Women and Cancer Issue Brief: A focus on breast, cervical and lung cancer

Global Cancer Burden:

Cancer is a leading cause of death worldwide, second only to cardiovascular disease. Cancer is the result of multiple dynamics, including genetic factors and associated with risk from environmental, lifestyle and behavioral exposures. Cancer can affect any part of the body. The most common cancers include lung, breast, prostate and colorectal cancers. In countries undergoing economic development and lifestyle transitions, these cancers are increasingly common, largely due to increased cigarette smoking, low fiber/high fat diets and physical inactivity.[1]

These emergent cancers compound existing pressures from high incidence of poverty- and infection-related cancers, notably stomach, esophagus, cervix and liver cancers. In low- and middle-income countries (LMICs), late-stage diagnosis of cancer is the norm as health systems are often unprepared to address the dual burdens of infectious and non-communicable diseases (NCDs). With limited access to timely and effective treatment, high case fatality from cancer is far too common in LMICs.

Given significant progress in controlling infectious diseases, millions of individuals in LMICs, who previously would have died young, are now living into old age. Since the risk of cancer rises significantly with age, LMICs are experiencing a disproportionate increase in cancer incidence. In 2012, of the 14.1 million new cases of cancer and 8.2 million cancer deaths across the world, Africa, Asia, and South America accounted for more than 60% of new cases and about 70% of cancer deaths. [2] For women in LMICs, the risk and toll of cancer is particularly high.[3,4]

The top three cancer types diagnosed in women in LMICs, are breast (23% of new cases and 14% of deaths), cervical (12% and 10%, respectively) and lung cancer (8% and 12%, respectively). The International Agency for Research on Cancer (IARC) estimated that, in 2012, 47% of the new cancer cases and 43% of cancer deaths occurred in women in 2012.[5] In total, 42% of new cancers in women were either breast or female-specific cancers. There are also cancers that are unique to women, such as cervical and ovarian cancers. Likewise, some cancers are not exclusive, but are most often detected in women, such as breast (99% of cases) and thyroid cancer (77% of cases).

Deaths from breast and cervical cancer now outnumber pregnancy-related deaths in most of Asia and Latin America, and some African countries.[6] In LMICs, around 60% of the mortality from breast and cervical cancers occur in women under 60 years of age, most often taking women in the prime of their lives, when they are making the greatest contribution to their families and communities. [7]

Breast Cancer

Breast cancer is, by far, the most commonly diagnosed cancer in women worldwide, with an estimated 1.7 million new cancer cases in 2012 (25% of all female cancers).[8] Despite the misconception that breast cancer is primarily a problem of high-income countries, more cases are currently diagnosed in LMICs (883,000 cases in 2012) than in more developed countries (794,000 cases in 2012)[9]. While breast cancer mortality has been decreasing steadily in North America and much of Europe over the past 25 years, largely due to improved early detection and treatment, both incidence and mortality rates have been increasing rapidly in LMICs. [10]

Breast cancer is the leading cause of death by cancer in LMICs, with 324,000 deaths estimated in 2012. While 53% of new cases of breast cancer occurred in LMICs, 62% of the deaths happened in those same countries. Five-year survival rates for breast cancer are higher in Europe and North America (around 80-85% in women diagnosed in the late 1990s), than in LMICs. For instance, five-year survival rates are as low as 52% in India, 46% in Uganda and 12% in The Gambia.[11]

Limited access to early detection services and treatment, as well as the increasing prevalence of obesity and physical inactivity and changes in reproductive patterns all contribute to these negative breast cancer trends in LMICs. Further, limited research has been conducted on the earlier age of onset in LMICs.[12]

Cervical Cancer

Human Papilloma Virus (HPV) is the primary cause of cervical cancer. The majority of sexually active individuals will be infected by HPV during their life. Among infected women, a small subset will have persistent HPV infection and go on to develop pre-cancer.

Cervical cancer is the fourth most commonly diagnosed cancer in women, with an estimated 528,000 new cases worldwide in 2012, and the second most common cancer among women in LMICs. More than 84% of cases are diagnosed in LMICs, where it accounts for almost 12% of all female cancers.[13] In general, the highest incidence rates are in Central and South America, the Caribbean, sub-Saharan Africa and Southern Asia; and lowest are in Australia/New Zealand and Western Asia.[14] Of the 266,000 deaths from cervical cancer worldwide in 2012, 87% (230,000) occurred in less developed regions.[15]

Lung Cancer

Tobacco smoking, including second-hand tobacco smoke, is the leading cause of lung cancer worldwide. The current lung cancer trends reflect smoking patterns from 20-30 years ago. Other risk factors play an important role in lung cancer in LMICs, such as outdoor air pollution (including particulate and diesel engine exhaust), indoor air pollution (specifically, smoke and emissions from household combustion of coal), occupational exposures (asbestos, certain metals, working in the rubber industry) and other environmental hazards including arsenic in drinking water, radon and other volatile contaminants.[16]

Lung cancer is the third most common cancer in women. The mortality burden for lung cancer among females in developing countries is higher than the burden for cervical cancer, accounting for 12% of total female cancer deaths. Lung cancer is one of the most aggressive cancers, with a 5-year survival rate of 10-15%.[17] Hence, patterns and trends in lung cancer mortality match those for incidence rates. In 2012, of an estimated 583,000 new cases in women worldwide, 54% (315,000 new cases) were among women in LMICs.[18]

Age-standardized incidence rates vary 80-fold from one country to another, with the highest rates in North America, Europe and East Asia. Rates are still relatively low in many African countries and some Asian countries due to the low smoking prevalence. Nevertheless, since women in many countries are traditionally responsible for household chores that expose them to pulmonary toxins, such as cooking with solid fuels in unventilated homes, they are particularly vulnerable. Nonsmoking women in some parts of China, for instance, experience very high lung cancer rates due to indoor coal burning. The use of solid fuels for cooking is highest in sub-Saharan Africa and South and East Asia.[19]

Current Situation:

Breast Cancer

Early detection of breast cancer through screening is critical to reducing breast cancer deaths, as the stage of cancer at the time of diagnosis correlates directly to the cost and effectiveness of treatment. As part of a multi-year effort to release the first comprehensive international guidelines on breast cancer, the World Health Organization (WHO) has recently published a position paper on mammography screening, citing it as “the only breast cancer screening method that has proved to be effective in organized population-based programmes.”[20] Mammography uses low-energy x-rays to search for irregular growths within the breast. However, the benefits

and risks of mammography vary widely by setting, and there is disagreement among experts about the appropriate age groups for screening.

In well-resourced settings, as well as low-resource settings with strong health systems, the WHO now recommends mammography for women aged 50-69 every two years. Policy-makers in well-resourced settings are also advised to consider population-based screening programs for women aged 40-49 and 70-75, depending on a set of conditions, including feasibility and monitoring and evaluation capacity. These recommendations are in line with those of the Breast Health Global Initiative (BHGI), an alliance of organizations that has pioneered the development of international breast health and cancer control guidelines for LMICs since its founding in 2002.[21]

Mammography requires expensive equipment and materials, medical staff with advanced training, including radiologists, and often involves follow-up procedures such as ultrasound or magnetic resonance imaging (MRI) to confirm diagnosis. Due to these resource demands, there is a need for low-cost alternatives for limited resource settings. Breast self-examination (BSE) is not currently recommended by the WHO as a screening method, as there is no evidence of its effectiveness.[22] Clinical breast exam (CBE), in which a doctor, nurse or physician assistant examines the breasts by hand for abnormalities, is a more viable method for LMICs. Because CBE does not require advanced equipment or electricity, the BHGI's guidelines recommend it as a screening method for limited resource settings, in conjunction with an evaluation of the patient's clinical history and a referral system to facilities that offer advanced diagnostic procedures. Abnormal results are then further examined and diagnosed using mammography, ultrasound or fine needle aspiration cytology, in which cells are sampled from the suspicious lump and biopsied.

Although the WHO does not currently recommend CBE for limited resource settings, it does mention it as a promising method that needs more careful validation through research. A recent study found that CBE reduced the incidence of advanced stage breast cancer compared to no screening.[23] This reduction of advanced stage cancer, often referred to as 'down-staging,' is a critical goal of early detection, as it allows providers to identify cancer in women at earlier stages while treatment is still within the capacity of resource-limited health systems. Ukraine and Peru provide examples of successful CBE programming, where PATH, an international health organization, collaborated with local health officials to expand screening of at-risk women in underserved areas using nurses and midwives, and strengthened referral pathways to local hospitals for diagnosis and treatment.[24]

Surgical treatment options for breast cancer include modified radical mastectomy, in which the affected breast is removed, and lumpectomy, in which only the cancerous cells are removed. Chemotherapy, endocrine and radiation therapy are also used to treat breast cancer, sometimes in conjunction with surgical procedures. These require advanced laboratory tests and facilities, well-trained staff and complex supply chains. In LMICs, effective breast cancer treatment may be limited by small numbers of medical personnel, insufficient medical equipment including pathology services and radiotherapy machines and the high cost of cancer drugs.[25]

Cervical Cancer

HPV vaccination remains the sole tool for the primary prevention of cervical cancer, with the potential to reduce cervical cancer deaths globally by up to two-thirds if widely adopted.[26] The two available vaccines, Cervarix and Gardasil, are widely licensed around the world, and approved by the WHO, the European Medicines Agency and the US Food and Drug Administration. Both are given in a series of 3 shots over 6 months and are effective for a minimum of six years. Recent WHO recommendations indicate a two-dose regime is sufficient to achieve protection with these vaccines when the first dose is given by age 14.

Cervarix protects against HPV types 16 and 18, which are responsible for 70% of cervical cancer cases around the world as well as many cancers of the anus, vagina and vulva, while Gardasil protects against types 16 and 18, as well as types 6 and 11, which cause 90% of genital warts. Gardasil is the only vaccine licensed for boys, as it protects against genital warts and reduces transmission to girls. The WHO recommends these vaccines for preteens between 9 and 13 years old. A third vaccine, Gardasil-9, which was licensed in the US in 2014, contains the original four types plus five additional oncogenic HPV types. It is estimated that the HPV types covered in this vaccine are responsible for 90% of all cervical cancer globally. Gardasil-9 has not yet approved by the WHO.

However, vaccination is only effective for those who have not been infected with HPV; screening, on the other hand, is the best hope for the millions of women worldwide who have already been exposed to HPV. Screening a woman only once between the ages of 35 and 40 reduces her lifetime risk of cervical cancer by 25–36%.[27] The three screening methods for cervical cancer are cytology (Pap test), visual inspection with acetic acid (VIA) and HPV DNA testing.

In cytology screening, cervical cell samples are examined, and abnormal results are followed by colposcopy and biopsy of the suspicious tissue to confirm a diagnosis. These tests can take weeks to process and require highly trained staff and costly laboratory equipment to analyze, making them difficult to administer in low-resource settings. VIA, which uses 5% acetic acid (vinegar) to identify pre-cancerous lesions, can be completed rapidly through visual identification by a clinician without sophisticated technology, and has been shown to have comparable sensitivity to cytology-based screening.[28,29,30] . Given its rapid processing time, VIA has been important in developing the 'screen-and-treat' approach, in which treatment is provided soon, if not immediately, after screening. As such, VIA is considered "an attractive alternative to cytology-based screening in low-resource settings" by the WHO.[31]

HPV DNA tests are administered by trained providers, processed rapidly by machine and offer the most sensitive assessment of risk for cervical cancer by identifying strains of the virus that have been known to cause pre-cancerous lesions. The WHO's latest screening guidelines recommend that, when possible, women aged 30 to 49 should receive an HPV test for vulnerability to cervical cancer at an interval of five years. If a woman tests positive for HPV, she may then be evaluated either by cytology or VIA to determine the need for treatment. A woman with no access to HPV testing should be screened using VIA or Pap.

Following screening, there are a number of preventive treatment options for women with irregular results. In the case of pre-cancerous lesions, depending on certain characteristics of the lesion, including visibility and size, she may be eligible for cryotherapy, a process that involves freezing the pre-cancerous cervical tissue. In settings where VIA and cytology are not available, women with a positive HPV test result may seek cryotherapy directly, if a visual assessment shows they are eligible, though this may lead to overtreatment according to the WHO.

Cryotherapy is the least expensive and the simplest of the preventive treatment options, and can often be conducted in a single-visit, without electricity, and, where allowed, by trained nurses instead of doctors.[32] It is more than 70-80% effective for lesions diagnosed at early pre-cancerous stages.[33] In the event that a woman is not eligible for cryotherapy, the WHO recommends preventive treatment with Loop Electrosurgical Excision Procedure (LEEP, sometimes referred to as LLETZ), which uses a low-voltage electrified wire to remove abnormal tissue. Though LEEP has a higher cure rate than cryotherapy, its equipment and resource demands make it more difficult to adopt in low-resource settings.

A third treatment method, Cold Knife Conization (CKC), uses the same procedure as in a biopsy, excising tissue directly with a knife, or sometimes, a laser. Although the cure and recurrence rates associated with CKC are similar to those of cryotherapy and LEEP, it has a higher risk of complications, requires regional anesthesia, and should be done in a hospital. Therefore, CKC is not recommended for screen-and-treat programs if either of the other two options are available.

It is all the more important to catch cervical cancer early, ideally at the pre-cancerous stage, as the treatment of this cancer can leave lasting sequelae for the women, including infertility, incontinence and dyspareunia, after hysterectomy.

Lung Cancer

Rates of newly diagnosed cases of lung cancer continue to rise among women living in LMICs, with the highest incidence of new LMICs cases occurring in East Asia and Micronesia.[34] The WHO's surveillance of lung cancer deaths in women also reflect a steady rise in lung cancer over the past three decades, with a global increase in incidence of 4.6% per year between 2001-2003. Some experts predict that by 2050, more than half of all lung

cancer cases will be diagnosed in LMICs.[35] For this reason, many health experts are focusing their attention on the regions hardest hit by this rising trend, in order to understand the factors putting women (and men) at higher risk for lung cancer in LMICs.

Tobacco use appears on the rise among college students in some LMICs.[36] Though female students are significantly less likely than males to use tobacco, female students in some countries report significant tobacco use. In a recent study on tobacco use among students from 24 LMICs, many students reported poor awareness of potentially harmful effects of tobacco, which suggests the need for broad-based public awareness campaigns aimed at reducing the use of tobacco products.

Given that prevalence of tobacco use in LMIC remains relatively low, with increasing rates in only a few countries, smoking and use of smokeless tobacco cannot explain all new cases of lung cancer in women. Women living in East Asia who do not smoke are four times more likely to develop lung cancer compared with women of the same age living in Europe or Africa.[37] These new cases of lung cancer are likely due to a variety of factors including exposure to toxic fumes from cooking oils, passive smoking and exposure to other carcinogens. Dietary influences and infectious agents have also been studied but none have been confirmed to have a strong causal relationship to lung cancer in women.[38]

Future efforts to reverse the rising incidence of lung cancer in women will require strong global public awareness campaigns. These campaigns will need to sensitize populations about risk factors specific to their country or region. Campaigns should be based upon documented risks such as those confirmed by the WHO's International Agency for Research on Cancer, in order to provide accurate, evidence-based information for at-risk populations. Prevention strategies will also need to focus on youth, including university students, so they will be motivated to avoid tobacco use. Cancer registries are also emerging as a useful mechanism to improve governments' capacity to be proactive in decisions concerning lung cancer prevention, detection and management.

What can be done:

The type and stage of cancer, as well as in health system strength and resource availability, demands informed, contextually appropriate approaches to cancer programming. Many LMICs lack the staff, training, equipment, drugs, facilities and referral pathways necessary for comprehensive cancer treatment and control. With limited resources, the most cost-effective approaches to cancer involve HPV vaccination, the promotion of healthy behaviors and identifying irregular cellular growth early. The widespread approval and distribution of the HPV vaccine has been an integral part of responding to the increasing rates of cervical cancer in LMICs, and the development of affordable and pragmatic screening techniques like VIA offer excellent opportunities for prevention in the world's most underserved areas. CBE may prove a similarly feasible technique for identifying breast cancer in its early stages, as PATH's work in Peru and Ukraine attest.

However, to capitalize on these technical advances, LMICs need national cancer plans that develop human resource capacity, improve supply chains for required technologies and medicines and expand communications campaigns and equitable policies to deliver these services to those women that face the most risk. Cancer planning should be integrated within broader health systems strengthening efforts to improve efficiency and standardization of protocols. Special attention to women's cancers and gender-specific questions of equitable access to services and information should be an important consideration in the development of national cancer plans and programs.

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The Task Force on Women and NCDs seeks to respond to the unique and growing burden of non-communicable diseases on women in low and middle income countries (LMICs) by mobilizing leadership, expanding technical expertise and disseminating evidence to inform policymaking, planning and services. The Task Force seeks to inform its partner organizations, local and national governments, and leaders within the health community about the important role of NCDs in women's health. Together, we can improve health outcomes for women.