Review Article

Current status of breast cancer in Nepal

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ABSTRACT

Breast carcinoma is one of the most common and dreaded diseases of women, and in Nepal, it is second most common cancer. The situation is more alarming in the rural areas where the majority of women are illiterate and ignorant about the hazards of breast cancer. Different screening strategies such as rural cancer registries and camp approach for cancer detection have been found useful in minimizing the problem of breast cancer in the villages. Advanced presentation of breast cancer and the problem of late diagnosis is well documented in Nepal. Moreover, diagnostic workup, treatment and palliative services are inadequate in most parts of Nepal. A better understanding current situation of breast cancer can help government to formulate breast cancer prevention strategy in Nepal. In this review, authors present an overview of the burden of breast cancer, risk factors, screening, and cancer care among Nepalese women.

Keywords: Breast cancer, Nepal, Risk factors, Screening, Treatment

INTRODUCTION

Breast cancer has emerged as an impending public health problem for developing countries. One in eight women is affected by invasive breast cancer in United States (12.4%) during their lifetime. By the end of 2019, an estimated 268,600 new cases of invasive breast cancer are expected to be diagnosed in women in the U.S., along with 62,930 new cases of non-invasive (in situ) breast cancer.[1,2] Health care costs of cancer in 2010 surpassed $124.5 billion (USD) with highest costs for breast cancer ($16.5 billion) and according to the agency for healthcare research and quality the direct medical costs for cancer were $80.2 billion in 2015 in United States, and this figure is estimated to be as high as$157.8 billion by 2020, among which the highest costs will be for breast cancer.[3] Breast cancer accounts for more than 1 in 10 new cancer diagnoses each year and regarded as the most frequently diagnosed cancer women. Breast cancer is second most

common causes of cancer-related death among women in the world.

Breast cancer rates in Asian women in recent generations are even surpassing the historically high rates in the United States, requiring an urgent need to adopt new breast cancer prevention and treatment strategies among Asian populations. The incidence rates of breast cancer in developing countries throughout the Asia-Pacific region is increasing and a study by Youlden DR et al, showed that among women in Asia breast cancer has become fourth leading cause of cancer-related mortality.[4] Studies had also revealed that cervix uteri was the most common cancer for females in Nepal and breast cancer is the second most common cancer among women.[5,6]

The vast majority of human malignancies are age-associated cancers, showing incidence rates that increase exponentially with age during adulthood while breast cancer is a heterogeneous malignancy; its age-specific

incidence profile rises exponentially until menopause and increases more slowly thereafter.[7] Timely diagnosis and treatment of breast cancer are of paramount importance, especially for vulnerable groups, such as low-income women. The incidence of breast cancer is increasing in the developing world due to increased life expectancy, urbanization and adoption of western lifestyles. Nevertheless, there is a need for culturally appropriate, intervention strategies to prevent and enhance knowledge and awareness regarding breast cancer. A study by Gupta A et al, concluded that the breast cancer is low in India, but rising, but the awareness about the symptoms, early diagnosis, and screening tests of breast cancer was very poor.[8] The results of the previous studies revealed that there remains a lack of awareness, knowledge of risk factors and screening among Nepalese women.[9,10] An economic burden of breast cancer is a considerable issue in most middle and low income countries, especially in Nepal, and prevention has been regarded as the most effective long-term strategies to decrease the increasing chronic disease burden.[4] However, till date, due to socioeconomic disparities, insufficient financial resources obstacles to cancer prevention, early detection, and treatment services the prevention of breast cancer has not been well conducted in Nepal.[5] As developing nations such as Nepal strive to meet the needs of growing patients of breast cancer due to inadequate funding, inappropriate distribution of resources and services, and uneven distribution of health-care personnel and equipment are attributable to sharp rising in the incidence of breast cancer in Nepal.[5]

Current status of breast cancer in Nepal

Breast cancer can have profound social and financial consequences for people in Nepal, often leading to impoverishment families and social inequality. The increasing burden of breast cancer in Nepal is due to higher cost of treatment, low economic status, and lack of clinically validated molecular treatment options. The estimated cost of breast cancer treatment is much higher in private hospitals than government hospitals.[11] Furthermore, higher cost of surgical procedures and treatment regimens cause significant economic burden to the cancer victims. According to Globocan 2018, female breast cancer is most frequently diagnosed cancer in the vast majority of the countries.[12] There were an estimated 2.1 million newly diagnosed female breast cancer cases and 600 thousand breast cancer-related deaths occurred in 2018.[13]

Asian countries now account for 40% of breast cancer cases diagnosed worldwide followed by Europe (25 %), North America, Latin America and the Caribbean, Africa and Oceania. In female, breast cancer is the most commonly diagnosed cancer (22.3% of the total cases) and the leading cause of cancer death in Asia. Using the Globocan 2018 estimates of cancer incidence and mortality, in 2018 an estimated 2068 new breast cancer cases were diagnosed in Nepal, with an age standardized

rate (ASR) of 15 cases per 100,000 women, while 1018 deaths occurred, with an ASR of 7.6 cases per 100,000 women (Figure 1).[12]
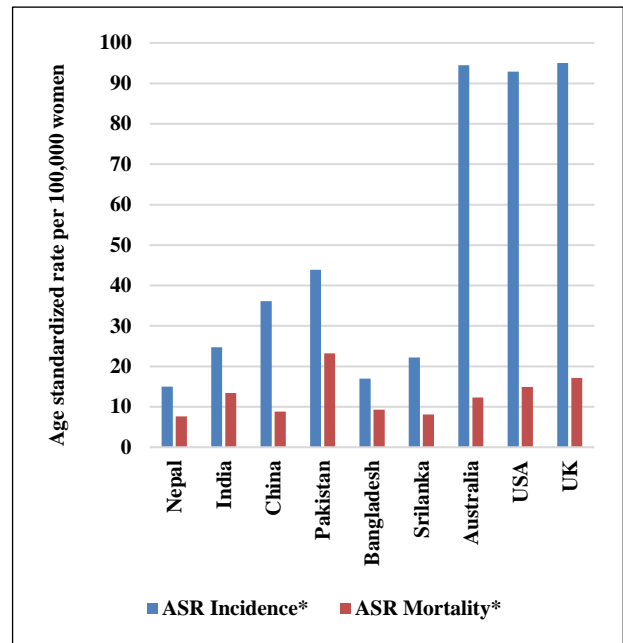

Figure 1: Comparison of breast cancer incidence and mortality rates in Nepal and other countries.

(Figure 1) Comparison of age standardized rate (ASR) of incidence and mortality related to breast cancer in women in Nepal and other countries. ASR incidence rate is lower in Nepal in comparison to the developed countries.

Nepalese data were compared with those of neighboring and other countries (Figure 1) (http://globocan.iarc.fr) including India (ASR incidence: 24.7 and ASR mortality:13.4), China (ASR incidence: 36.1 and ASR mortality: 8.8), Pakistan (ASR incidence: 43.9 and ASR mortality: 23.2), Bangladesh (ASR incidence: 17 and ASR mortality: 9.3), Srilanka (ASR incidence: 22.2 and ASR mortality: 8.1), Australia (ASR incidence: 94.5 and ASR mortality: 12.3), the United States of America (ASR incidence: 84.9 and ASR mortality:12.7), and United Kingdom (ASR incidence: 93.6 and ASR mortality:14.4).

Authors compared the age-standardized incidence rates (ASRs) of breast cancer in Asian and Western countries. The ASRs of breast cancer in western countries were considerably higher than in Asian countries such as Nepal, India and China, this may be due to rapid socioeconomic development and urbanization in western countries.[12] Population-based cancer registries are considered the best option for measuring indicators of cancer.[14] Breast cancer is most commonly diagnosed cancer and the second leading cause of cancer death in women; however, economic development and social and life factors affect the risk of developing breast cancer. In low income countries like Nepal there is lack of cancer registry data and cancer control programs. Government

should give priority to the local collection and use of data, to prioritize and evaluate national cancer control efforts. There is multi-institution hospital-based cancer registry in Nepal, but population-based cancer registry is still in its infancy. Various population-based studies performed in different parts of Nepal have demonstrated that the common age of breast cancer patients was 40-50 years.[15,16] Breast cancer occurs at a younger premenopausal age in Nepalese and Asian women compared to western women who get it more than a decade or later.[17]

Breast cancer risk factors

Aging

The incidence of breast cancer increases with age. New global cancer data in 2018 showed that risk of developing cancer before the age of 75 years was 22.8 % and risk of dying from cancer before the age of 75 years 18.8 % in Nepalese women.[12] Study by Thapa B et al, found that the majority of breast cancer patients were ≥40 years of age and had an earlier age of menarche.[18] Therefore, timely a mammography screening should be mandatory in women aged 40 or older.

Family history

A family history of breast cancer in first-degree relatives is associated with increased risk of breast cancer.[19] The mutation of genes such as BRCA1 and BRCA2 is associated with increased risk of female breast and ovarian cancers, as well as increased risks of several cancer types.[20] In Indian familiar breast cancer patients the prevalence of BRCA1 and BRCA2 is gene mutations ranged from 2.9% to 28.0%.[21] Similarly, a pilot study Screening of BRCA1 Mutations (185delAG, 1294del40) in Nepalese breast cancer patients showed that BRCA1 Mutations (185delAG) was 8 %.[22]

Reproductive factors and estrogen

Early menarche, late menopause, late age at first pregnancy is associated with increased risk of breast cancer. Similar to the other Asian countries, breast cancer in premenopausal Nepalese patients was associated with late menarche (>14 years), early first full-term pregnancy (before 40 weeks of pregnancy) and longer duration of breastfeeding.[23-25] Studies conducted in Western countries have shown that menopausal hormone replacement therapy (HRT) is associated with increased risk of breast cancer; however, there are fewer reports from the Asian population.[26]

Lifestyle

Excessive alcohol consumption and higher intake of fat has been linked to the increased risk of breast cancer. Meanwhile, studies have revealed that in addition to westernized lifestyle, smoking and exposure to radiation may be associated with an increased risk of breast cancer in Nepalese women.[27]

Breast cancer screening in Nepal

Most of the Asian countries, including Nepal have not initiated population-based breast cancer screening programs.[28] Early cancer detection could reduce breast cancer death rates significantly in the long-term. Breast self-examination (BSE) is still considered effective methods for early detection of breast cancer. A study by Bhandari PM et al, showed that the overall knowledge level of breast self-examination among Nepalese women was low to moderate.[29] In remote areas of Nepal women's disbelief that events are governed by fate and no one could change the course of the events. These kind fatalistic attitudes are responsible for late detection of breast cancer in Nepal. More efforts are required in creating awareness and to increase knowledge among women in order to detect early breast cancer and enhance prevention strategies that would decrease the burden of breast cancer in Nepal. Along with breast self-examination the clinical breast exams performed by well-trained clinicians, is paramount for early detection of breast cancer.

In asymptomatic women screening mammography is most commonly used tool for the detection of early breast cancer and mammography screening could significantly reduce breast cancer mortality.[30] Diagnostic mammogram is available at only few centers in Nepal and there is no nationwide systematic program for breast screening at the present time. Recently, pseudo-three-dimensional tomosynthesis, digital breast tomosynthesis (DBT) technique is being used as adjunct screening tool for the detection of breast cancer which enables better assessment of overlapping breast tissue and provided better assessment of tumor margins.[31] DBT is not yet routinely available in all screening centers and is still in its clinical infancy around the world. It may be available in developing countries like Nepal in near future. In addition, supplemental screening with breast ultrasonography, breast magnetic resonance imaging, and contrast-enhanced mammography provides considerable detection benefit for the women at higher risk of breast cancer.

Modalities of treating breast cancer

The main forms of breast cancer treatment are: surgery, radiation therapy, chemotherapy, hormone therapy, targeted therapy and bone-directed therapy. These treatments can also be classified into local therapy (surgery and radiotherapy) and systemic treatment (chemotherapy, endocrine, and targeted therapies). Late stage diagnosis of breast cancer is common in Nepal and most commonly used treatment modalities for breast cancer in Nepal are surgery, radiotherapy, chemotherapy and endocrine therapy.[24] Depending on staging and biologic characteristics of the tumor, surgical treatment of

invasive breast cancer may consist of lumpectomy or total mastectomy.[32] Surgical treatment of breast cancer in Nepal has changed over time. Previously most of the breast cancer cases were managed with either radical or modified total mastectomy. However, now days most of Nepalese women prefer breast-conserving surgery over total mastectomy. For the early stage breast cancer it provides the same level of overall survival as mastectomy and much better cosmetic effect, less anxiety and depression and improved body image compared to radical treatments.[33] Another reason for preferring breast-conserving surgery is, mastectomy have negative impact on women psychosocial state as they are develop stress due to loss of body part, afraid of disease recurrence, fear of cost and prolonged treatment.[34]

The information obtained from pathologic examination of the lymph nodes obtained from axillary lymph node dissection plays an important role in the determine the pathologic staging of the disease and is an integral part of the treatment of breast cancer. Although axillary lymph node dissection has largely been practiced by many hospitals in Nepal, this technique is currently replaced by sentinel lymph node biopsy (SLNB) in some centers.[35] Radiation therapy (RT) plays an essential role in the management of breast cancer and remains an important curative treatment modality for uncomplicated locoregional tumors. Radiotherapy is typically administered to the breast following conservation surgery, but the use of breast reconstruction and post-mastectomy radiotherapy has increased over the past decade. Sapkota et al. revealed that radiotherapy is one of the essential treatment modalities for breast cancer, for both curative and palliative intent in Nepal.[36] In Nepal delivery of radiotherapy for breast cancer treatment is usually done by teletherapy and brachytherapy.[37] Treatments such as chemotherapy, hormonal therapy, and targeted therapy are used as systemic treatment for breast cancer. The aims of systemic treatment are to palliate symptoms, prolong survival, and improve quality of life. The commonly used cytotoxic chemotherapy drugs are taxanes (paclitaxel and docetaxel), cyclophosphamide, cisplatin and anthracyclines (doxorubicin and epirubicin). Anthracyclines and taxanes are the two most active classes of cytotoxic agents for early and advanced stage breast cancer and are the mainstay in first-line treatment of breast cancer in the adjuvant, neoadjuvant and metastatic settings.[38] Anthracycline-based chemotherapy regimens are increasingly being used in Nepal but the use of anthracyclines as initial chemotherapy in early breast cancer may continue to be replaced by taxane-based and novel regimens in the future.[5,39] Anthracyclines are the drug class most closely associated with acute and late cardiac toxicity as well as myelosuppression.[40] Active monitoring of patients cardiac function can help guide the optimal delivery of chemotherapy and to minimize cardiotoxicity.

Hormonal therapy has significantly improved outcomes for patients with early-and advanced-stage hormone-receptor (HR)-positive breast cancer. Endocrine therapies such as tamoxifen have revolutionized the treatment of breast cancer, while aromatase inhibitors such as anastrozole and letrozole significantly improve disease-free and distant disease-free survival.[41] Tamoxifen is the commonly used hormonal medicine for the management of breast cancer in Nepal but choice of endocrine treatment should be based on patient comorbidities and the toxicity profiles of the various drugs.[38] However, tamoxifen is associated with menopausal symptoms, thromboembolic events, and endometrial hyperplasia.[42] Recently, a study by Pistelli M et al, has shown that aromatase inhibitors have superior efficacy to tamoxifen in the metastatic, neoadjuvant and adjuvant settings in postmenopausal women.[43] Unfortunately, aromatase inhibitors are usually more costly than tamoxifen and because of this they are not readily available in developing country like Nepal. Targeted therapies are used to treat over-expression of breast cancer. The HER2 protein is most commonly overexpressed receptor in breast cancer and therapies targeting HER2 have revolutionized the treatment of breast cancer. Trastuzumab is the first-generation targeted therapy drug and has been used widely to treat women with HER2-positive breast cancer. Trastuzumab, pertuzumab, trastuzumab-emtansine, and lapatinib are currently approved HER2-targeted agent for breast cancer.[44] These targeted agents are not the concerns in Nepal, where people are not able to afford even trastuzumab.[45] The Nepalese government should implement universal health coverage which will assures all types of health service including cancer treatment and protects all citizens financially in any conditions due to illness.

Palliative care for breast cancer

Palliative care aims to assist patients in relieving pain, minimizes severe distress and improves the quality of life of patients and their family members. In women with metastatic breast disease the primary goal of palliative care for breast cancer is to prevent and ease suffering and improve the quality of life. The most common site of breast cancer is bone and bone metastases can cause chronic pain. The first line therapies in neuropathic pain caused by breast cancer metastases are adjuvant analgesics such as antidepressants and anticonvulsants like gabapentin or pregabalin.[46] The treatment of pain from bone metastases involves the use of multiple classes of drugs such as NSAIDs, opioid and nonopioid analgesics, corticosteroids, adjuvant agents, interventional procedures, and local radiation therapy.[47] Cognitive behavior therapy, benzodiazepines, benzodiazepine receptor agonists, mindfulness medication, and yoga may help to address sleep issues caused by metastasis of breast cancer.[48] For the diffuse bone pain resulting from metastases bisphosphonates, glucocorticoids or systemic administration of radioisotopes should be considered. Only few Asian countries have started advanced palliative care it has yet to be established in parts of Nepal. At present in Nepal

only few hospitals are providing palliative care to cancer patients, but palliative services are not available to rural populations.

Challenges in breast cancer prevention and future directions

In low income countries like Nepal economic burden of breast is negatively impacting healthcare budgets. The financial impact of breast cancer may be much worse in future and affected patients are at increased risk of financial hardship. The role multidisciplinary treatment team is becoming vital in the management of breast cancer patients.[49] However, in Nepal a significant percentage of patients still do not have the opportunity to meet with a medical oncologist or radiation oncologist in most of the hospitals. Government should prioritize the establishment of hospitals with of multidisciplinary treatment teams which will help patients to understand all the components of their breast cancer treatment prior to starting treatment and this increased knowledge may have an impact on treatment decisions regarding surgery for breast cancer. Majority of the Nepali women are living in poor conditions and cannot afford expensive screening tests and Illiteracy is also a major cause of breast cancer among women because women have no awareness about personal hygienic conditions. Adopting healthy lifestyle, including limiting alcohol consumption, maintenance of ideal body weight, regular physical activity, and avoidance of postmenopausal hormone replacement therapy, may reduce breast cancer incidence.[50] Rural women are at risk of late stage breast cancer due to poor education and lack of awareness, fear, familial and social stigma, myths and misconceptions, neglect, and fear the potential loss of the breast. Using media and including men while creating awareness about women's issues to promote an attitude change regarding breast cancer in women are quite important for effective breast cancer control. Some limited studies in Nepal have shown that the awareness level about risk factors and early detection measures of breast cancer among Nepalese women such as clinical breast examination (CBE) and breast self-examination (BSE) was low.[9,10,29] Furthermore a cross-sectional study conducted in western Nepal among higher secondary students found that the students have a poor knowledge on many breast cancer risk factors, symptoms and curability and most of them had misleading information about age, early menarche and delayed menopause as the risk factor.[29] In Nepal cancer prevention, education, and access to cancer screening tests as well as cancer treatment are inadequate. In collaboration with national and international organizations government should develop a policy and guidelines for effective control of breast cancer in all seven provinces of Nepal.

CONCLUSION

Breast cancer is the most frequently diagnosed life-threatening cancer in women and the leading cause of cancer death among women. The detection of breast cancer in Nepal is significantly delayed leading to diagnosis at advanced stages associated with poor prognosis. It is urgent to have a national breast cancer program in Nepal, while at local level is necessary to raise awareness of the symptoms and their attitudes towards treatment. Due to the unavailability of a population-based cancer registry it is difficult to precisely predict of future incidence rates. Hence government should initiate a population-based cancer registry in at least every province of Nepal.

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