OUTLOOK

Breast Cancer: Increasing Incidence, Limited Options

Breast cancer is the most common cancer and leading cause of cancer deaths among women worldwide.[1] In 2000, breast cancer resulted in an estimated 189,000 deaths in developed countries and 184,000 deaths in developing countries, accounting for 16 and 12 percent, respectively, of all cancer deaths in women.[1] While the age-standardized incidence of breast cancer is generally lower in developing countries than in developed countries (23.1 versus 63.2 per 100,000 women), incidence rates vary widely between and within countries (see Figure 1).[1] In temperate areas of South America, for example, the incidence of breast cancer is almost as high as in North America and Western Europe.[2]

Over the past several decades, the risk of breast cancer in developed countries has increased by one to two percent annually.[3] While data for developing countries are limited, cancer registries suggest that age-standardized incidence rates are rising even more rapidly in low-incidence regions such as Africa and Asia.[4] Researchers believe that socio-economic and lifestyle changes (for example, later childbearing and dietary changes) and associated changes in menstrual patterns are responsible for rising risk in developing countries.[3,5] In addition, increases in life expectancy will cause the burden of breast cancer in developing countries to rise sharply in the years to come, since older women are far more likely than younger women to get the disease.[3] As a result of these trends, breast cancer is already more common than cervical cancer in a number of developing countries.[1] (For more information on cervical cancer, see *Outlook*, Volume 18, Number 1.)

These trends, along with highly publicized advances in the detection and treatment of breast cancer, are drawing attention to the disease even in regions where its incidence remains low. As this article shows, however, policy makers must carefully weigh the costs and benefits of fighting breast cancer against competing health needs. Furthermore, diagnostic, treatment, and palliative services—which require substantial technological and financial resources—must be put in place before launching a screening program.

Risk Factors

Although the causes and natural history of breast cancer remain unclear, epidemiological research has uncovered genetic, biological, environmental, and lifestyle risk factors for the disease. Most of this research has been conducted in Europe and North America, but studies conducted in other countries generally confirm these patterns.

Age is the single most important risk factor for breast cancer. Compared with women in their twenties, women are 10 times as likely to develop breast cancer in their thirties,

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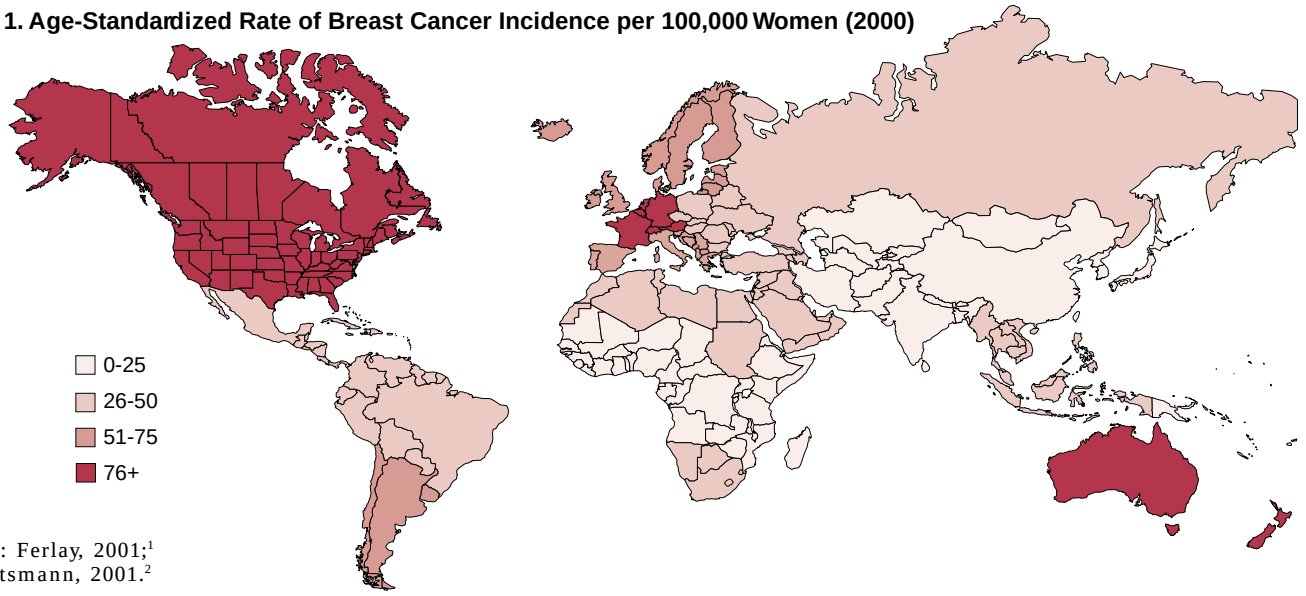
Figure 1. Age-Standardized Rate of Breast Cancer Incidence per 100,000 Women (2000)



Sources: Ferlay, 2001;[1] Schwartsmann, 2001.[2]

40 times as likely in their forties, 60 times as likely in their fifties, and 90 times as likely after age 60.[3]

Hormones, especially estrogens, play a crucial role in the development and growth of breast cancer, and they may be the common factor behind the many reproductive variables associated with breast cancer.[4] In theory, the more years a woman is exposed to hormones during her lifetime, the greater her risk of breast cancer. For example, women are two times more likely to get breast cancer if they reach menopause after the age of 54, and three times more likely if they have their first child after age 40.[6,7] Similarly, breast cancer risks fall with each year of delay in onset of menstruation. Studies also suggest that extended breastfeeding—for a lifetime total of six years or more—reduces the risk of breast cancer, at least among pre-menopausal women.[8]

Some case-control studies have raised concern that the abrupt hormonal changes accompanying induced abortions might increase the risk of breast cancer later in life. However, these studies suffer from a serious bias: because abortion is so controversial, healthy women in control groups are far less likely to share information about it than women with cancer. Larger, more rigorous cohort studies that lack this bias have found no link between induced abortion and breast cancer risk.[9]

A large body of research has explored the link between breast cancer and two common hormonal supplements: oral contraceptives and hormone replacement therapy. Oral contraceptives are associated with a small increase in breast cancer risk that persists for 10 years after women stop taking them, but the cancers diagnosed among users are likely to be less advanced than breast cancers diagnosed among non-users.[4,6] Hormone replacement therapy is associated with a small increase in risk for each year of use, which continues for four years after therapy is stopped.[6,7]

A woman's family and personal medical history are also critical. Women are twice as likely to develop breast cancer if their mother or sister had breast cancer prior to age 50, and their risk doubles again if two immediate family members had breast cancer.[6] While this risk may reflect a genetic component of the disease, genetic mutations appear to account for only five percent of all breast cancer cases.[6,10] Women also are four times as likely to develop breast cancer if they have a history of certain types of benign breast disease.[6]

Certain environmental exposures, most notably to radiation, may increase the risk of breast cancer. Japanese women exposed as teenagers to atomic bomb blasts were twice as likely as unexposed women to develop breast cancer later in life.[6] Radiation treatments for disease, especially at a young age, also increase breast cancer risks.[10,11]

Researchers also have explored links between breast cancer and women's lifestyles and found some associations. Most are very small, however. For example, drinking alcohol probably increases the risk of breast cancer.[4,6,11] Exercise, both in adolescence and adulthood, may reduce the risk.[12] Consumption of fruits and vegetables may reduce risk, while dietary fat intake seems to increase risk even among non-Western populations with low-fat diets.[10] Obesity as an adult is associated with a lowered risk of breast cancer before menopause but a heightened risk after menopause.[6,7,13]

Keys to Reducing Mortality

Little can be done to prevent breast cancer. Although diet, exercise, obesity, and alcohol consumption seem to be related to risk, research does not indicate that women can prevent breast cancer by changing their lifestyles.[10]

One approach to prevention focuses on interventions for women at high risk of breast cancer (using a woman's reproductive and medical history to calculate her risk of developing breast cancer).[14] A large-scale U.S. trial of tamoxifen, an estrogen-like compound used as an adjuvant therapy for breast cancer, found that five years of use cut the risk of invasive breast cancer in half among high-risk women; smaller British and Italian studies did not confirm these results.[10] Further investigations of tamoxifen and a related compound, raloxifene, are underway. Some women with a strong family history of breast cancer have opted for prophylactic mastectomies. Data on the effectiveness of this approach are limited; clearly the psychological and financial costs are enormous.[10]

In the absence of effective methods to prevent breast cancer, health care systems have turned to a combination of early detection and improved treatment to increase survival among women who develop breast cancer. In the United States, these strategies increased five-year survival rates among white women from 65 percent in 1973 to 84 percent in 1991;[15] rates in Singapore climbed from 46 to 71 percent over same time period.[16] Survival rates remain low, however, in the many countries that have not yet systematically implemented these strategies.

Early detection. Breast cancer is more easily and effectively treated in its early stages. Survival rates drop dramatically when women present with advanced cases, regardless of the setting. Five-year survival rates in Bombay, for example, are 80 percent for cancer confined to the breast, 46 percent for cancer that has spread to the lymph nodes, and 10 percent for cancer that has metastasized to more distant parts of the body; comparable figures for white women in the United States are 97 percent, 76 percent, and 20 percent, respectively.[15] Therefore, one key strategy for reducing breast cancer mortality is increasing the proportion of cases that are detected early. This approach is called downstaging.[2,17,18] Unfortunately, women in low-resource countries generally present at a later stage of disease than women elsewhere (see Figure 2).[15]

One factor that contributes to later detection is women's delay in having breast lumps evaluated. Some may not realize how serious their condition is or that cancer treatments are available, while others may believe their symptoms are best treated with local remedies.[18-20] In many countries, the social stigma associated with breast cancer and the potential disfigurement of mastectomy pose obstacles to care. Educating women about breast cancer may encourage them to seek medical care promptly (see box on page 4).

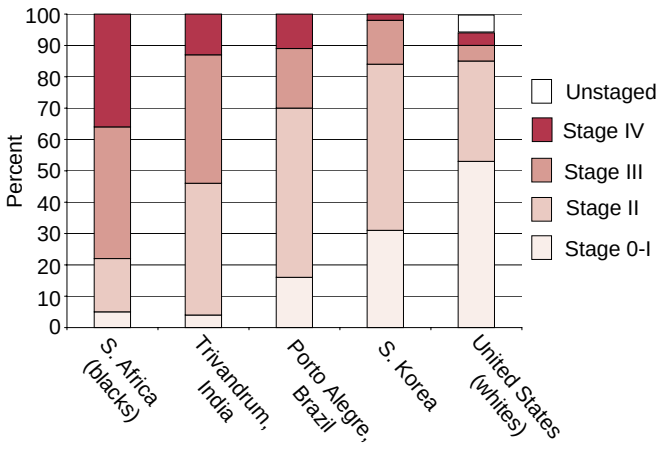
The absence of mass screening programs in many countries also contributes to the problem. Regular screening of all women over a certain age has the potential to sharply increase the proportion of breast cancer cases diagnosed in the earliest stages.[3] In Singapore, for example, a large randomized trial of mammography found that 64 percent of cancers detected through screening were either *in situ* or Stage I disease, compared with only 26 percent of cancers in a control group of women, whose cancers were diagnosed after the women or their doctors noticed symptoms.[21]

Screening approaches. There are three approaches to screening for breast cancer. Two of them—clinical breast examinations (CBE) and breast self-examination—rely on manual palpation of the breast. CBE is conducted by health workers who have been taught how to palpate and inspect women's breasts for lumps and other symptoms of cancer. In mass screening programs, all women over age 35 or 40 receive annual CBE. The technique has been estimated to have a sensitivity of 54 percent and a specificity of 94 percent.[22] CBE can detect some lumps that mammograms miss, especially in younger women whose dense breast tissues can obscure x-rays. Cancers detected by CBE tend to have poorer prognoses than those detected by mammography, since they are large enough to be felt.[23]

The effectiveness of CBE in reducing mortality, however, has not been clearly established, as none of the trials conducted to date compared routine CBE with no screening. A few studies suggest that this approach may offer some benefit: a large-scale mammography trial in Canada, for example, concluded that CBE alone was as effective in reducing mortality as a combination of CBE and mammography.[24] Mass screening with annual CBE in Japan also has been associated with reduced breast cancer mortality.[25] Further research is needed, however, to determine what the benefits of mass screening with CBE may be.[26]

Because the effectiveness of CBE depends entirely on health workers' skills, it is important to use proven training strategies and standardized techniques.[22,24] Training in breast examination techniques yields better results when silicone breast models are used to practice palpation.

Figure 2. Distribution of Breast Cancer Cases by Stage



Sources: Vorobiof, 2001;[18] Chopra, 2001;[27] Schwartsmann, 2001;[2] Korean Breast Cancer Society, 2000;[5] Forbes, 1997.[3]

Because health workers' technique may alter over time, periodic monitoring is needed to ensure that they continue to adhere strictly to protocols.[28] Research indicates that trained nurses can perform CBE as well as physicians,[28] and that it is possible to train community health workers to conduct the exams.[29]

The other manual screening method, breast self-examination, has been endorsed and widely promoted by cancer organizations around the world, and research into its effectiveness continues.[30] Yet there is insufficient evidence to show that regular breast self-exams reduce breast cancer mortality rates.[26,31] A large randomized trial in Shanghai, for example, reported no positive impact on the rate or stage of diagnosis or on five-year mortality rates, despite the fact that women received intensive instruction and continuing reinforcement on the technique.[33]

The third screening method, mammography, uses x-rays to detect tumors and anomalies in the breast. Mammography can identify cancers and benign breast abnormalities that are too small to palpate, so its sensitivity (83 to 95 percent) is far higher than the sensitivity of CBE, particularly among post-menopausal women who have less dense breast tissue.[34] It is not clear, however, how many of these smaller lesions eventually progress to invasive cancers.[24] Furthermore, mammograms do not find every tumor; they miss 10 percent of all cancers in women over 50 and even more in younger women.[35,36] Because mammography is less sensitive in younger women, and because breast cancer rates are lower in younger women, experts disagree whether it is cost-effective to screen women under age 50. They agree, however, that there is no benefit to screening women under age 40. The frequency of screening is also under debate: various country programs repeat mammograms at one-, two-, and three-year intervals.

Because mammography is the only screening method for which efficacy has been established (see box on page 5), it is relied upon in most developed countries. Its costs are high, however, relative to its benefits. Mammography requires sophisticated machinery, continuing supplies of film and chemicals, skilled technicians to take the pictures, experienced radiologists to read the films, and constant quality control to achieve reasonable levels of accuracy.[34]

Establishing a screening program. Before introducing any kind of screening program for breast cancer, policy makers in settings with limited resources should carefully assess its costs and potential health benefits. In countries where the incidence of breast cancer is low, screening may drain resources away from more pressing health problems without significantly reducing mortality. Further, screening programs will be ineffective if quality control is not maintained or diagnostic work-ups and treatment services cannot be offered to all women who have suspicious findings.[17] Coverage is another consideration: At least 70 percent of women must participate to significantly lower mortality levels; fear, modesty, inconvenience, cost, and fatalistic attitudes may keep women away.[21]

Where incidence rates are high enough to require action—for example, in parts of South America—the first step is to ensure that diagnostic tests and treatment are accessible and affordable to women with symptoms. Depending on available resources, decision-makers may want to consider a screening program based on CBE rather than mammography. Although CBE has not been definitively shown to reduce mortality, the exam can be used to detect most of the tumors found by mammograms,

Raising Awareness

In many countries where the incidence of breast cancer is great enough to pose a public health problem, the government, medical professionals, and the public may not recognize its importance. Advocacy directed to government officials and policy makers can place breast cancer on the national agenda, encourage the development of systematic health policies and service protocols, and increase women's access to detection and treatment services.[32] Before such policies can be implemented, however, health care systems must raise the awareness of front-line providers and teach them skills to recognize the symptoms of breast cancer and make appropriate referrals.[17]

It is equally essential to inform the general public that breast cancer is curable if detected early. Even in countries where breast cancer is relatively uncommon, women should understand the need to seek care promptly if they find a lump in their breast or other symptoms of cancer. Men also are an important audience, since they frequently detect breast lumps in their partners and may control women's access to the health care system.

By speaking openly about breast cancer in public forums, awareness campaigns have the added benefit of reducing the stigma associated with breast cancer. Survivors are especially credible spokespersons. Their first-hand testimony can defuse stigma and gather public support for breast cancer initiatives. Multimedia campaigns around the world have publicized the issue of breast cancer on television and radio, in posters and leaflets, and during sports competitions and walkathons.[19] In countries such as Brazil, nongovernmental organizations are training community volunteers to raise the awareness of local women, teach breast self-examination techniques, and help women access screening, diagnostic, and treatment facilities.[2] In Nigeria, schools have added cancer awareness to the health curriculum.[19]

with fewer false-positives and fewer non-invasive tumors of uncertain importance.[17,23] CBE also is less expensive, does not require equipment, and can be performed by nurses and other primary health workers.[17,37] Given the lack of data regarding the efficacy of CBE in reducing mortality, however, countries deciding to introduce it as their primary screening method are urged to closely evaluate its effect on mortality over time.

In Ukraine, where breast cancer incidence rates are moderate, an analysis found that mammography would cost four to six times more per breast cancer case detected than CBE—and this included only the recurrent costs of labor and supplies.[37] The disparity would be even wider if the up-front costs of training and machinery were included. Therefore, a screening system based on annual CBE beginning at age 35 was recommended. A similar screening program based on CBE has been employed in Japan since 1987.[25]

Improved treatment. Improved treatment of women who develop breast cancer also is essential to reducing breast cancer mortality. Along with mammography screening, advances in the treatment of breast cancer have fueled a sharp drop in breast cancer mortality over the past 15 years in the United States and the United Kingdom.[38,39]

Whether an abnormality is detected by the woman herself, a CBE, or a mammogram, further investigation is needed quickly. While mammography and ultrasound (a technique sometimes used to further pinpoint the location of a lump and guide biopsy) can be helpful, ultimately a pathologist will require a biopsy—either by needle or surgery—to examine the suspicious tissue and diagnose the disease.[40]

Treatment approaches can be fine-tuned by taking into account the stage of disease (see box on page 6), the tumor's histologic grade (that is, how closely it resembles normal cells under the microscope), hormone receptor status, proliferative capacity (or growth rate), and/or the presence of genes that favor growth and recurrence.

The treatment of breast cancer has expanded beyond surgery to a rapidly growing list of adjuvant therapies. These therapeutic changes are affected by an ongoing debate over whether breast cancer begins as a localized disease that can be cured by surgically removing the primary tumor, or whether it is a systemic disease that requires additional therapies even in early stages.[41] Today doctors routinely employ a combination of local treatments that remove or destroy cancer in the breast (such as surgery and radiation) and systemic treatments that

Does Mammography Reduce Breast Cancer Mortality?

From the 1960s through the 1980s, eight randomized clinical trials involving almost half a million women from Canada, Sweden, the United Kingdom, and the United States were conducted to test the impact of mammography screening on breast cancer mortality.[42] These trials found a 20- to 30-percent decrease in breast cancer mortality associated with routine mammography screening among women aged 50 to 69. A recent critical review of these trials has questioned this conclusion, however, pointing to methodological flaws and biases that may have distorted the data and their analysis.[43,44] Potential problems cited include inadequate randomization of study and control groups, unreliable assessments of cause of death, a bias in survival times due to early detection, and the detection and treatment of slow-growing cancers and benign abnormalities with good prognoses. After eliminating most of the original trials because of methodological flaws, and considering overall mortality instead of breast cancer mortality, these reviewers concluded that mammography screening has no benefit.[43,44]

The ensuing debate has prompted researchers to re-examine the evidence for mammography screening. After thoroughly reviewing the original clinical trials, two expert groups—the International Agency for Research on Cancer Working Group and the U.S. Preventive Services Task Force—have concluded that many of the criticisms are unfounded and that the evidence continues to support a significant decrease in breast cancer deaths associated with mammography screening among women 50 and older.[42,45] After concluding that the methodology was fundamentally sound, researchers also have extended the follow-up of the Swedish trials to nearly 16 years. Results show that mammography screening reduced breast cancer mortality among women aged 50 to 69 by 21 percent and overall mortality by 2 percent, and that the benefit persisted over the long term.[46] Heated discussion over the benefits of mammography continues, however, as scientists analyze all available data.

Others point to the potential harm caused by screening mammography. Of the approximately five percent of screening mammograms that are suspicious, more than 80 percent are false-positives that cause women anxiety and demand expensive follow-up procedures that are complicated and uncomfortable.[36] Furthermore, as is the case with all cancer screening programs, mammography may be identifying cancers that are unlikely to be life-threatening. Current medical technology cannot distinguish between harmful and harmless tumors in their early stages. Treating these non-invasive or slow-growing tumors absorbs resources and injures women without lowering mortality.[29,43] Finally, there is evidence that exposure to mammography radiation increases breast cancer risk, although it has been widely held that this small risk is greatly outweighed by the benefits of mammography screening.[35]

destroy or control cancer cells throughout the body (such as chemotherapy and hormonal therapy).

In recent years, doctors have shifted to more conservative, breast-conserving surgery that, in combination with radiotherapy, has proven to be as effective as more radical procedures but far less debilitating for women.[40] Instead of mastectomy, which removes the entire breast (and sometimes the chest muscles as well), surgeons may choose to perform lumpectomies or partial mastectomies that remove just the cancer and some surrounding tissue. Where radiotherapy is not available, however, breast-conserving surgery should not be undertaken. Axillary lymph node dissections, which remove all of the lymph nodes under the arm, remain the standard of care. They too are being challenged by a new, more conservative procedure called sentinel lymph node biopsy, in which a single lymph node is removed and tested to determine whether the cancer has spread; this procedure is not yet accepted as standard care, however.[47]

Adjuvant therapies are used to prevent recurrence of breast cancers and, more recently, to shrink large tumors before surgery.[47] Radiotherapy employs high-energy rays to destroy remaining cancer cells after surgery. While conventional radiotherapy relies on an external machine to generate the radiation, newer techniques implant radioactive materials in the breast. Chemotherapy involves administering combinations of drugs several times over a period of months, with breaks between treatments. Hormonal therapy, which is effective when tumors have estrogen or progesterone receptors, blocks the cancer from accessing the hormones that promote its growth. This kind of therapy may consist of drugs, such as tamoxifen and raloxifene, or the surgical removal of the ovaries.

After treatment, breast cancer patients need regular follow-up to manage the side effects of therapy, monitor the outcomes of treatment, and detect possible recurrences of cancer. Exercises and medication can ease some of the effects of surgery. Counseling and supportive care can help patients cope with common side effects of radiotherapy (fatigue and skin problems), chemotherapy (fatigue, nausea, hair loss, mouth sores, and infections) and hormonal therapy (hot flashes, vaginal discharge, and irregular periods). Annual mammograms and physical exams are important to monitor for recurrences, which are especially likely during the first two or three years.

Access to the diagnostic and treatment process outlined here generally is limited in low-resource countries. Outside the major cities, oncologists, radiologists, pathologists, trained technicians, equipment, and drugs often are in short supply.[15,18] This leaves most cases to general surgeons with limited training in breast cancer, who rely on mastectomies without adjuvant therapy.[5] Health workers also may lack training even in basic skills and knowledge. For example, hospital nurses caring for breast cancer patients in many settings may not know that they should avoid procedures such as taking blood pressures or drawing blood from the arm affected by lymphedema (fluid build-up) after surgery. They also may not know how to teach exercises that prevent lymphedema, manage patient pain, or mitigate the side effects of chemotherapy.[20]

To improve the quality of care and survival rates for breast cancer patients, health care systems with limited resources need to formulate evidence-based diagnostic and treatment plans and protocols that reflect the technical and financial resources available.[15,32] They often must make difficult but pragmatic choices. For example, chemotherapy and tamoxifen may be the mainstays of adjuvant therapy because they are easier to offer than radiotherapy, and chemotherapy may be limited to a few cost-effective drug combinations. Community-based trials and operational research in low-resource settings can help identify cost-effective, feasible diagnosis and treatment interventions and test the best ways to implement them.[15]

Keys to Improving Quality of Life

Inexpensive psychosocial support and palliative care can improve the quality of life for women with breast cancer and their families. From the moment women are diagnosed

Staging Breast Cancers

Doctors use TNM (primary **t**umor, regional lymph **n**odes, distant **m**etastasis) classification to assess a breast cancer patient's prognosis and help make treatment decisions. A growing body of literature suggests that progression of breast cancer may not be linear, however; research into the origins and pathways of the disease is ongoing.

Stage 0:	Carcinoma *in situ* (non-invasive cancer).
Stage I:	Tumor is small (2 cm or less), and cancer has not spread to the lymph nodes.
Stage II:	Tumor is small, but cancer has spread to the lymph nodes; OR tumor is moderate in size (2 to 5 cm), with or without lymph node involvement; OR tumor is large (over 5 cm), but cancer has not spread to the lymph nodes.
Stage III:	Tumor is large, and cancer has spread to the lymph nodes; OR tumor is of any size, but lymph node involvement is substantial; OR tumor is of any size, but cancer has spread to chest wall or skin.
Stage IV:	Cancer has metastasized beyond the underarm lymph nodes to other parts of the body.

with breast cancer, they face anxiety, loneliness, and depression.[48] Women worry about the stigma of disease, whether they will be able to continue caring for their families, and whether changes in their appearance will disrupt their intimate relationships. They may find support in individual counseling sessions, patient-education classes, peer support groups, or spiritual activities. These interventions can help women cope with the experience, reduce anxiety and feelings of isolation, increase their sense of control, provide positive role models, and instill a sense of hope. Equally important, these interventions can give women access to information about their condition, including treatments, prognosis, and self-care, which doctors often fail to explain.[49] Thus empowered, women can make informed decisions about their own treatment, and they can organize to advocate for better care and changes in public attitudes.[19]

Since 1988, for example, the Penang Breast Care Society of Malaysia has trained volunteers, usually breast cancer survivors themselves, to offer newly diagnosed women emotional support and practical advice.[50] The Society has also stocked a room in the local hospital with pamphlets and books on breast cancer, video cassettes on rehabilitation, and samples of wigs and breast prostheses. A similar organization in Costa Rica, Fundacion Nacional de Solidaridad Contra el Cancer de Mama (FUNDESO), organizes hospital visits after surgery, sponsors support groups, operates a shelter for women undergoing chemotherapy and radiotherapy who live at a distance from the city, and imports prostheses and special bras.[51]

While palliative care should be integrated with curative treatments throughout the course of the illness, it becomes paramount when women have advanced stages of breast cancer for which there is no cure. A key element of palliative care is relief of symptoms; women with breast cancer should have ready access to pain medications. Where available, chemotherapy may help control metastatic disease and improve the quality of life.[47] As the cancer progresses, women will need nursing care, typically provided by a woman's family. Palliative care should offer these family members practical advice and emotional support.

Conclusion

Despite the increasing incidence of breast cancer and corresponding increase in awareness, detection and treatment options are limited in low-resource settings. Where the incidence of breast cancer remains relatively low, decision-makers must carefully weigh the public health benefits of investing precious resources in screening and treatment programs against the costs and benefits of addressing other pressing health problems. Where the incidence of breast cancer is high, diagnostic tests and treatments must be accessible and affordable to women with symptoms. Providing psychosocial support and palliative care to women with breast cancer and their families is equally important.

Decision-makers must carefully weigh the costs and benefits of fighting breast cancer against competing health needs.

Only after diagnostic, treatment, and palliative services are in place should health care planners consider early detection programs. Mass media campaigns and health education activities are simple ways to raise awareness and encourage symptomatic women to seek medical care promptly. In contrast, mammography is costly and technically difficult to implement, and its benefits are relatively modest. Screening with clinical breast examination is more feasible in low-resource settings, but its benefits remain unproven. Countries, therefore, face difficult choices in determining whether and how to combat this disease, especially in regions where incidence is growing but resources are scarce.

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