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Assessing Breast and Cervical Cancer in India: A Literature Review

Rachel Maggi
University of Iowa

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Rachel Maggi

A thesis submitted in partial fulfillment of the requirements
for graduation with Honors in the International Studies

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Christopher Squier
Thesis Mentor

Spring 2018

All requirements for graduation with Honors in the
International Studies have been completed.

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Emily Wentzel
International Studies Honors Advisor

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Christopher Squier, Faculty Mentor

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Abstract

This thesis reviews the existing literature on breast and cervical cancer in India with the goal of assessing the health-care infrastructure that supports diagnosis and treatment of these cancers. Through a comprehensive review of global health databases, governmental frameworks, and quantitative as well as qualitative assessments from research institutions, I argue that the existing health-care system in India does not adequately address the rising burden of breast and cervical cancer nor the barriers that impede women from seeking care, such as lack of knowledge, cost of care, and social stigma. Although the Indian Ministry of Health and Family Welfare recently implemented a framework for the management of common cancers in late 2016, many women still present with cancers at a stage at which 5-year survival outcomes are very poor. To address the burden of late-stage breast and cervical cancer, I argue that India must place a higher priority on implementing a comprehensive national screening program to increase rates of early detection and strengthen health-care facilities at every level of care to provide accessible care to both urban and rural populations.

Introduction

Non-communicable diseases, also known as chronic diseases, are responsible for approximately 58 percent of deaths in low and middle-income countries. Although this number is far from the 87 percent non-communicable disease mortality burden in high-income countries, many low and middle-income countries do not have the same early detection and treatment capacities as high-income countries, leading to a significantly greater rate of mortality. Of the many deadly and debilitating non-communicable diseases, cancer remains a significant burden in low, middle, and high-income countries, accounting for 15 percent of all deaths globally, according to the 2010 Global Burden of Disease Study. Despite the perception that high-income countries experience most of the non-communicable disease and cancer burden globally, of the 14.1 million new cancer cases recorded in 2012 by the World Health Organization, 8 million came from low and middle-income countries. In addition, 65 percent of all cancer deaths recorded in the same year were also in low and middle-income countries.

In India, the most populous of all low and middle-income countries, breast and cervical cancer top the list of most prevalent cancers among both sexes and all age groups, with roughly 112,00 and 91,000 current cases respectively, in 2012. The high prevalence of breast and cervical cancer as compared to oral, lung, and stomach cancers, that affect both women and men is a symptom of the gender disparity that exists in the Indian health-care system. Although incidence of breast and cervical cancer in India is low in comparison with the United States and Western Europe (130/100,000 in the United States compared to 18-20/100,000 in India), these cancers are on the rise with roughly 145,000 new cases of breast cancer and 123,000 new cases of cervical cancer a year. In India, breast cancer is the most common cancer of urban women and the second most common cancer of rural women, largely due to shifting behaviors in urban settings such as

late childbearing and low rates of breastfeeding, circumstances that can increase breast cancer risk (Agarwal and Ramakant, 2008). The scenario is reversed for cervical cancer, which is more common among rural women than urban women. This is largely attributed to traditional customs including marriage at an early age and multiple pregnancies, as well as lack of awareness of symptoms, resulting in late presentation (Das and Patro, 2010). In addition, there is very low vaccination coverage against human papillomavirus (HPV), an infectious agent strongly correlated with development of cervical cancer. Although India has increased funding to combat cancer and other non-communicable diseases through prevention and better information, there is difficulty reaching remote communities due to a lack of trained manpower, poor infrastructure, logistics, and quality assurance, low frequency of screening, and the unaffordable costs for patients (Mittra et al, 2010). In high-income countries, screening is considered paramount in cancer prevention. In November 2016, the Indian government's Ministry of Health and Family Welfare published an operational framework for the country's first national cancer screening program. However, with millions of vulnerable women to screen, it has been frequently argued that India simply does not have the capacity to conduct a comprehensive program of mammograms or cervical exams. This paper will investigate the breast and cervical cancer burden in India as well as the existing health-care infrastructure that supports the diagnosis and treatment of these cancers. Through the examination of several effective public health interventions, I will argue that to fill the gaps in care surrounding breast and cervical cancer prevention and treatment, vulnerable women must be educated about the risk factors and warning signs of breast and cervical cancer and be encouraged to understand what is normal for their own bodies. Reduction of exposure to risk factors and early recognition of tissue abnormalities would

reduce the number of new cases of breast and cervical cancer and increase survival outcomes if cancer is detected, thus saving thousands of lives.

The Burden of Breast Cancer and Contributory Factors

Breast cancer is not only the most prevalent type of cancer among women in India, but the most prevalent type of cancer among both women *and* men. In fact, the 112,000 current cases of breast cancer in India dwarf the roughly 53,000 current cases of the most prevalent cancer among men, lip and oral cavity cancer (IARC, 2012). In 2011, the Indian Council of Medical Research released an analysis of cancer cases among women in four of India's largest urban centers (Delhi, Mumbai, Chennai, and Bangalore). This analysis revealed that since 2000, average incidence of breast cancer has risen from 10 per 100,000 women to 23 per 100,000 women (Shetty, 2012), likely a reflection of increased surveillance and data collection. These age-standardized incidence rates fall anywhere between 6.2 and 39.5 in different urban registries, and often vary by region, ethnicity, and religion. In the urban centers of Delhi, Mumbai, Ahmedabad, Calcutta, and Trivandrum, breast cancer constitutes more than 30 percent of all cancers in women. The highest age-standardized incidence rate of breast cancer can be found among the Parsi community in Mumbai, at a staggering 48.3 per 100,000 women (Agrawal and Ramakant, 2008). According to recent data from Laura Nyblade and colleagues, there were roughly 145,000 new cases of breast cancer diagnosed in India in 2015, and this number is expected to increase to 180,000 new cases annually by 2020 (Nyblade et al, 2017).

In a spatial-temporal analysis of the pattern of breast cancer in southern Karnataka, urban districts were consistently found to be at most risk for breast cancer, with Mysore and Bangalore districts topping the list (see Figure 1). This seems to indicate a correlation between the

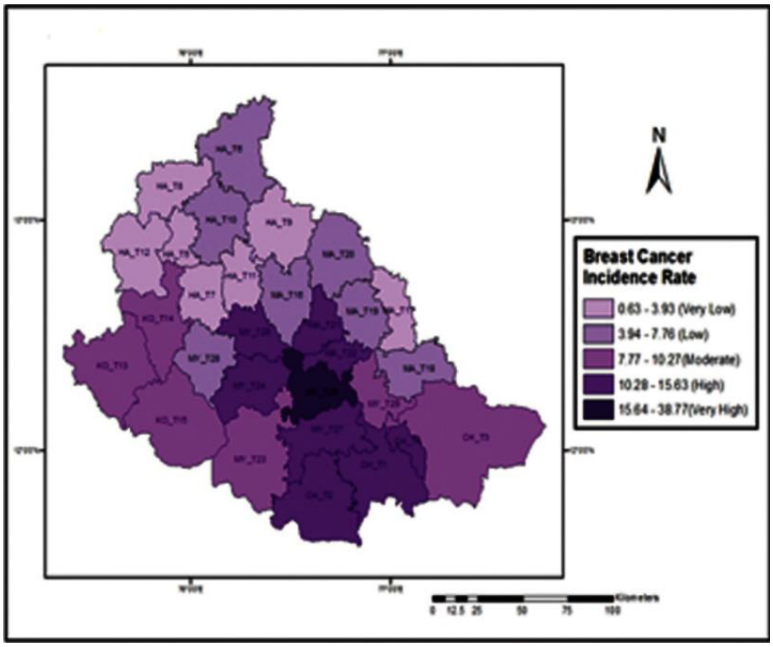

Figure 1. Breast Cancer Incidence Rate in Southern Karnataka. Incidence rate was calculated by dividing the number of breast cancer incidences in each taluk by the female population in each taluk and then multiplying by 100,000. Mysore taluk, indicated in dark purple, had the highest breast cancer incidence rate (Madhu et al, 2016).

sedentary lifestyle and poor diet often associated with urban living and the development of breast cancer and other non-communicable diseases. In the study, 6 out of 29 districts were observed to have increased breast cancer incidences during the study period of 2007-2011. Moderate incidences were present in districts adjacent to high incident districts and low incidences were reported in districts designated as forest and tribal areas. According to the study, approximately 20 percent of the districts in the state of Karnataka warrant concern, a percentage that represents approximately 814,000 women (Madhu et al, 2016).

There are several risk factors that contribute to the development of breast cancer, especially in urban populations. Historically, women in India often bore children at a very young age and breastfed for a long period of time after birth. However, the urban educated class in India is moving away from these traditional behaviors, bearing children later in life with little to no breastfeeding to accommodate changing social values and the emergence of working women in Indian urban society. In one case-controlled study in Mumbai, single women were 4-5 times more likely to develop breast cancer as compared to married women in the same age group of 40-54 (Agrawal and Ramakant, 2008). Genetics and family history of breast cancer also play a

significant role in the presence of breast cancer. In a study of 226 breast cancer patients, approximately 21 percent were found to have a family history of breast cancer, and the BRCA1 and BRCA2 mutations were found in 6-10 percent of studied patient populations (Agrawal and Ramakant, 2008). Lastly, associations between religious affiliation and breast cancer incidence have appeared within India's highly diverse population. In a study done in Mumbai, Parsis and Christians were found to have the highest breast cancer incidence rates and Jains and Buddhists, the lowest. Another study done in Chennai saw a similar trend, with Christians having the highest incidence rates followed by Hindus and Muslims (Agrawal and Ramakant, 2008). The role and expectations of women within these religious cultures may contribute to these disparities, with traditional customs of early childbearing in Hindu, Muslim, Buddhist, and Jain cultures reducing incidence rates compared to the increasingly "Westernized" cultural behavior within Parsi and Christian communities. It can also be argued that meat-based diets prevalent in Christian and Parsi communities may also contribute to higher rates of breast cancer as compared with the typically vegetarian-based diets of groups such as Hindus and Buddhists. However, dietary factors seem to have less correlation than childbearing and breastfeeding patterns.

As breast cancer incidence continues to rise, late detection remains a cause of serious concern. According to an assessment done by Agrawal and Ramakant, "Almost all Indian breast cancer patients self-detect their disease at a stage when it presents with a palpable lump, or even at a stage when it has resulted in secondary changes such as local skin or chest wall changes or distant metastases" (Agarwal and Ramakant, 2008). Das and Patro emphasize this by estimating that roughly 50-70 percent of breast cancer patients in India present at late-stages when tumors can reach more than 10 centimeters in diameter, decreasing survival outcomes (Das and Patro, 2010). According to the Indian government's Operational Framework for the Management of

Common Cancers, “The five-year survival rates for early stage cancers are 76.3 percent for breast cancer” (Ministry of Health and Family Welfare, 2016). However, the prognosis for advanced stages of breast cancers drops significantly to only 14.9 percent. Stigma surrounding cancer care still acts as a significant psychosocial barrier to seeking care for breast cancer. This stigma can be defined in several ways, but most notably in experienced stigma through personal discrimination of the stigmatized individual. However, stigma surrounding breast cancer can also be perpetuated through the observed stigmatizing of others in a community, or stigmatization by association because a family member has been diagnosed with breast cancer (Nyblade et al, 2017).

In a study done at St. John’s Medical College Hospital in Bangalore, Karnataka, researchers conducted focus group discussions and in-depth interviews, in which stigma was addressed by participants. In the study, researchers sought to assess breast cancer patients, their primary caregivers and healthcare providers’ understanding of breast cancer, as well as their perspectives on cancer care, care trajectories, and multilevel influences such as stigma. These perspectives included family and community reactions to symptoms and diagnosis of breast cancer, as well as availability and access to different types of healthcare facilities (Nyblade et al, 2017). As the study developed, three major themes emerged as driving manifestations of cancer stigma, described by the researchers as: “fear of cancer transmission; personal responsibility for having caused cancer, and; belief in and fear of the inevitability of disability and death with a cancer diagnosis” (Nyblade et al, 2017).

From these perceptions, women in the study reported experiencing isolation, harassment, loss of employment, and reduced marriage prospects for not only themselves, but also their family members. One breast cancer patient expressed her fear for her daughter’s future, stating,

"...they may say that 'your mother had [breast cancer] and you may also get like that'...they would have avoided me and that would affect my daughter's future life" (Nyblade et al, 2017). In fact, many breast cancer patients discussed non-disclosure as a solution to ward off stigma and to protect themselves and their families. This non-disclosure behavior has inhibited many women from seeking care and adhering to treatment. During Nyblade and colleagues' study, a local healthcare provider explained the role stigma played in inhibiting women from seeking care. According to her experience, because the village and community is so small, once it is discovered that a family has a member diagnosed with breast cancer, the information is spread quickly, and the stigma perpetuated. Thus, women are discouraged from seeking screening services or treatment for fear of what their health facility visits would imply to others (Nyblade et al, 2017). Improving access to information, screening, and treatment for breast cancer in India can only be accomplished once the factors driving risk, including the fear of social stigma, are addressed and reduced.

Breast Cancer, Health Infrastructure and Gaps in Care

It is of note that India has allocated increased funding to the problem of late detection of cancer and other non-communicable diseases. According to a fiscal assessment by Shetty, "[India's] latest 5-year plan allocates $12.7 billion USD to tackling non-communicable diseases, of which cancer gets nearly $3.3 billion USD" (Shetty, 2012). With this money, the country plans to open two national and 20 state cancer institutes, support 100 extra tertiary cancer centers, increase the number of district cancer centers to 640, and increasing the number of institutes contributing to India's cancer registry to 122 (Shetty, 2012). As India increases its network of data surveillance institutions, appropriate resources can be more effectively allocated

towards cancer prevention and treatment interventions based on data that more accurately portrays the burden of cancer in the nation.

Following this funding increase, the Indian government's Ministry of Health and Family Welfare published an operational framework for the country's first national cancer screening program in early 2016, which has since been implemented. In this framework, women and other vulnerable groups such as marginalized tribal populations are specifically noted as requiring easily accessible care.

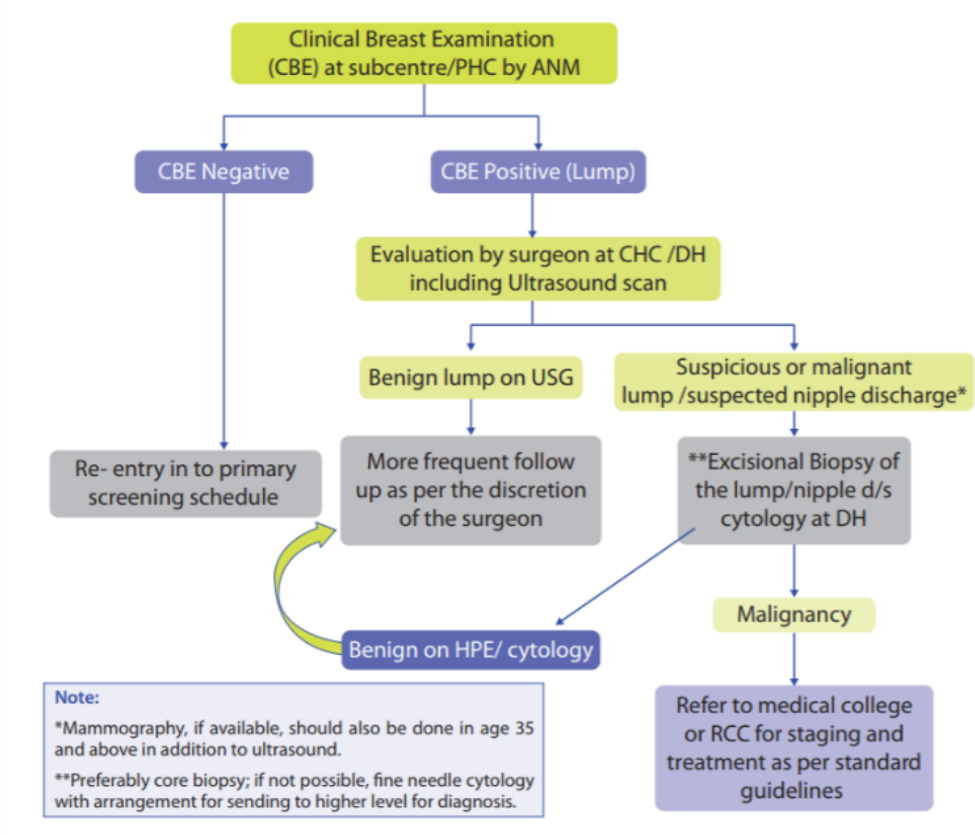

Figure 2. Screening and Management Algorithm for breast cancer. This diagram details the referral and treatment protocol for all stages of the breast cancer screening and diagnosis process as outlined in the Indian government's Operational Framework for the Management of Common Cancers. ANM- auxiliary nurse midwife, CBE- clinical breast exam, CHC- community health center, DH- district hospital, HPE- histopathology examination, PHC- primary health center, RCC- regional cancer center, USG- ultrasonography (Ministry of Family Health and Welfare, 2016).

The Ministry of Health and Family Welfare proposes a decentralization of breast cancer care and that cancer screening be undertaken on a population-wide level for certain age groups (see Figure 2). In the case of breast cancer, this includes all women aged 30-65, performed once every five years. The first level of screening consists of breast exams conducted by auxiliary nurse midwives/mid-level providers at Health and Wellness Centers and by staff nurses at smaller primary health centers (PHCs). Following a positive result, the patient is then referred to a surgeon at a community health center/district hospital for confirmation using breast ultrasound probes followed by biopsy once there is significant suspicion of tissue abnormality. Following determination of the status of the tumor as benign or malignant, appropriate follow-up or treatment is then assigned.

Within the first three years of the program's implementation, 80 percent coverage of all women ages 30-65 is expected. To accomplish this ambitious goal, technological and human resource capacity must be improved at all levels of care including primary health centers, community health centers, and district hospitals in order to effectively diagnose and treat cancers from preliminary to advanced stages. Lack of trained personnel in low-resource settings such as India is a huge limitation in improving health outcomes for any disease, including cancer. Thus, this framework requires a team representing a range of relevant medical specialties at all levels of care. For example, the framework requires the presence of a medical officer, staff nurse, and auxiliary nurse midwife at primary healthcare centers and a surgeon, gynecologist, ENT specialist, pathologist, dentist, and nurse at the district hospital level.

Prior to the implementation of India's first national cancer screening program, clinical breast examinations and mammograms were only available as a part of research studies at select institutions or to women who self-presented at a tertiary hospital and could afford the costs

associated with breast cancer diagnosis and follow-up treatment. Many researchers do not consider mammograms to be the most effective method of mass screening and argue that it is not a cost-effective solution considering the millions of unscreened women in India. Thus, public health initiatives such as 'Health for All' and the National Rural Health Mission have emphasized breast awareness and self-examinations to promote early detection of breast cancer (Agarwal and Ramakant, 2008). Breast self-examinations (BSEs) are defined as monthly examinations of both the breasts by a woman at the end of menstrual flow (see Figure 3). BSEs are recommended to women starting at the age of 20 (Khokhar, 2013). Theoretically, this monthly routine will help women become familiar with their breasts and thus help them more easily identify abnormalities should they appear. These examinations fall under the concept of breast awareness (BA) which in turn falls under the greater umbrella of body awareness. Breast awareness emphasizes knowing what is normal for each individual woman, knowing what abnormalities to look for, and reporting these abnormalities without delay. In addition, women over 50 are highly encouraged to attend routine breast screenings (Khokhar, 2013). Abnormalities to look for include change in

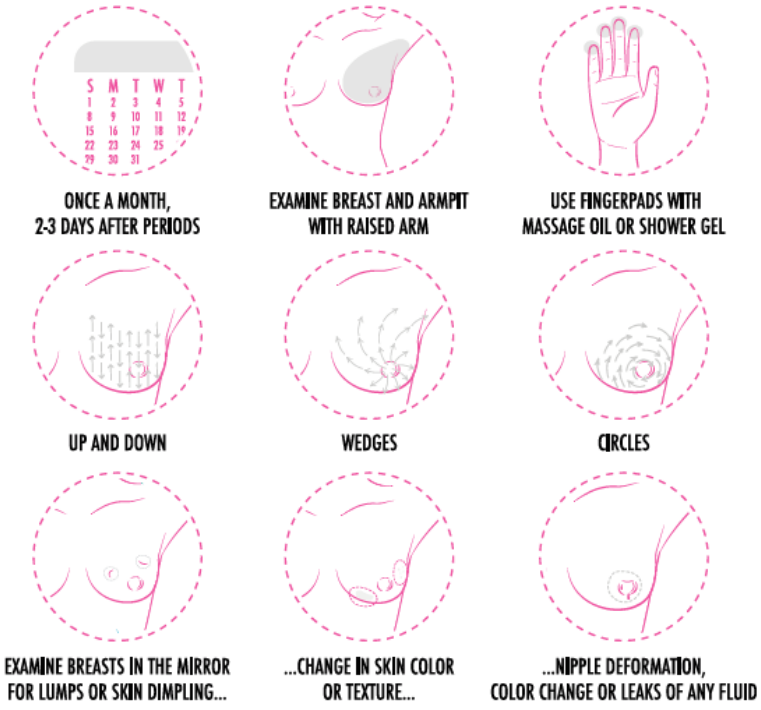

Figure 3. Breast Self-Exam. In low-resource settings like India, self-breast exams can be utilized to help detect breast cancer at early stages and improve survival outcomes (wellness360magazine.com, 2017).

size of the breasts, size or position of the nipples, rashes, discharge, skin changes, swelling, pain, and lumps or thickening in either breast. In Mumbai, breast awareness has been addressed through the implementation of door-to-door mobile services through Helping Hand 4 Cancer Care, a non-governmental organization. Through this service, check-up and consultation together cost approximately 100 rupees ($1.50 USD) a year. Another organization, SGPGI Breast Health Initiative, provides an email and telephone helpline for patients to get a free second opinion on suspected abnormalities as well as general advice on various breast health issues, including screenings.

Breast awareness can also be implemented through participation in research studies such as the study conducted by Nair and colleagues in coastal Karnataka. During this study, at-risk women were invited to attend a clinical breast examination and mammography at a tertiary health facility at no cost. Transportation and assistance were also provided. Of the 600 total participants, it was reported that 79 percent were unaware of the risk factors for breast cancer and nearly 60 percent were not aware of breast cancer screening methods prior to participation in the study. In this study, it was determined that anxiety, possible pain involved with the screening procedure, and cost factors were the main barriers to breast cancer care (Nair et al, 2011).

That being said, breast awareness only goes so far in self-identifying breast cancer. Various studies have suggested that technique and skill level may be highly important variables when considering the accuracy and effectiveness of breast self-examinations. There are three key components of the BSE: visual inspection of the breast, palpation with the finger pads, and examination with the three middle fingers. In a case-controlled study by Newcomb and colleagues, it was concluded that self-examinations that incorporated all three components resulted in a 35 percent decrease in the occurrence of late-stage breast cancer when compared

with women who did not perform breast self-exams (Khokhar, 2013). It was further concluded that due to participants' reported lack of self-proficiency in BSE, the use of BSE by untrained individuals to identify breast cancer in its early stages is likely ineffective. However, in areas such as rural India where trained health personnel are in short supply, other researchers argue that self-examinations are better than nothing. In a study conducted at an oncology clinic at Kuala Lumpur among Malaysian women, "there was an increasing trend in the proportion of delayers among those who performed BSE regularly (23.6%), performed BSE irregularly (27.9%), and never performed BSE (41.6%)" (Khokhar, 2013). It is important to note that many of the studies that prompted criticism of BSE were published before effective training methods of BSE were implemented. Even the most influential BSE critics admit that BSE, when done correctly, could be of significant value in early detection. David Thomas, senior author of a study in Shanghai that ultimately concluded that BSE did not reduce breast cancer mortality rates between study and control groups says, "It is possible that highly motivated women could be taught to detect cancers that develop between regular screenings, and that the diligent practice of BSE would enhance the benefit of a screening program" (Khokhar, 2013). From these studies, it can be concluded that breast self-examinations are most effective when performed by properly trained health professionals or individuals and when self-examinations occupy a complementary role within a greater national cancer screening program rather than as a single intervention.

Although improvements have been made in training women to detect breast cancer through breast awareness and breast self-examinations, treatment options once breast cancer is diagnosed remain inaccessible to a large portion of the population. In addition, compliance and follow-up rates remain low due to the social stigma attached to cancer, as discussed previously. Women who do decide to seek treatment often face inadequate treatment in the form of non-

protocol surgery. According to Agrawal and Ramakant, "Such patients referred following an inadequate operation often pose a challenge in terms of the evaluation of the need/extent of re-operation," which include revision of wide local excisions of the cancerous tissue, clearance for axillary lymph node dissections, or repeat modified radical mastectomies. Although breast conservation surgery followed by radiotherapy has become standard procedure for early stages of breast cancer in developed countries, mastectomies remain the preferred primary surgical treatment in developing regions such as India, including in urban centers (see Figure 4). In a study done at a community hospital in Southern India, it was found that 93.8 percent of patients with invasive breast cancer underwent mastectomies and only 6.3 percent of patients underwent breast conservation surgery (Kuraparthy et al, 2007). Although mastectomy is the typical procedure for almost all stages of breast cancer in India, the completeness of these mastectomies is sometimes questionable. At a teaching hospital in Mumbai, almost 40 percent of patients referred for management had to undergo re-operation (Agrawal and Ramakant, 2008). The Indian Ministry of Health and Family Welfare's Operational Framework for the Management of Common Cancers emphasizes the training of surgeons to mitigate the occurrence of re-operations. Following the cascade approach to the

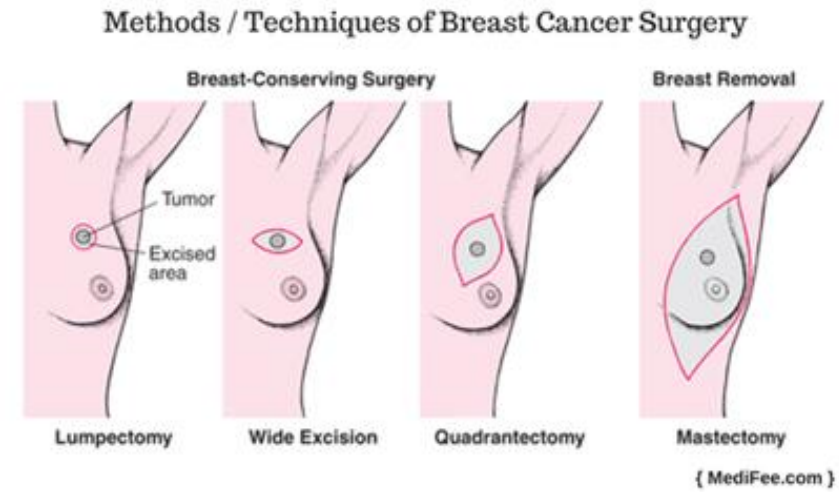

Figure 4. Methods/Techniques of Breast Cancer Surgery. Treatment for breast cancer largely depends on the size and location of the tumor in the breast tissue, as well as if the cancer has spread to other parts of the body. In India, mastectomies are the most common form of breast cancer treatment (MediFee.com, 2017).

training framework, national, state, and district trainers will ensure that key competencies are built at each facility level so care providers can appropriately conduct required screening and follow-up procedures. Given the recent implementation of the framework and consequential lack of data, it is difficult to assess whether or not the above-mentioned gaps in screening and treatment have been adequately addressed. Thus, breast cancer care remains largely in the hands of non-governmental organizations and research institutions.

The Burden of Cervical Cancer and Contributory Factors

Although cervical cancer is the second most prevalent cancer in India behind breast cancer, it is the leading cause of cancer mortality among women. Every year, roughly 122,844 women are diagnosed with cervical cancer and 67,477 women die of the disease. India has the highest age-standardized rates of cervical cancer in South Asia at 22, with Bangladesh and Sri Lanka trailing at 19.2 and 13 respectively (Sreedevi et al, 2015). As with breast cancer, this high mortality rate correlates with low rates of cancer screening. According to the World Health Organization, more than 85 percent of all cervical cancer deaths occur in developing countries where cervical cancer accounts for 13 percent of all female cancers (WHO, 2010). Developing countries around the world are estimated to have only 19 percent screening rates for cervical cancer coverage compared to 63 percent in developed regions. In India, opportunistic screening rates for cervical cancer (conducted independently of an organized screening program) vary from 6.9 percent in Kerala to 0.006 percent and 0.002 percent in Maharashtra and Tamil Nadu respectively (Sreedevi et al, 2015). Opportunistic screening is not often formally checked or monitored and thus does not contribute effective data on cervical cancer burden. Such low rates of cervical cancer screening leads to late presentation, which is the case in as many as 85 percent

of cervical cancer diagnoses. According to the Indian Ministry of Health and Family Welfare's Operational Framework for the Management of Common Cancers, the five-year survival rate for cervical cancer detected in its early stages is 73.2 percent compared to a five-year survival rate of 7.9 percent for late-stage detection (Ministry of Health and Family Welfare, 2016). National Cancer Registry Program data between 2009 and 2011 indicated that the Aizawl district in the state of Mizoram had the highest age-adjusted rates of cervical cancer at 24.3, followed by the Barshi district in the state Maharashtra at 19.5, and the Bangalore district in the state of Karnataka at 18.9 (Sreedevi et al, 2015).

The main risk factor for cervical cancer in India is infection with human papillomavirus, also known as HPV. The high burden of cervical cancer in South and Southeast Asian countries is due to high prevalence of HPV, which is estimated to infect 10 percent of women over the age of 30 in these populations (Sreedevi et al, 2015). Of the over 100 types of HPV, 18 types are categorized as high-risk. Although most infections of HPV remain asymptomatic, persistent genital HPV infection is linked to 99 percent of all cervical cancer cases. An Indian done by Bhatla and colleagues, HPV was found in 94.6 percent of the 558 participants with invasive cervical cancer, which is higher than the worldwide average of HPV infection invasive cervical cancer cases which is reported as 83-89 percent. The study found that HPV was more common in North India (98.1 percent) than South India (93.4 percent), although the difference was not statistically significant (Bhatla et al, 2008). HPV -16 and -18 strains were found to be the most prevalent strains, though it was noted that HPV -16/18 were more prevalent in North India (87.7 percent) than in South India (77.2 percent). Although HPV -16/18 were the most prevalent strains of HPV in both North and South India, HPV -45, -59, and -33 were found to be the next most prevalent strains in North India, while the next most prevalent strains in South India were

HPV -33, -35, and -45 (Bhatla et al, 2008). Nevertheless, Bhatla and colleagues concluded that first generation HPV -16/18 vaccines could provide 75-80 percent protection against invasive cervical cancer in India. However, given that HPV -45, -33, -35, and -58 infections make up the remaining 20 percent of cervical cancer cases, it is essential that these strains be included in second generation vaccines to provide total coverage.

HPV is spread through sexual intercourse, but symptoms often appear years after infection, making it difficult to identify the source of infection. In the Bhatla study for example, 11.9 percent of participants with normal cervical cytology/histology were found to harbor an HPV infection. Women in developing regions, including India, are often at higher risk of HPV infection compared to women in developed regions due to associated cultural norms. In a study done by Vinodhini and colleagues, the main risk factors for the development of HPV-associated cervical cancer were found to be marriage at an early age and increased number of pregnancies (Vinodhini et al, 2011). It was also noted that marriage to older men and/or men with multiple partners is associated with increased risk of HPV infection and cervical cancer development. This may also explain the higher rates of cervical cancer in rural areas of India where such traditional practices are the norm, compared to urban areas.

Women infected with human immunodeficiency virus (HIV) are at an increased risk of invasive cervical cancer due to the decreased capacity of their immune systems to resist HPV infection. There is also evidence suggesting that HIV-positive women without cytological abnormalities may be infected with more strains of HPV than HIV-negative women. In a study done by Clifford and colleagues, 26 individual strains of HPV were found among more than 1 percent of HIV-positive women. It is of note that HPV -16 did not dominate over other strains of HPV among HIV-positive women to the same extent that it dominates in the general population

(Clifford et al, 2006). This data reinforces the need for second generation vaccines that protect not only against predominate HPV -16 and -18 strains, but also less common strains that may disproportionately affect more vulnerable groups such as HIV-positive women.

Unsafe sex with multiple sexual partners is another significant risk factor for HPV, which is why the roughly 3 million sex workers in India are particularly at risk. In a study done in West Bengal, HPV was found in 25 percent of the 229 participating sex workers, with 17 percent diagnosed with type -16 and 14 percent diagnosed with type -18 HPV (Sarkar et al, 2008). Sarkar and colleagues found a decreasing trend of HPV prevalence with increasing age, with sex workers aged 25 years or younger 3.7 times more at risk than their older counterparts. This statistic supports the possibility of acquired immunity to HPV with age, though this inference still lacks sufficient, confirmatory data. It was also found that women who had been working in the sex industry for one year or less were 3.3 times more likely to acquire HPV than those of longer working duration, likely because most sex workers working for more than one year are relatively older (Sarkar et al, 2008). It is also important to note that sex workers with the highest average number of daily clients (six or more) had an HPV prevalence of 67 percent compared to 10 percent HPV prevalence among sex workers with a daily average of one client or less (see Figure 5). In fact, it was

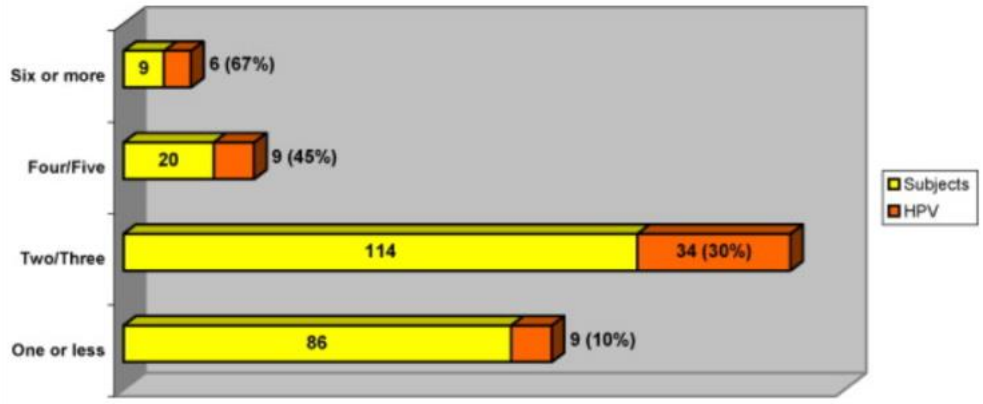

Figure 5. Average number of clients per day and corresponding HPV prevalence. Although a larger percentage of the study group only had an average of two or three daily clients, HPV prevalence was much higher (67 percent) among sex workers with an average of six or more daily clients (Sarkar et al, 2008).

determined that sex workers with an average of four or more daily clients were at four times the risk of acquiring HPV compared to sex workers with fewer daily clients (Sarkar et al, 2008). Using this data, Sarkar and colleagues determined a need for a HPV vaccination intervention for sex workers in India, especially those at younger, at-risk ages.

Other risk factors for cervical cancer include other sexually transmitted diseases, nutritional deficiency, smoking, genetic susceptibility, and use of hormonal contraceptives. However, the most common risk factor for cervical cancer development is low socioeconomic status. In a study by Parikh and colleagues on the correlation between social inequality and the risk of cervical cancer, women in the middle social class group had a 26 percent increased risk of cervical cancer and women in the lower social class group had a staggering 80 percent increased risk of cervical cancer compared to women in the upper social class group (Parikh et al, 2003). In this study, social class was determined using indicators of socio-economic status including the women's level of education, personal or family income level, region of residence, and smoking status. In Western Europe, low social class groups had an approximate 45 percent increase in risk of cervical cancer compared to upper social class groups. However, studies from South America, Asia, and Africa showed a staggering 100 percent increased risk among low social class groups compared to upper social class groups in these regions (Parikh et al, 2003). Not only does this data indicate that women from low social classes are more likely to face exposure to HPV but are also less likely to have access to affordable screenings to detect cervical cancer in its early stages or to HPV vaccines. In studies done in high income countries, "the preventable fraction of invasive cervical cancer ranges from 82 percent for screening every five years between the age of 20 and 64 to 93 percent for screening every year" (Parikh et al, 2003). Parikh and colleagues note that nonparticipation is most prevalent among women of lower socioeconomic statuses, and

that the existence of inefficient screening programs in low and middle-income countries lose most initial participants to follow-up. Given this disparity, it is essential to design and implement comprehensive and affordable cervical cancer screening programs in low and middle-income countries, especially amongst those who are at high risk.

Cervical Cancer, Health Infrastructure and Gaps in Care

According to the Indian Ministry of Health and Family Wellness' Operational Framework for the Management of Common Cancers, visual inspection using acetic acid is the most widely investigated and accepted method of screening for cervical cancer in low resource settings, as opposed to cytology (Pap smear). This method of cervical screening is recommended for women ages 30-65 once every five years. Under the framework, if this initial screening shows positive evidence of lesions that could develop into invasive cervical cancer (see Figure 6), women are to be referred to primary health centers, community health centers, or district hospitals for further evaluation and management by a gynecologist or trained female medical officer (Indian Ministry of Health and Family Wellness, 2016). Within the framework, all community health centers would be equipped to provide confirmatory tests via cytology for those who have been screened using acetic acid tests and are suspected of having abnormal results. The framework also proposes the strengthening of

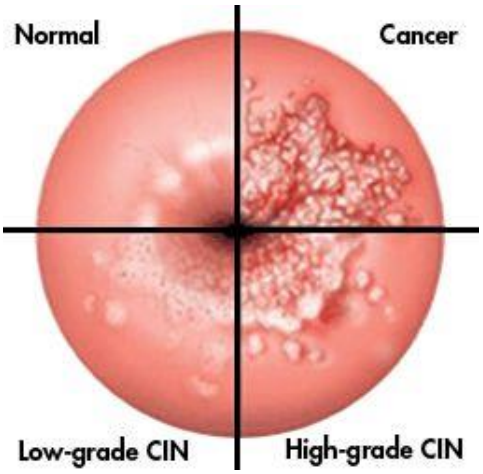

Figure 6. Stages of cervical cancer. In low-grade CIN (cervical intra-epithelial neoplasia), also referred to as CIN1, only about one-third of cervical cells are considered abnormal. In moderate-grade CIN (CIN2) about two-thirds of cells are abnormal. In high-grade CIN (CIN3), almost all cervical cells are abnormal and are considered pre-cancerous. High-grade CIN may develop into cancerous cells over time if left untreated (cervivor.org, 2016)

facilities to provide cryotherapy treatment for women diagnosed with premalignant cervical lesions (see Figure 7). Depending on the Indian state context, the framework proposes the placement of cryotherapy-trained gynecologists at the community health center and district hospital level, and cryotherapy-trained female medical officers at the primary health centers (India Ministry of Health and Family Wellness, 2016).

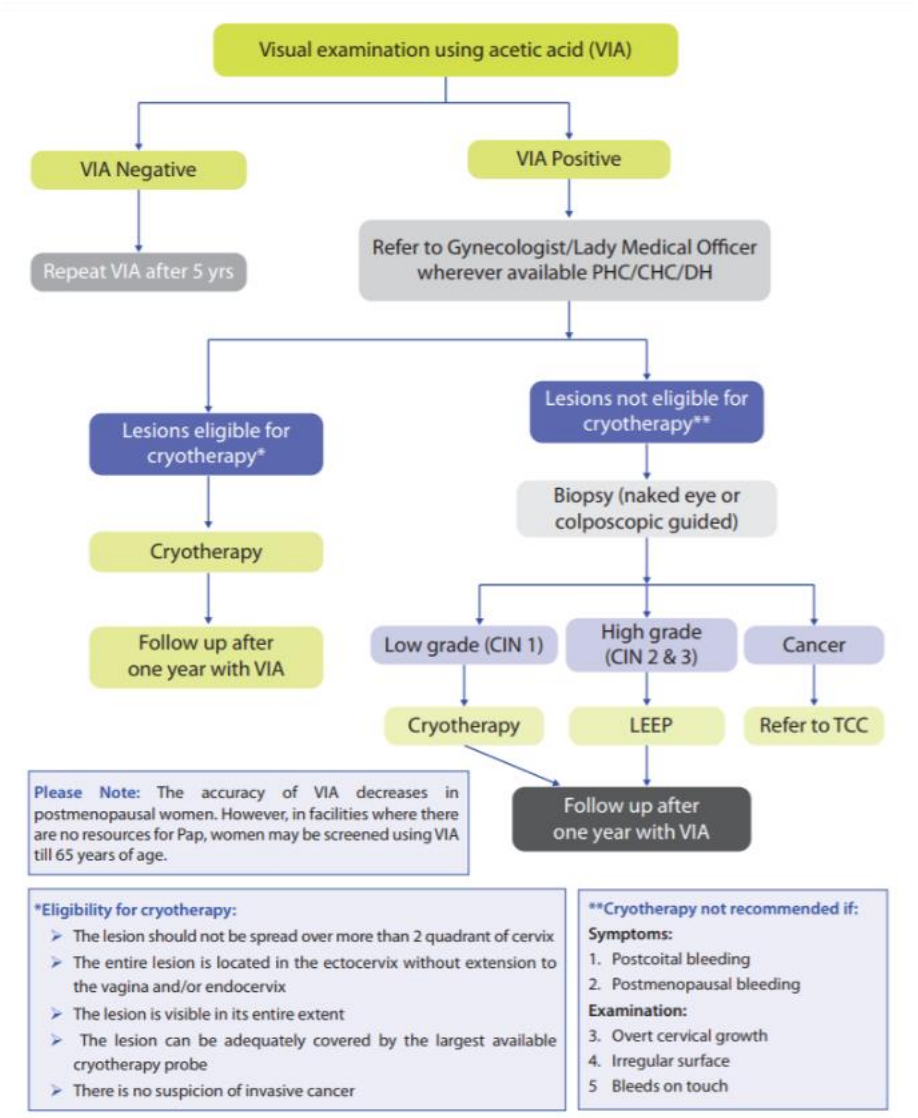

Figure 7. Screening and Management Algorithm for cervical cancer. This diagram details the referral and treatment protocol for all stages of the cervical cancer screening and diagnosis process as outlined in the Indian government's Operational Framework for the Management of Common Cancers. CIN- cervical intra-epithelial neoplasia, CHC- community health center, DH- district hospital, LEEP- loop electrosurgical excision procedure, PHC- primary health center, TCC- tertiary cancer center, VIA- visual examination using acetic acid (Ministry of Family Health and Welfare, 2016).

If detected lesions are not eligible for cryotherapy based on a series of criteria, the patient will undergo a biopsy (naked eye or colposcopy guided) to determine the degree of premalignant cervical intra-epithelial neoplasia (CIN1, CIN2, or CIN3) or presence of invasive cancer and be referred to treatment accordingly. Cases of CIN1 will be re-referred for cryotherapy treatment and cases of CIN2 and CIN3 will undergo a loop electrosurgical excision procedure (LEEP) to remove the abnormal tissue from the cervix (see Figure 8). Visual acetic acid screenings are recommended within one year of cryotherapy or LEEP treatment. Lastly, cases of invasive cancer will be referred to a tertiary cancer center (India Ministry of Health and Family Wellness, 2016). The accessibility of cervical cancer diagnosis and treatment as described in this proposed framework is essential given that current 5-year survival rates would increase by more than 90 percent if treatment such as cryotherapy or LEEP were administered at premalignant stages. However, it is estimated that 95 percent of women in India have never been screened for cervical cancer (Beining, 2012). Low-

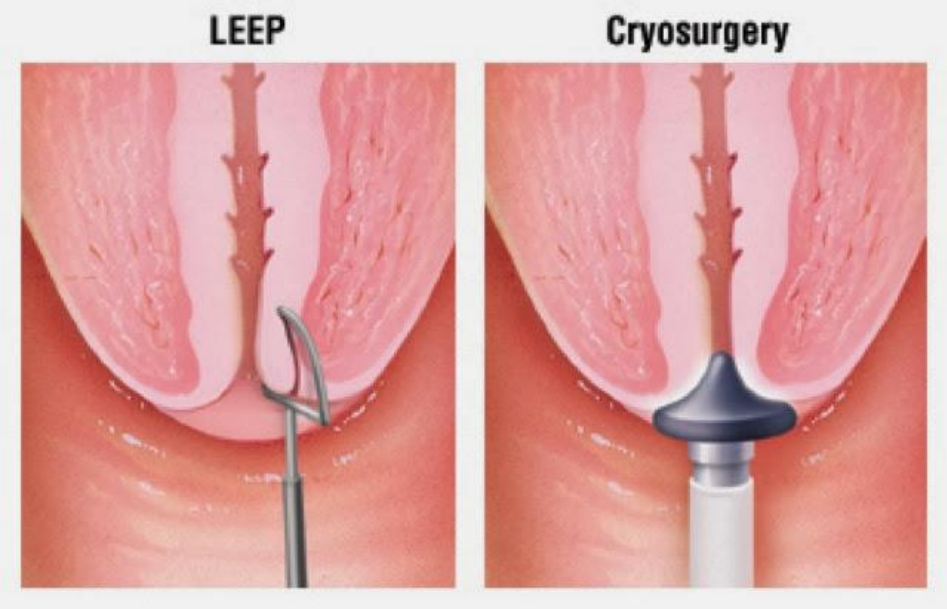

Figure 8. Pre-cervical cancer treatment: LEEP versus cryotherapy. The above image shows two of methods mentioned for the treatment of abnormal cervical cells in the Operational Framework for the Management of Common Cancers. LEEP (loop electrosurgical excision procedure) is a procedure that uses a fine wire loop carrying a safe electrical current to remove abnormal tissue. In the framework, LEEP is to be used for women with high-grade CIN. Cryotherapy uses a very cold probe to freeze and destroy abnormal cervical cells. In the framework, cryotherapy is used to treat lesions detected in the VIA (visual acetic acid) test, usually a low-grade CIN (health.harvard.edu, 2014).

resource settings such as rural India often face a lack of trained healthcare providers. In some areas, trained auxiliary nurse midwives (ANMs) are being utilized in the effort to provide cervical cancer screening and care at the primary health-care facility level. In a study conducted in the Udupi district of Karnataka, trained ANMs identified 368 women with symptoms of cervical lesions. According to Rao and colleagues, "When clinical findings of the ANMs were compared with the results of the cytological examination, a high degree of sensitivity (78.4 percent) and positive predictive value (97.1 percent) were observed in diagnosing abnormal cytological findings" (Rao et al, 2007). The capacity to train auxiliary nurse midwives to perform cytological examinations and successfully identify abnormal results is essential in bringing cervical cancer screening and care to all community levels. Such an intervention has the potential to serve otherwise severely underserved and at-risk groups.

To better utilize the existing health infrastructure to address cervical cancer, at-risk women must be aware of the risk factors of cervical cancer and the benefits of screening. In a study done by Beining, it was noted that knowledge of cervical cancer and screening opportunities were essential in increasing early detection and improved survival outcomes. Out of the 207 women who participated in her Chennai study, the majority (69.6 percent) of women were not aware of cervical cancer, and fewer (16.4 percent) possessed any knowledge about screening. It was noted that women possessing secondary or higher levels of education were significantly more likely to have heard of cervical cancer and screening. Women who reported an awareness of cervical cancer screening gained their information via television (33 percent) or a healthcare provider (28.6 percent). Perhaps the most encouraging information from the study was the participating women's receptiveness to participating in free cervical cancer screening regardless of their level of knowledge about cervical cancer (Beining, 2012). Of the socio-

demographic groups compared, younger and more educated women were the most receptive to screening both before and after receiving information about cervical cancer. Unscreened, less educated, and illiterate women were most likely to acquire a positive attitude towards cervical screenings after receiving information (Beining, 2012).

Given the strong correlation between HPV and development of invasive cervical cancer, it is essential that women are aware of HPV, receptive to HPV vaccination, and can access it at an affordable cost. According to a study done by Montgomery and colleagues, approximately 36 percent of the 202 women surveyed knew of HPV, with 51 percent of those being informed through media and 30 percent informed by a doctor. However, only 28 percent of women reported understanding HPV as a cause of cervical cancer (Montgomery et al, 2014). Despite this, the study indicated a moderate understanding of other cervical cancer risk factors and symptoms. For example, 50 percent knew that HPV can be transmitted sexually, 60 percent recognized that HPV can be prevented by using condoms during sexual intercourse, and 33 percent knew that cervical cancer risk increases with multiple sexual partners. The lowest levels of knowledge were displayed when only 7 percent of participants knew what a Pap smear was, and 26 percent were aware that a vaccine existed for HPV (Montgomery et al, 2014). Of the study participants, 57 percent were interested in receiving more information regarding HPV and cervical cancer. However, only 21 percent were willing to get a Pap smear. In general, women were much more receptive to HPV vaccination than receiving a Pap smear, although 39 percent of participants indicated concern over the cost of HPV vaccines. This is not surprising considering that only 27 percent of participants indicated that they can always afford to go to the doctor. In addition, cost of transportation and care as well as distance from a health-care facility were described as major barriers to seeking cervical cancer care (Montgomery et al, 2014).

Gardasil, perhaps the most well-known HPV vaccine, costs at least $300 USD for a three-dose regimen, with its private market price being upwards of $500 USD. Such exorbitant costs are out of reach for most residents of high-income countries, let alone residents of low and middle-income countries. Merck, the company responsible for the manufacture of Gardasil, introduced the three-dose regimen in India at about $173 USD. Although this price enables a select portion of the Indian middle-class to afford the vaccine, it still left out many at-risk groups including women of low socioeconomic status. According to a study done by Padmanabhan and colleagues, "Prices must fall below $2 per dose to make broad access possible in low-income populations, especially in countries where gross domestic product per capita is below $1,000 USD" (Padmanabhan et al, 2010). Although Merck donated about 130,000 doses of Gardasil for demonstrations in India, Peru, and Vietnam and pledges to increase donations to 3 million in the future, in low and middle-income countries reliance on pharmaceutical company donations alone is not sustainable. However, in recent decades, manufacturers in low and middle-income countries have demonstrated their capacity to produce low-cost, effective vaccines locally. For example, developing country vaccine manufacturers (DCVMs) successfully reduced the price of Hepatitis B vaccines from $50-80 USD per dose to $0.30 USD per dose between the 1980s and 1990s by introducing competition into the market which reduced prices (Padmanabhan et al, 2010). One barrier DCVMs face, however, is the barrier of intellectual property rights. To overcome this, the study recommends that academic research institutions and DCVMs participate in technology transfer and favorable intellectual property management practices to help expedite access to low-cost HPV vaccines in low-resource settings.

The results gathered from these studies emphasize the importance of patient awareness about the risk of cervical cancer, as well as information on cervical cancer screenings. Increasing

awareness through health education interventions will increase positive attitudes towards cervical screenings, increase diagnosis in early and treatable stages, and dramatically increase survival outcomes.

Discussion and Future Research

This literature review began with the goal of preparing the author for nine months of qualitative research studying breast and cervical cancer knowledge and perceptions in Karnataka, India. At the end of this review, more questions than answers remain. Despite the implementation of a national cancer screening program framework by the Indian government in late 2016, breast and cervical cancer screening still largely remains in the hands of research institutions and NGOs. India, like many low and middle-income countries, suffers from a double burden of communicable and non-communicable disease. However, addressing non-communicable diseases in India remains a low priority, not only for the Indian government, but also for private organizations investing in global health in India. The current trend of opportunistic screening in India is not the solution for breast and cervical cancer care, as it leaves millions of at-risk women unscreened and vulnerable to late-stage diagnosis and poor survival outcomes. To properly address the burden of non-communicable disease such as cancer in India and elsewhere, the prevalence of these diseases must be accurately assessed, and the data must be disseminated to national governments and finance ministries to fund non-communicable disease infrastructure.

A part of strengthening non-communicable health-care infrastructure is ensuring that non-communicable disease treatment is available at an affordable cost. The HPV vaccine, as discussed in this paper, remains inaccessible to many Americans because of its outrageous

market cost. For many Indians living on less than $1 USD a day, the HPV vaccine might as well not exist at all. As this paper discussed, introducing competition to the HPV vaccine market could help lower costs over time. Or, as was demonstrated with the HIV retroviral Tenofovir, India could oppose HPV drug patents entirely. Cipla, India's largest generic drug market, joined with Indian and Brazilian NGOs in 2006 to file opposition against the American pharmaceutical company Gilead's patent applications on Tenofovir. As a result, Gilead handed over the patent license in exchange for a 5 percent royalty so Indian manufacturers could make and distribute Tenofovir at a fraction of the cost (Butler, 2009). This form of vigilante-behavior could be a possible solution for affordable HPV vaccines. However, as mentioned above, Indian drug manufacturers and the health system must first identify HPV and cervical cancer as a health concern worth the time and logistics needed to battle foreign pharmaceutical companies.

Building non-communicable disease treatment capacity also includes utilizing global-standard treatment at all levels of care. As discussed previously, mastectomies are the standard treatment for all stages of breast cancer in India. In the United States, Western Europe, and other high-income regions, the standard treatment for early-stage cancers is lumpectomy coupled with radiation treatment. Mastectomies are largely reserved for late-stage breast cancers or women at risk for developing breast cancer due to a family history. In India, where breast cancer is highly stigmatized, lumpectomies and radiation therapy might be more appropriate given the much less drastic physical impact on the individual, compared to complete mastectomies. Whether this pattern of care is due to limited training of surgeons in India or some other preventative intent is unclear from current data.

At the start of this research, the primary question of the author was why breast cancer seems to affect women in urban communities and cervical cancer, in rural communities.

Although this question has since been explained through research gathered on the correlation with differing behaviors within urban and rural communities. Such research does not provide a concrete behavioral intervention. It is not the role of the public health researcher to alter the culture and tradition of different communities, but to work within perceived "barriers" to find a solution based on an acceptable compromise. Thus, the author plans on expanding this research by conducting focus group discussions and in-depth interviews within both urban and rural communities in the state of Karnataka, India to better assess individual and community understanding of breast and cervical cancer, including knowledge of risk factors, access and utilization of screening services, and barriers to care. Ideally, it is within conversations like these that mutual understanding between community members and researchers can be achieved, and interventions designed that work within cultures rather than around them.

Conclusion

Breast and cervical cancer are significant causes of mortality among women in India, with approximately 70,000 and 67,000 annual deaths respectively. Breast cancer has numerous risk factors, the most prominent involving behavioral patterns associated with urban lifestyles. These risk factors include bearing children later in life and engaging in little to no breastfeeding. Breast cancer is also more prevalent in certain religious communities, with Parsi and Christian Indian women presenting with very high rates of breast cancer. Cervical cancer, by contrast, typically affects Indian women from rural communities. Human papillomavirus (HPV) is the main risk factor for developing cervical cancer. Other risk factors include marriage at an early age and numerous pregnancies. Unsafe sexual practices as well as marriage to older men and/or men with multiple partners is also associated with increased risk of HPV infection and cervical

cancer development. In response to these risks, the Indian government has increased its funding for managing non-communicable diseases and cancer. Most remarkably, the Indian Ministry of Health and Family Planning published a document entitled *Operational Framework for the Management of Common Cancers*, which was implemented in late 2016. Within the document, health-care facilities at every community level were given frameworks for personnel training, facility management, and metrics for improving service capacity. Despite this, numerous studies have indicated a need for additional interventions while the framework establishes a foothold in India's health-care system. To encourage early diagnosis of breast cancer, many researchers have suggested training health care workers at every level to provide breast examinations. In addition, some have pointed to the value of training women to perform self-breast examinations and create incentives for women to report abnormalities to their doctor. For cervical cancer, visual acetic acid tests have also been recommended for their value in diagnosing cervical abnormalities in low-resource settings such as rural India. Using these simple tests, women with positive diagnosis can be identified before the disease develops into late stages that are increasingly difficult to treat. There is also promotion of increased HPV vaccination coverage. By incorporating an HPV vaccine that not only covers the most prevalent types of HPV (-16 and -18), but also types -45, -33, -35, and -58 into second generation vaccines, almost total coverage of HPV infections could be achieved. However, cost barriers must be eliminated by supporting domestic vaccine manufacturers, and while working within intellectual property laws, introducing competition into the HPV vaccine market to reduce prices. Thus, to fully address the issue of breast and cervical cancer in India, healthcare professionals and researchers must first establish a reliable network for data collection to accurately assess the burden of breast and cervical cancer and monitor progress. Second, diagnosis and treatment for these cancers must be

accessible and affordable at every level of care. Although India still faces a significant challenge in combating breast and cervical cancer and managing non-communicable diseases, realistic steps are being taken to strengthen the health-care system and improve breast and cervical cancer-related health outcomes.

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