whose mother or sister has a breast cancer, are prone to this disease. A cohort study of over 113,000 women in UK demonstrated that women with one first-degree relative with breast cancer have a 1.75-fold higher risk of developing this disease than women without any affected relatives. Moreover, the risk becomes 2.5-fold or higher in women with two or more first-degree relatives with breast cancer [65]. The inherited susceptibility to breast cancer is partially attributed to the mutations of breast cancer related genes such as BRCA1 and BRCA2.

2.1.3 Reproductive factors

Reproductive factors such as early menarche, late menopause, late age at first pregnancy and low parity can increase the breast cancer risk. Each 1-year delay in menopause increases the risk of breast cancer by 3%. Each 1-year delay in menarche or each additional birth decreases the risk of

breast cancer by 5% or 10%, respectively [66-68]. A recent Norwegian cohort study showed that a hazard ratio (HR) is 1.54 between late (≥35 years) and early (<20 years) age at first birth [69]. Reproductive factors are strongly associated with the ER status, with differences in the odds ratios (OR) between ER+ and ER– breast cancer for parity (OR: 0.7 vs. 0.9 for ≥3 births vs. nulliparae) and age at the first birth (OR: 1.6 vs. 1.2 for age ≥30 vs.<25 years) [70].

2.1.4 Estrogen

Both endogenous and exogenous estrogens are associated with the risk of breast cancer. The endogenous estrogen is usually produced by the ovary in premenopausal women and ovariectomy can reduce the risk of breast cancer [71]. The main sources of exogenous estrogen are the oral contraceptives and the hormone replacement therapy (HRT). The oral contraceptives have been widely used since 1960s and the formulations have been upgraded to reduce side-effects. However, the OR is still higher than 1.5 for African American women and Iranian populations [72,73]. Nevertheless, oral contraceptives do not increase the risk of breast cancer in women who stop to use them for more than 10 years [66]. HRT involves the administration of exogenous estrogen or other hormones for the menopausal or postmenopausal women. A number of studies have shown that the use of HRT can increase the breast cancer risk. The Million Women Study in UK reported a relative risk (RR) of 1.66 between current users of HRT and those who never used it [74]. A cohort study of 22,929 women in Asia demonstrated HRs of 1.48 and 1.95 after HRT use for 4 and 8 years, respectively [75]. However, the risk of breast cancer has been shown to significantly decrease after two years of stopping HRT [76]. The recurrence rate is also high among breast cancer survivors who take HRT, and the HR for a new breast tumor is 3.6 [77]. Since the adverse effects of HRT were published in 2003 based on the Women's Health Initiative randomized controlled trial, the incidence rate of breast cancer in America has decreased by approximately 7% due to the reduction in the use of HRT [78].

2.1.5 Life style

Modern lifestyles such as excessive alcohol consumption and too much dietary fat intake can increase the risk of breast cancer. Alcohol consumption can elevate the level of estrogen-related hormones in the blood and trigger the estrogen receptor pathways. A meta-analysis based on 53 epidemiological studies indicated that an intake of 35-44 grams of alcohol per day can increase the risk of breast cancer by 32%, with a 7.1% increase in the RR for each additional 10 grams of

alcohol per day [79,80]. Modern western diet contains too much fat and excess intake of fat, especially the saturated fat, is associated with mortality (RR=1.3) and poor prognosis in breast cancer patients [81]. Although the relationship between smoking and breast cancer risk remains controversial, mutagens from cigarette smoke have been detected in the breast fluid from non-lactating women. The risk of breast cancer is also elevated in women who both smoke and drink (RR=1.54) [82]. Up to now, accumulating evidences demonstrate that smoking, especially at an early age, has a higher risk on breast cancer occurrence [83-86].

Types of breast cancer

Non-invasive breast cancer

It is a cancer that has not extended away from the lob- ule or ducts where it situated. (West et al., 2017) An example of a kind of non-invasive breast cancer is ductal carcinoma in situ. Ductal carcinoma in situ appears when atypical cells develop within the milk ducts, however have not extended to close proximity of tissue or outside. The word “in situ” describes “in place.” Even though the atypical cells have not extended to tissues outer the lobules or ducts, they can progress and grow into invasive breast cancer. The normal background of every scientific unit is demonstrated and a biological understanding of the accessible information is presented. Lobular carcinoma in-situ is understood merely a risky sign moderately than a predecessor for the successive growth of invasive cancer, so that one time the judgment is made, additional operative involvement is avoidable and sequential follow-up only is suggested. The management of ductal carcinoma in-situ should be kept in mind that breast- preserving treatment is at the present considered best therapy of breast cancer, the illness we are attempting to stop. (Posner and Wolmark, 1992) The pitfalls of suggested management based on retrospective statistics are have been taken into account and the requirement to conduct clinical studies intended to establish the best possible beneficial treatment of non- invasive breast cancer is affirmed. (Hang et al., 2017)

Invasive breast cancer

It exists when abnormal cells from within the lobules or milk ducts split out into close proximity of breast tissue. (Harris et al., 2016) Cancer cells can pass through the breast to different parts of the body through immune system or the systemic circulation. (Ziperstein et al., 2016) They may move early in the development when the tumor is a minute or afterward when the tumor is huge Invasive breast cancer is most occurring general carcinoma in females. The regions of elevated

threat are the prosperous populations of Australia and Europe wherever 6% of females suffer from invasive breast cancer prior to 75 years of age. The prevalence of breast cancer enhances quickly with increasing age. (Prabhakaran et al., 2017) Invasive breast cancer that extends to different organs of the body is also recognized as metastatic breast cancer. (Stevanovic et al., 2006) Most common organ to which these cells spread are brain, bones, lungs and liver. These cells once more segregate and expand irregularly and produce new cancers. The new forming cells are developing in different part of the body, it is still breast cancer. (Page et al., 2017)

Stages of breast cancer

According to the report of breast cancer.org Stages of the breast cancer depends upon the size and type of tumor and how much the tumor cells have been penetrated in the breast tissues (Heim et al., 1997). Whereas stage 0 describes the non-invasive and stage 4 describes the invasive kind of tumor. Descriptions of those tumor stages are:

Stage 0

This is the non-invasive stage of tumor which indicates that both cancerous and non-cancerous cells are within the boundaries of that part of the breast in which the tumor begins to grow and no evidence found of their invasion in the surrounding tissues of that part, the example of this tumor stage is ductal cell carcinoma in situ (DCIS). (Bednarek et al., 1997)

Stage 1

This stage describes as the invasive breast carcinoma and microscopic invasion is possible in this stage. It has two categories that are 1A and 1B stage. The category 1A describes the tumor which measures up to 2 cm and none of the lymph nodes are involved in it while stage 1B describes that small group of cancer cells larger than 0.2 mm founds in lymph node. (Segal et al., 2001)

Stage 2

This stage describes as the invasive breast carcinoma and microscopic invasion is possible in this stage. It has two categories that are 1A and 1B stage. The category 1A describes the tumor which measures up to 2 cm and none of the lymph nodes are involved in it while stage 1B describes that small group of cancer cells larger than 0.2 mm founds in lymph node. (Moran et al., 2014)

Stage 3

It has been divided into three sub categories that are 3A, 3B and 3C. Amongst which stage 3A describes that no tumor is found in breast but it can be found in 4–9 axillary lymph nodes or in sentinel lymph nodes while stage 3B describes that the tumor can be of any size but have caused swelling or ulcer on the skin of the breast and can have spread up to 9 axillary lymph nodes or to sentinel lymph nodes stage 3B can be considered as inflammatory breast cancer which includes red, warm and swollen skin of the breast. However, stage 3C describes the spread of tumor up to 10 or more than 10 axillary lymph nodes and it also have involved the lymph nodes above and below the clavicle. (Jacquillat et al., 1990)

Stage 4

This is the advanced and metastatic stage of cancer and this stage describes the spread to other organs of the body that is lungs, bones, liver brain…etc. (Neuman et al., 2015)

Diagnosis of breast cancer

Innovative treatments of breast cancer

1. Nano-chemotherapy

Nanoparticles have considerable potential for drug delivery and are widely used in the treatment of cancer. Nano- particles have shown several advantages, such as good stability, high encapsulation, and the ability to incorporate both hydrophilic and hydrophobic drugs. However, nano- particles have also shown some potential risks (Table 6). For example, nanoparticles with small particle size can easily pass through membranes, access many areas of the body, interact with cells in an unfavorable manner, and potentially cause intrinsic toxicity in many normal cells.

In addition, materials can limit the preparation of nanoparticles. For instance, PLGA is a safe material with low toxicity, but it degrades quickly and does not circulate in tissues long enough for sustained drug/gene delivery resulting in decreased treatment efficiency (Jain et al. 2011; Nguyen 2011). Therefore, the disadvantage of PLGA can be overcame by changing the poly-lactic/ glycolic acid ratio (Makadia and Siegel 2011). For example, with the ratio of 50:50 (PLA/PGA), PLGA exhibited a faster degradation than PLGA with a ratio 65:35 (PLA/ PGA) due to preferential degradation of glycolic acid pro- portion assigned by higher hydrophilicity. Subsequently PLGA 65:35 (PLA/PGA) shows faster degradation than PLGA 75:25 (PLA/PGA) and PLGA 75:25 (PLA/PGA) than PLGA 85:15 (PLA/PGA). Therefore, the absolute value of the degradation rate depends on the ratio of glycolic acid. The amount of glycolic acid is a critical parameter in tuning the hydrophilicity of the matrix and thus the degradation and drug release rate (Park 1995; Lu et al. 1999, 2000). On the other hand, inorganic materials, such as carbon nanotubes, are durable and can per- sist in the body for weeks, months, or even years, making them potentially toxic and limiting their use for repeated treatments. In addition, some cancer cells can develop a resistance to the drug over the course of treatment, rendering the drug released from the nanoparticle ineffective (Nguyen 2011).

In recent years, the surfaces of nanoparticles have been modified using active targeting ligands to improve the distribution of anticancer drugs to target cells (Sohn et al. 2017; Choi and Park 2017). For example, a docetaxel liposome was prepared using d-α-tocopheryl polyethylene glycol 1000 succinate (vitamin E TPGS) and further conjugated to trastuzumab for cellular uptake intended to produce cytotoxicity in SK-BR-3 cells, while in vivo pharmacokinetics were

also investigated in rats (Raju et al. 2013). The IC50 value of a marketed preparation of docetaxel, TPGS liposomes, and trastuzumab-conjugated TPGS liposomes after a 24 h incubation with SK-BR-3 cells was 20.23 ± 1.95, 3.74 ± 0.98, and 0.08 ± 0.4 μg/mL, respectively. In addition, the half-life of trastuzumab-conjugated TPGS liposomes was tenfold higher compared to docetaxel alone in the pharmacokinetic study. In another study, PLA-TPGS was used as a polymer in the preparation of emtansine nanoparticle that were subsequently conjugated with trastuzumab for the treatment of HER2-positive breast cancer (Rong et al. 2017). The toxicity of emtansine nanoparticle-trastuzumab in breast cancer cells was higher that than of emtansine and trastuzumab alone.

In vivo, the nanoparticle showed fewer toxic effects and inhibited tumor growth by 88% compared to the non-targeting group after administration in MDA-MB-453 xenograft- bearing mice. To modify the surface of the docetaxel-PLGA nanoparticles with Herceptin® (HCT), different methods such as adsorption, bio-conjugation, and charged adsorption were applied to enhance internalization and cytotoxicity in BT-474, SK-BR-3, and MCF-7 breast cancer cells (Choi et al. 2018a). The cellular uptake of HCT-bioconju- gated nanoparticles in BT-474, SK-BR-3, and MCF-7 breast cancer cells was 5.0-, 4.4-, and 4.6-fold higher than that of the nanoparticles, respectively. In addition, the cytotoxicity of HCT-bioconjugated DTX-nanoparticles in BT-474, SK-BR-3, and MCF-7 breast cancer cells was higher com- pared to other formulations. Moreover, tumor-targeting gold nanorod (AuNR)-photosensitizer conjugates were designed using glutathione-sensitive linkages for effective photo- dynamic (PDT)/photothermal (PTT) therapies to improve active tumor-targeting activity and stability and in vitro cytotoxicity and cellular localization were also investigated in MCF-7 breast cancer cells (Choi et al. 2018b). The AuNR-photosensitizer conjugates presented good stability and biocompatibility. In addition, more than 99% of MCF-7 breast cancer cells showed AuNR-photosensitizer conjugate uptake in vitro.

2. Apitherapy

Apitherapy is a CAM method in which honeybee products are used for therapeutic purposes. In addition to being used as nutrients, apitherapy products have also been used for the treatment of diseases throughout history due to the substances they contain that have biologically active properties. The most commonly used apitherapy products are honey, propolis, pollen, beeswax, royal jelly, and bee venom. (Şenel et al., 2018) There are many studies in the literature reporting that apitherapy products have antimicrobial, antioxidant, anti-inflammatory, immunomodulatory, and anticancer effects. (Ali and Kunugi, 2020)

Imbalance in estrogen signaling pathways and propagating levels of estrogens have important roles in breast cancer growth and propagation. Treatments for breast cancer are associated with targeting the estrogen receptor (ER) signaling pathway. Phytoestrogens are a subclass of phytochemicals with a common structure to the mammalian estrogen that enables them to bind to estrogen receptors. Several experimental studies have investigated the efficiency of honey in modulating the ER signaling pathway (Erejuwa et al., 2014). On the other hand, cytotoxic activities of Tualang honey in human breast cancer cells were demonstrated by elevated secretion of lactate dehydrogenase (LDH) and further illustrated the cytotoxic properties of honey. The study also showed that honey only exerts cytotoxic effects on breast cancer line and not on nonmalignant breast cells. Therefore, this indicates that Tualang honey shows highly specific and selective cytotoxic effects towards breast cancer cell lines and has a good potential as a chemotherapeutic agent (Fauzi et al.,2011).

Aim

The current review study aims at overviewing cancer and specifically breast cancer and go over innovative treatment solution such as nano-chemotherapy and Apitherapy.

References

1. Uronis, H.E. and Bendell, J.C., 2007. Anal cancer: an overview. *The Oncologist*, *12*(5), pp.524-534.
2. Fauzi, A. N., Norazmi, M. N., & Yaacob, N. S. (2011). Tualang honey induces apoptosis and disrupts the mitochondrial membrane potential of human breast and cervical cancer cell lines. *Food and Chemical Toxicology*, *49*(4), 871-878.
3. Erejuwa, O. O., Sulaiman, S. A., Wahab, M. S., Sirajudeen, K. N. S., Salleh, M. M., & Gurtu, S. (2010, September). Antioxidant protection of Malaysian tualang honey in pancreas of normal and streptozotocin-induced diabetic rats. In *Annales d'endocrinologie* (Vol. 71, No. 4, pp. 291-296). Elsevier Masson.
4. Rawla, P., 2019. Epidemiology of prostate cancer. *World journal of oncology*, *10*(2), p.63.
5. Gordon, R., 2013, August. Skin cancer: an overview of epidemiology and risk factors. In *Seminars in oncology nursing* (Vol. 29, No. 3, pp. 160-169). WB Saunders.
6. Coleman, M.P., Quaresma, M., Berrino, F., Lutz, J.M., De Angelis, R., Capocaccia, R., Baili, P., Rachet, B., Gatta, G., Hakulinen, T. and Micheli, A., 2008. Cancer survival in five continents: a worldwide population-based study (CONCORD). *The lancet oncology*, *9*(8), pp.730-756
7. Anderson, B.O., Yip, C.H., Smith, R.A., Shyyan, R., Sener, S.F., Eniu, A., Carlson, R.W., Azavedo, E. and Harford, J., 2008. Guideline implementation for breast healthcare in low-income and middle-income countries: Overview of the Breast Health Global Initiative Global Summit 2007. *Cancer*, *113*(S8), pp.2221-2243.
8. Siegel, R., Naishadham, D. and Jemal, A., 2013. Cancer statistics, 2013. *CA: a cancer journal for clinicians*, *63*(1), pp.11-30.
9. Berry, D.A., Cronin, K.A., Plevritis, S.K., Fryback, D.G., Clarke, L., Zelen, M., Mandelblatt, J.S., Yakovlev, A.Y., Habbema, J.D.F. and Feuer, E.J., 2005. Effect of screening and adjuvant therapy on mortality from breast cancer. *New England Journal of Medicine*, *353*(17), pp.1784-1792.
10. Peng, J., Sengupta, S. and Jordan, V.C., 2009. Potential of selective estrogen receptor modulators as treatments and preventives of breast cancer. *Anti-cancer agents in Medicinal Chemistry (formerly current Medicinal Chemistry-Anti-cancer agents)*, *9*(5), pp.481-499.
11. Reeder, J.G. and Vogel, V.G., 2008. Breast cancer prevention. *Advances in Breast Cancer Management, Second Edition*, pp.149-164.
12. Abdull Razis, A.F. and Noor, N.M., 2013. Cruciferous vegetables: dietary phytochemicals for cancer prevention. *Asian Pacific Journal of cancer prevention*, *14*(3), pp.1565-1570.
13. Mary, J.S., Vinotha, P. and Pradeep, A.M., 2012. Screening for in vitro cytotoxic activity of seaweed, Sargassum sp. against Hep-2 and MCF-7 cancer cell lines. *Asian Pac J Cancer Prev*, *13*(12), pp.6073-6076.

14. West, A. K. V., Wullkopf, L., Christensen, A., Leijnse, N., Tarp, J. M., Mathiesen, J., ... & Oddershede, L. B. (2017). Division induced dynamics in non-Invasive and invasive breast cancer. *Biophysical Journal*, *112*(3), 123a.
15. Posner, M. C., & Wolmark, N. (1992). Non-invasive breast carcinoma. *Breast cancer research and treatment*, *21*, 155-164.
16. Hang, J. A., Sim, L., & Zakaria, Z. (2017). Non-invasive breast cancer assessment using magnetic induction spectroscopy technique. *International Journal of Integrated Engineering*, *9*(2).
17. Harris, L. N., Ismaila, N., McShane, L. M., & Hayes, D. F. (2016). Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology clinical practice guideline summary. *Journal of oncology practice*, *12*(4), 384-389.
18. Ziperstein, M. J., Guzman, A., & Kaufman, L. J. (2016). Evaluating breast cancer cell morphology as a predictor of invasive capacity. *Biophysical Journal*, *110*(3), 621a.
19. Prabhakaran, S., Rizk, V. T., Ma, Z., Cheng, C. H., Berglund, A. E., Coppola, D., ... & Soliman, H. H. (2017). Evaluation of invasive breast cancer samples using a 12-chemokine gene expression score: correlation with clinical outcomes. *Breast Cancer Research*, *19*, 1-11.
20. Stevanovic A, Lee P, Wilcken N. (2006). Metastatic breast cancer. *Aust Fam Phys*. *35*:309–11.
21. Page, K., Guttery, D.S., Fernandez-Garcia, D., Hills, A., Hastings, R.K., Luo, J., Goddard, K., Shahin, V., Woodley-Barker, L., Rosales, B.M. and Coombes, R.C., 2017. Next generation sequencing of circulating cell-free DNA for evaluating mutations and gene amplification in metastatic breast cancer. *Clinical chemistry*, *63*(2), pp.532-541.
22. Heim, E., Valach, L., & Schaffner, L. (1997). Coping and psychosocial adaptation: Longitudinal effects over time and stages in breast cancer. *Psychosomatic medicine*, *59*(4), 408-418.
23. Bednarek, A. K., Sahin, A., Brenner, A. J., Johnston, D. A., & Aldaz, C. M. (1997). Analysis of telomerase activity levels in breast cancer: positive detection at the in situ breast carcinoma stage. *Clinical cancer research: an official journal of the American Association for Cancer Research*, *3*(1), 11-16.
24. Segal, R., Evans, W., Johnson, D., Smith, J., Colletta, S., Gayton, J., ... & Reid, R. (2001). Structured exercise improves physical functioning in women with stages I and II breast cancer: results of a randomized controlled trial. *Journal of clinical oncology*, *19*(3), 657-665.
25. Moran, M. S., Schnitt, S. J., Giuliano, A. E., Harris, J. R., Khan, S. A., Horton, J., ... & Morrow, M. (2014). Society of Surgical Oncology–American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. *International Journal of Radiation Oncology* Biology* Physics*, *88*(3), 553-564.

26. Jacquillat, C., Weil, M., Baillet, F., Borel, C., Auclerc, G., De Maublanc, M. A., ... & Khayat, D. (1990). Results of neoadjuvant chemotherapy and radiation therapy in the breast-conserving treatment of 250 patients with all stages of infiltrative breast cancer. *Cancer*, *66*(1), 119-129.
27. Neuman, H. B., Morrogh, M., Gonen, M., Van Zee, K. J., Morrow, M., & King, T. A. (2010). Stage IV breast cancer in the era of targeted therapy: does surgery of the primary tumor matter?. *Cancer: Interdisciplinary International Journal of the American Cancer Society*, *116*(5), 1226-1233.
28. Ali, A. M., & Kunugi, H. (2020). Apitherapy for Parkinson's disease: A focus on the effects of propolis and royal jelly. *Oxidative medicine and cellular longevity*, *2020*.
29. Şenel, E., & Demir, E. (2018). Bibliometric analysis of apitherapy in complementary medicine literature between 1980 and 2016. *Complementary therapies in clinical practice*, *31*, 47-52.