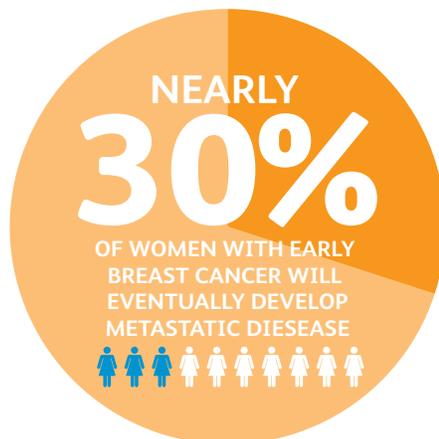


The Value of Medicine in Metastatic Breast Cancer (mBC)

With an estimated 1.7 million new cases each year, breast cancer is the most common cancer among women worldwide.¹ It is also the leading cause of cancer death among women, taking the lives of over 450,000 annually.² Metastatic breast cancer (mBC) occurs when the cancer spreads beyond the breast to other parts of the body.³ In addition to the patients who are diagnosed with metastatic disease at initial diagnosis, nearly 30 percent of women diagnosed with early breast cancer will eventually develop metastatic disease.⁴ Patients diagnosed with mBC today face a median survival (the time when half the patients are expected to be alive) of two to four years.⁵ The patient, family, health, and economic burdens of mBC are large. While mBC currently remains incurable,³ there's reason to be hopeful. Extensive drug development efforts are underway to address this high unmet need.

One Name, Many Diseases

Breast cancer is not just one disease, but a group of diseases characterized by different molecular subtypes. Biological markers such as the presence or absence of hormone receptors (HR) (i.e., estrogen receptor [ER] or progesterone receptor [PR]), and/or a protein known as human epidermal growth factor receptor 2 (HER2), help to classify the disease. These markers define disease subtypes that are also distinguishable by their risk factors, clinical behaviors, and responses to treatment.⁶ Hormone receptor positive (HR+) is the most common type of breast cancer, representing nearly two of every three breast cancer cases.⁷ Breast cancers that overexpress the HER2 protein (known as HER2+) tend to grow and spread more aggressively, and make up about 20 percent of cases.³ Another subtype that lacks receptors for estrogen and progesterone, and does not have an overexpression of the HER2 protein, is known as “triple negative” and represents between 10 and 20 percent of breast cancer cases.⁸



KEY TAKEAWAYS

Breast cancer is the most common cancer in women worldwide.⁵

The global impact of breast cancer due to disability and premature deaths, not including medical costs, was estimated to be \$88 billion (2008 USD).¹⁷

Nearly 30 percent of women diagnosed with early breast cancer will eventually develop metastatic disease.⁴

Nearly 2 out of 3 breast cancer cases are hormone receptor (HR) positive.⁷

For ER+/HER2-, no significant advance in the first-line treatment setting has been seen in more than a decade.

Hope exists as efforts to develop newer, more effective treatments continue.

Adapted from: O'Shaughnessy J. (2005) Extending survival with chemotherapy in metastatic breast cancer. *The Oncologist*. 2005;10:20:20-29

HORMONE RECEPTOR POSITIVE (HR+) IS THE MOST COMMON TYPE OF BREAST CANCER, REPRESENTING



Adapted from: American Cancer Society. (2014). Hormone therapy for breast cancer. *Breast Cancer*.

Breast cancer is also classified by stage – a way of describing the tumor’s location, extent of spread, and its effect on other organs in the body. Outcomes strongly correspond to the extent to which the cancer spreads to other areas within the breast, to nearby lymph nodes, or to distant organs.⁶ Patients whose cancer has not spread (stage I) have an approximate 98 percent five-year survival rate. Indeed, strides made in early detection, research, and treatment have transformed early breast cancer into a manageable condition marked by low mortality rates.⁹ However, for mBC patients (stage IV), the five-year survival rate is only around 22 percent.¹⁰

Key Facts and Figures

- Breast cancer is the most common cancer in women worldwide. It is also the principal cause of death from cancer among women globally; in 2012, there were 6.3 million women alive worldwide who had been diagnosed with breast cancer in the previous five years.¹¹
- In the United States, mBC is the second leading cause of cancer death among women with 40,000 dying each year;¹² at any given time, an estimated 150,000–250,000 people are currently living with metastatic breast cancer.¹³
- In Europe, breast cancer is the most common cancer for females and the most common cancer overall, with more than 464,000 new cases diagnosed in 2012;¹⁴ for mBC, the age-standardized incidence and mortality was 62.8 per 100,000 and 16.7 per 100,000, respectively, in 2008.¹⁵
- In Latin America, breast cancer is the most frequent cancer among women, with about 150,000 new cases, accounting

for 30 percent of cancers diagnosed in 2012;¹ and in countries such as Peru, Colombia, and Mexico, approximately 50 percent of detected breast cancer cases occur in stage III or higher.¹⁶

- In the United Kingdom, age-specific incidence rates rise steeply from around 30–34, level off for women in their 50s, and then rise further to age 65–69. Rates drop slightly for women aged 70–74 and then increase steadily to reach an overall peak in the 85+ age group.¹⁴
- Globally, 1 in 3 women (33 percent) diagnosed with breast cancer were estimated to be under 50 at the time of diagnosis during 2008, compared to 42 percent throughout the Asia-Pacific region and 47 percent within the sub region of South-Eastern Asia. The proportion of female breast cancers that were diagnosed among women less than 50 years of age ranged from 21 percent in Australia to 55 percent in South Korea and Laos, and 58 percent in Vanuatu and Papua New Guinea.¹⁷
- Significant increases in breast cancer incidence in recent years were observed in several Asian countries with incidence rates increasing by 3 to 4 percent per year in China (Shanghai), Singapore, and Thailand. The largest rise was reported in Japan, where significant increases from 1980 onward culminated in an average increase of 6 percent per year between 1999 and 2008.¹⁷
- It is estimated that between 6 and 10 percent of U.S. patients present with primary metastatic disease at the time of diagnosis, according to the American Cancer Society.¹⁸

IN 2012, THERE WERE



ALIVE WORLDWIDE WHO HAD BEEN DIAGNOSED WITH BREAST CANCER IN THE PREVIOUS 5 YEARS.

Adapted from: International Agency for Research on Cancer (IARC). (2013). Press Release No. 223. Latest world cancer statistics. Global cancer burden rises to 14.1 million new cases in 2012: Marked increase in breast cancers must be addressed. *World Health Organization*.

Economic Impact

When it comes to breast cancer, improvements to the economic situation for patients and society are in need. The total global impact of cancer due to disability and premature death, not including medical costs, was estimated to be \$895 billion (2008 U.S. dollars). This is the equivalent of 1.5 percent of worldwide GDP. Breast cancer is responsible for 10 percent (\$88 billion) of that global economic impact based on disability-adjusted life years (DALYs) and is the third most costly type of cancer using this metric, following lung cancer (\$188 billion) and colorectal cancer (\$99 billion).¹⁹ Below are some indirect costs associated with breast cancer.

THE GLOBAL ECONOMIC IMPACT of Breast Cancer due to disability and premature death



Adapted from: American Cancer Society. (2010). The global economic cost of cancer. American Cancer Society. Assessed on Sept. 12, 2014 at <http://www.cancer.org/acs/groups/content/@internationalaffairs/documents/document/acspc-026203.pdf>

All Stages of Breast Cancer

- For all stages of breast cancer, annual productivity loss due to premature death was projected at \$5.49 billion in the U.S.²⁰ and €3.3 billion in the European Union.²¹
- In the EU, indirect costs of morbidity, mortality, and informal care represent 55 percent or €8.3 billion of the €15 billion total annual cost of breast cancer (2009 euros).²¹

Metastatic Breast Cancer

- In the U.S., annual indirect cost to society attributable to mBC for women under 65 was estimated to be over \$572 million, which included approximately \$270 million, \$253 million, and \$50 million from premature deaths, lost productivity, and caregiving, respectively; lost productivity costs alone were estimated at \$21,153 per patient-year (2010 U.S. dollars).²²

- In Canada, patients with mBC reported that living with their disease greatly impacted their capacity to work (44 percent) and their ability to exercise (23 percent).²³

Valuing the Gains of Improved Health

While the five-year survival rate for breast cancer has increased from 60 percent (in the 1950s) to 90 percent (from 1996 to 2004), and the share of life-expectancy gain from 1990 to 2000 due to improved treatments was 92 percent,²⁴ there remains a strong need for more effective treatments for those patients with mBC.

When it comes to what patients themselves value, studies have shown that treatments for metastatic cancer are more valued by patients than treatments for less advanced cases; that was true even where the value to patients in purely objective terms, such as life years gained, were the same.²⁵ This complements other research that shows that people value treatments more if they are aimed at conditions that have no alternative treatment compared to conditions for which there are current treatment options,²⁶ again, even where the value is objectively the same. Even to the extent that in theory, such treatments would show value to society if their effectiveness was still unproven using gold standards of evidence.²⁷

Improvements in cancer survival between 1988 and 2000 were estimated to have created 23 million additional life years and roughly \$1.9 trillion of additional social value. In one study, the return on investment from innovations in breast cancer treatment (based on gains in quality-adjusted life years) ranged from 112 to 3,681 percent, depending on treatment.²⁸ In another study, estimates comparing the cost of cancer care and the social value of survival gains from that care suggest that from 1990 to 2000, there was a net social surplus of \$1.9 trillion in the U.S. alone.²⁹ In other words, the value of the cancer treatments greatly outweighed their costs. In the same study, for breast cancer alone, 87 percent of those survival gains were because of advances in treatment; the social value from those gains were estimated to be worth \$443 billion.

These analyses help to illuminate the value already created by medicines, not just for the individual breast cancer patient but for society as well. They also shed light on the needs of patients and what is valuable to them. When we consider the high level of unmet need and the enormous burdens associated with mBC, improved health outcomes for mBC patients through advancements in new treatments or by other health technologies would go a long way in returning even more value to patients and society.

Patient Perspectives – A Stronger Voice Needed for Metastatic Breast Cancer

There are distinct challenges facing patients living with metastatic breast cancer compared to those with early breast cancer. For one, mBC patients undergo continual treatment and live with the pervasive sense of limited time. That emotional toll can be profound and can affect the ways people feel about themselves, communicate with others, and live their lives.³⁰ In a recent global metastatic breast cancer survey known as BRIDGE – Bridging Gaps, Expanding Outreach – 38 percent of women surveyed reported being afraid to talk openly about mBC, and 48 percent said their friends and family were uneasy talking about the disease. Furthermore, 52 percent of respondents reported that their condition receives too little public attention.³¹ A stronger voice for the mBC patient is needed that can move beyond a discussion of early detection and prevention, to a point where all people living with breast cancer, regardless of stage, can feel equally embraced.

“Metastatic breast cancer patients have unique needs that have to be realized not only by the patient, but by society as a whole, including the patient’s caregiver, family, co-workers, friends, and support network.”

– Lillie Shockney, RN, *Administrative Director*
Johns Hopkins Breast Cancer Center

“The mental demands facing metastatic patients are significant. Our need for support and encouragement never ends because we will always be in treatment.”

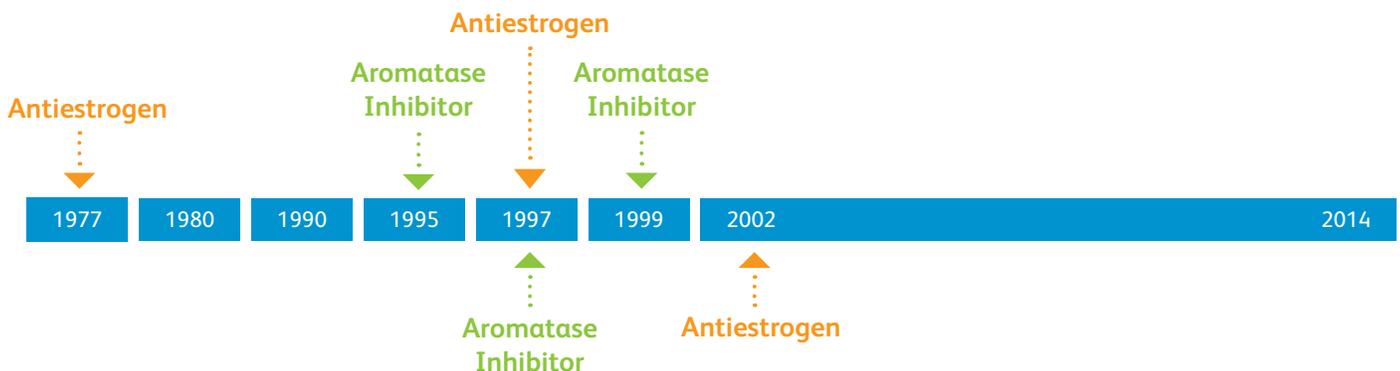
– Shirley Mertz, *President*
Metastatic Breast Cancer Network and metastatic breast cancer patient

Value of Targeted and Combination Therapies

Systemic therapy (treatment that travels through the bloodstream) is the main treatment option for mBC patients, whom surgery is unlikely to benefit. This includes chemotherapy, hormone therapy, and the targeted therapies.⁶ Over the years, clinical researchers have leveraged the insights gained from a greater understanding of cancer. As a result, combinations of systemic treatments have played an important role in improving outcomes for some mBC patients.

The identification of molecular and genomic alterations that contribute to cancer has facilitated the development of the targeted therapies. Used in combination with other treatments, significant survival improvements have occurred in a subset of mBC patients, due to the availability of these agents designed to specifically affect tumor growth for that particular breast cancer subtype. In one study, a targeted therapy was associated with a 33 percent reduction in the risk of death for HER2 positive mBC patients.³² These treatment advances are a welcome development, but the prognosis still remains unacceptably low for the majority of mBC patients.

TIMELINE OF FDA APPROVALS OF COMMON FIRST-LINE ER+ MBC TREATMENTS



Many recent benefits have affected a small subset of patients, the HER2+ population. There have been no innovative treatments in the first-line treatment setting for the largest subset of patients, ER+/HER2-, in more than a decade. Clearly, more effective treatments are needed for these patients.

Clinical research continues to inform the most optimal choice of treatment, and its timing and duration, for all types of cancers. Today, a substantial effort in finding newer treatments in mBC is well underway. Treating breast cancer based on hormone receptor and HER2 status has proven to be an effective strategy. Building on those advances, innovative compounds are currently being developed for potential use in combination with existing standards of care treatment for more mBC patients. For instance, a number of pharmaceutical companies are developing compounds called cyclin-dependent kinases 4 and 6 (or CDK 4/6) inhibitors that possess unique mechanisms of action that target a process that drives cell division. These compounds are being studied in a variety of cancers, including mBC.³³

Summary

There has been considerable progress in the detection, research, and treatment for breast cancer over the past few decades. While the gains in survival have mostly benefited patients with early stage breast cancer, for later stage breast cancer patients the story is quite different. More effective treatments are needed for the majority of mBC patients. In 2012, there were 6.3 million women alive worldwide who had been diagnosed with breast cancer in the previous five years,¹¹ and a metastatic breast cancer diagnosis will be made for a good proportion of them. The median survival following a diagnosis of mBC is around two to four years and is associated with significant humanistic burdens, including difficult physical symptoms, and emotional distress.⁵

The prognosis of metastatic breast cancer not only affects all women and men living with breast cancer, but also their caregivers, family members, and the health care system overall, who will bear mBC's significant socioeconomic toll. Considering the high degree of unmet need in mBC, the ongoing research for innovative treatments represents hope for many patients, their clinicians, and all those affected by this disease.

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