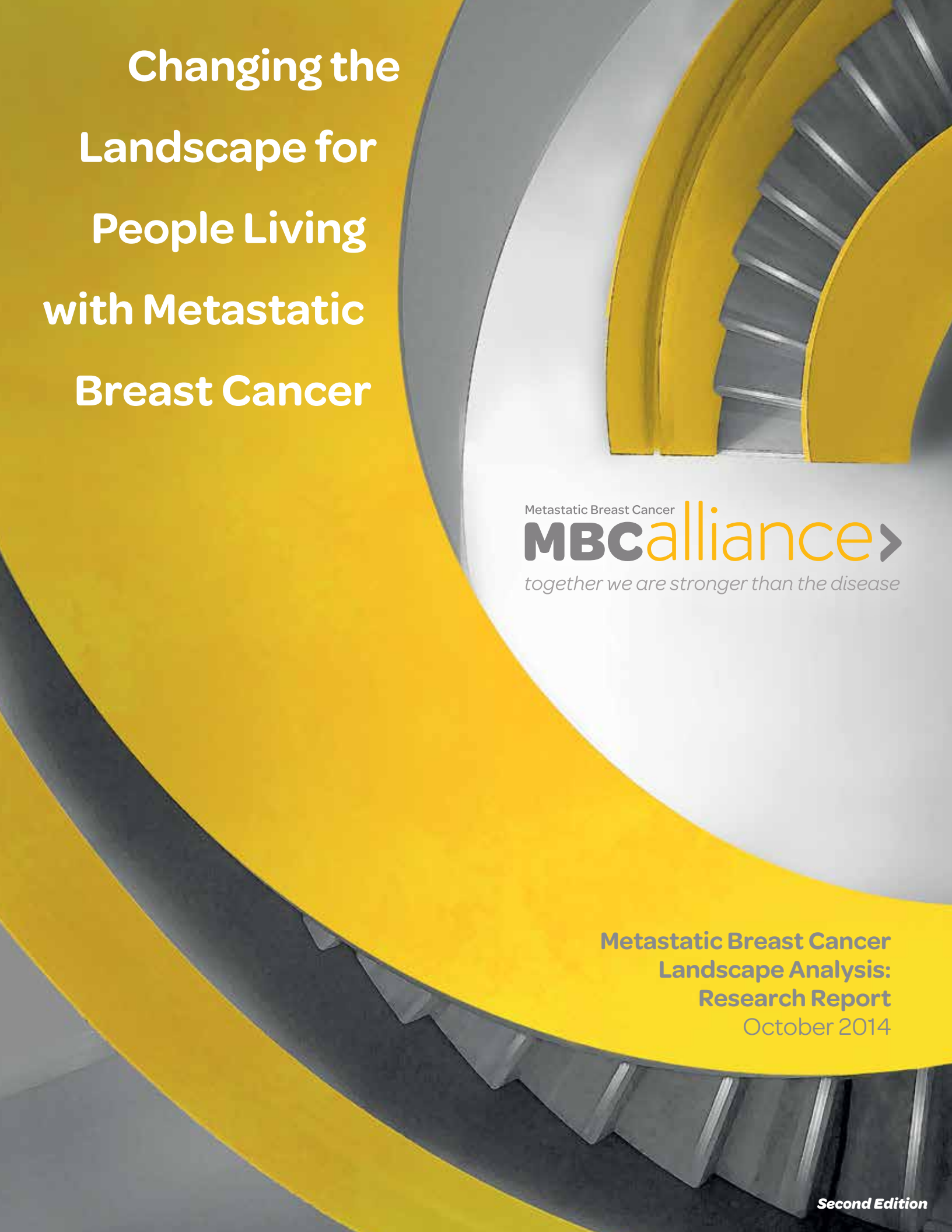
Changing the Landscape for People Living with Metastatic Breast Cancer



Metastatic Breast Cancer
MBCalliance
together we are stronger than the disease

Metastatic Breast Cancer Landscape Analysis: Research Report
October 2014

Second Edition

MBC Alliance members:

From bottom right: Katherine Crawford-Gray, MBC Alliance Project Director; Christine Benjamin, SHARE; Elly Cohen, BreastCancerTrials.org; Jo Dulay, Genentech; Janine Guglielmino, Living Beyond Breast Cancer; Jane Levy, Cancer*Care*; Elyse Spatz Caplan, Novartis Oncology; Michael Zincone, Pfizer; Musa Mayer, AdvancedBC.org; Julissa Viana, Cara Thompson, Celgene Corporation; Margaret (Peg) Mastrianni, Breast Cancer Research Foundation; Christine Wilson, Triple Negative Breast Cancer Foundation; Shirley Mertz, Metastatic Breast Cancer Network, Stacy Lewis, Young Survival Coalition; Katherine O'Brien, Virginia (Ginny) Knackmuhs, Metastatic Breast Cancer Network; Megan McCann, Young Survival Coalition; Catherine Ormerod, Living Beyond Breast Cancer; Lisa Schlager, Facing Our Risk of Cancer Empowered (FORCE); Kimberly Sabelko, Susan G. Komen; Marc Hurlbert, Avon Foundation for Women; Virginia (Ginny) Mason, Inflammatory Breast Cancer Research Foundation; Hayley Dinerman, Triple Negative Breast Cancer Foundation; Diane Rose, FORCE; Susan Brown, Susan G. Komen; Allison Harvey, Cancer Support Community; Stephanie Reffey, Susan G. Komen; Kerry Gruninger, SHARE; Jane Perlmutter, Consultant; Amy Bonoff, Dr. Susan Love Research Foundation

Photographer: Yasmeen Anderson Photography

Members absent from photo as of March 2014:
Christine Verini, Eisai; Kelly P. Hodges , Sisters Network® Inc.; Hope Wohl, Breastcancer.org; Elda Railey, Mary Lou Smith, Research Advocacy Network

Metastatic Breast Cancer

MBCalliance

together we are stronger than the disease

Our Vision

MBC Alliance members are driven by a vision to transform and improve the lives of people living with metastatic breast cancer.

Our Mission

The MBC Alliance unifies the efforts of its members to improve the lives of and outcomes for those living with metastatic breast cancer and their families through increasing awareness and education about the disease and advancing policy and strategic coordination of research funding specifically focused on metastasis that has the potential to extend life, enhance quality of life, and ultimately to cure.

AdvancedBC.org

Cancer Action Network

AVON Foundation for Women

BREASTCANCER.ORG
REAL. ANSWERS.

BCRF

BreastCancerTrials.org
find a trial that's right for you

CANCERcare

CANCER SUPPORT COMMUNITY

Celgene

Dr. Susan Love RESEARCH FOUNDATION

Eisai

Lilly | ONCOLOGY

FORCE EMPOWERED

Genentech

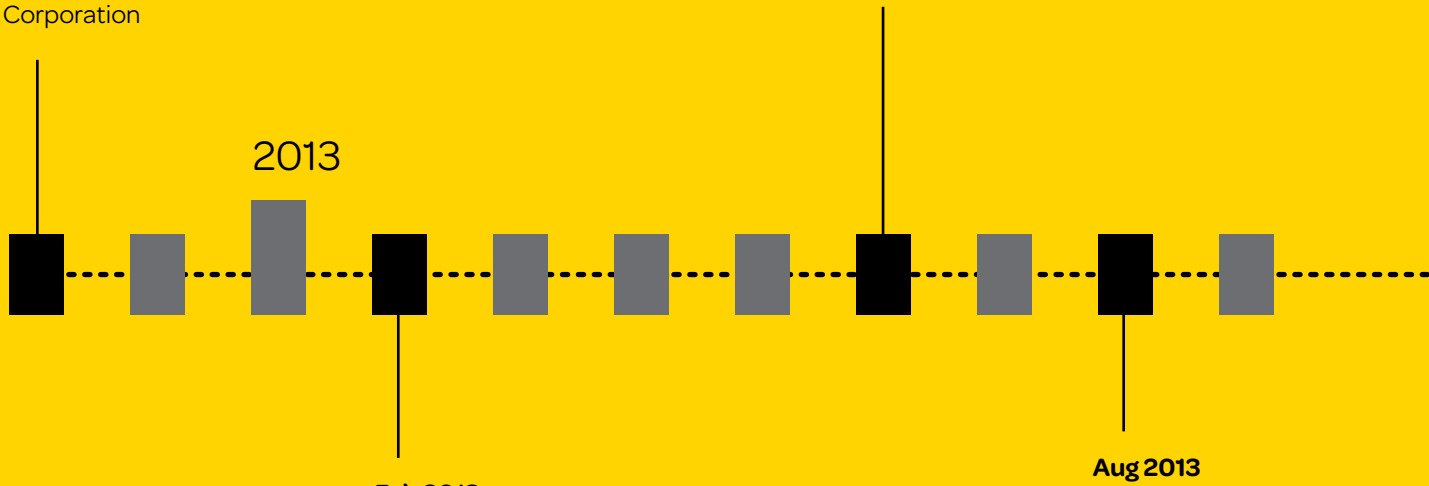
INFLAMMATORY BREAST CANCER


Eli Lilly
Inflammatory
Breast Cancer
Research Foundation
Breastcancer.org
Living Beyond
Breast Cancer
Celgene Corporation
Eisai
Novartis Oncology
Sharsheret
Triple Negative Breast Cancer Foundation
ACS CAN
Cancer Support Community
Nueva Vida
AdvancedBC.org
Avon Foundation for Women
Breast Cancer Research Foundation
CancerCare
Metastatic Breast Cancer Network
Pfizer
SHARE
Young Survival Coalition
Patient
Advocate
Foundation
FORCE

MBC Alliance

Nov 2012

Breast cancer nonprofits join MBC advocates to discuss how to increase MBC awareness and improve the lives of people living with MBC; all agree that through collaboration, far more can be achieved than by individual organizations; MBC Alliance is formed with support from Celgene Corporation



Feb 2013

Early members are AdvancedBC.org, Cancer Support Community, FORCE, Living Beyond Breast Cancer, Metastatic Breast Cancer Network, Research Advocacy Network, SHARE, Susan G. Komen, Triple Negative Breast Cancer Foundation, and Young Survival Coalition

Jun 2013

Mission and goals are adopted; governance approaches are considered; landscape analysis is identified as first initiative; Breastcancer.org, Breast Cancer Research Foundation, Genentech, and Pfizer join

Aug 2013

Avon Foundation for Women becomes the Alliance's administrative home with Dr. Marc Hurlbert as project leader

Oct 2013

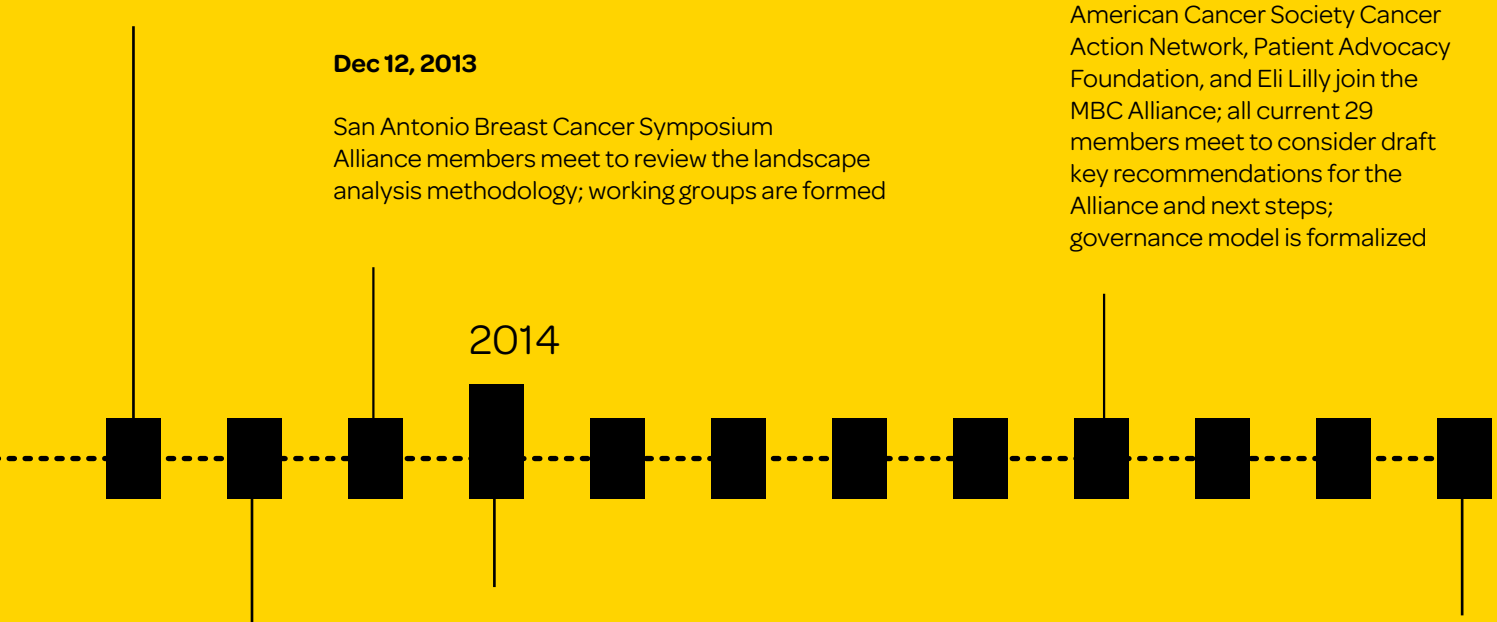
MBC Alliance launches on National Metastatic Breast Cancer Awareness Day; members now include Cancer*Care*, Dr. Susan Love Research Foundation, Sisters Network Inc., Eisai and Novartis

Dec 12, 2013

San Antonio Breast Cancer Symposium Alliance members meet to review the landscape analysis methodology; working groups are formed

Jun - Aug 2014

American Cancer Society Cancer Action Network, Patient Advocacy Foundation, and Eli Lilly join the MBC Alliance; all current 29 members meet to consider draft key recommendations for the Alliance and next steps; governance model is formalized



Jan - May 2014

Landscape analysis work continues; membership reaches 26 with the addition of BreastCancerTrials.org, Inflammatory Breast Cancer Research Foundation, Nueva Vida, Sharsheret, and Triple Step Toward the Cure

Oct 2014

Results of the landscape analysis are released along with actions for the MBC Alliance through 2016

Nov 2013

MBC Alliance project director is appointed; work begins on the landscape analysis; all members meet for the first time

Acronyms and Other Terms

advanced breast cancer	includes both metastatic breast cancer and locally advanced breast cancer (stage III) and locally recurrent breast cancer
Akt	a serine/threonine-specific protein kinase
BRCA mutation	mutation in the tumor-suppressor gene *BRCA1* or *BRCA2,* associated with hereditary breast cancer
CSO	Common Scientific Outline (www.icrpartnership.org/CSO.cfm)
de novo MBC	breast cancer that is metastatic at the time of *first* diagnosis
ER–	estrogen receptor negative/hormone insensitive breast cancer
ER+	estrogen receptor positive/hormone sensitive breast cancer
ErbB	epidermal growth factor receptor (protein family)
gHRAsp	Grants in the Health Research Alliance Shared Portfolio (www.ghrasp.org),
HCPs	HCPs
HER2	human epidermal growth factor receptor 2
hormone-sensitive MBC	MBC where tumor growth is promoted by estrogen and/or progesterone
HRA	Health Research Alliance
ICRP	International Cancer Research Partnership
incidence	Rate of occurrence of new cases in the population (measure risk of developing a disease)
IOM	Institute of Medicine
KOL	key opinion leader
MBC	metastatic breast cancer
MBC Alliance	Metastatic Breast Cancer Alliance (also called the Alliance)
mTOR	mechanistic target of rapamycin (serine/threonine protein kinase)
NCI	National Cancer Institute
PDQ	Physician Data Query
PI3K	phosphatidylinositide 3-kinase
prevalence	proportion of cases in the population (measures how widespread the disease is)
RECIST	Response Evaluation Criteria in Solid Tumors
SEER	Surveillance, Epidemiology, and End Results program of the National Cancer Institute (NCI)
stage IV breast cancer	another term for metastatic breast cancer
TBCRC	Translational Breast Cancer Research Consortium
TN MBC	triple-negative (hormone insensitive and HER2-negative) metastatic breast cancer
TNBC	triple-negative (hormone insensitive) breast cancer
US	United States


5

Chapter 5: Epidemiology of MBC—Challenges with Population-Based Statistics

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Abstract

To advocate most effectively for a population of patients, they must be accurately described and the course of the disease must be well characterized. Accurate epidemiologic statistics are currently lacking for the MBC population. ***Methods:*** We reviewed the availability of epidemiologic data related to MBC and the nature of those data. ***Results:*** The NCI SEER registries collect only incidence at first diagnosis, initial treatment, and mortality. Recurrent cancer is not tracked; the data on MBC are limited. While creative methods have been used to estimate the number of new cases of MBC and the number of those currently living with the disease, more accurate estimates of MBC incidence and prevalence do not currently exist. The modest increase in duration of MBC survival that has been documented over the past few decades has been observed primarily in ER+ and/or HER2+ MBC and appears to be attributable to the wide use of targeted therapies. During this time frame, the disparity between survival among black women with MBC and non-Hispanic white women with MBC has been increasing. ***Conclusions:*** Accurate epidemiologic information is needed to accurately and effectively demonstrate the need for services and plan and fund the application of services.

To advocate for a population of patients, they must be accurately described and the course of the disease must be well characterized.

Why Do Accurate Statistics Matter?

To advocate most effectively for a population of patients, they must be accurately described and the course of the disease must be well characterized. Accurate epidemiologic statistics are currently lacking for the MBC population.

Epidemiologic studies are needed to inform discussions about the size and characteristics of the MBC patient population as well as the numbers and types of resources and services needed. A true picture of the number of new cases each year and the number of people living with MBC could encourage drug development. Studies should also include analysis of trends in incidence and length of survival for future planning and investigations of the natural history of MBC to allow for evaluation of the impact of new interventions.

Of particular concern for advocates is having a realistic picture of the impact of emerging research on the issues that matter most to patients. For example, new drugs for MBC represent a source of hope that patients can live longer or even be cured. But do these drugs actually extend life or just increase health care costs? Do they improve quality of life?

Other related research questions include: How many new cases of MBC are diagnosed each year? How representative of the whole MBC population are patients in clinical trials? Does delaying cancer progression mean that overall survival is improved? What problems do MBC patients have with obtaining treatment, given existing co-payment and treatment access programs, and what impact does this have on MBC survival? Currently there are no population-based data-collection systems that can answer these questions.

Data from the NCI SEER Registries

Since 1973, the SEER registries of the NCI have been collecting population-based information on cancer cases and the initial course of treatment. These registries include 9 states, 5 metropolitan areas, and the Alaskan Native Tumor Registry. Together they represent about 28% of the entire US population, broadened in the past 20 years to offer a truly representative cross-section of the country with regard to our ethnic, immigrant, racial, educational, and socioeconomic diversity. Analyzing SEER data enables researchers and policy makers to monitor cancer trends and gather data on incidence, the extent of disease at diagnosis, initial therapy, mortality, and survival.

An estimated 3.1 million women in the US have a history of invasive breast cancer. We have no way of knowing how many of these people are actually living with MBC.

Unfortunately, because only incidence, initial treatment, and mortality are captured in the SEER registries, and recurrent cancer is not tracked, the data on all metastatic cancers, including MBC are limited.

Incidence

The actual number of new cases of MBC diagnosed each year is unknown. This is because SEER only records the 5% of newly diagnosed breast cancer patients who have de novo MBC. However, most patients with MBC were first diagnosed at earlier stages of breast cancer that then recurs, months to years later[30]. An estimated 20% to 30% of early stage breast cancer patients will develop MBC sooner or later. The SEER registries do not capture this much larger percentage. As a result, the actual annual incidence of MBC remains unknown.

Prevalence

The prevalence of breast cancer is increasing. Today, an estimated 3.1 million women living in the US already have a history of invasive breast cancer, and in 2014, an estimated 232,670 women will be newly diagnosed [99]. However, we have no way of knowing how many of these people are actually living with MBC as a chronic, progressive, and ultimately fatal disease or how many are "cured" of the disease, meaning they will go on to die of other causes. After early stage breast cancer is treated, it can lie dormant for as many as 20 or more years, with no way of determining whether it is actually cured or in a temporary state where there is "no evidence of disease." This complicates the already challenging assessment of MBC prevalence. Neither the total number of people living with MBC nor its burden in society can currently be determined.

Creative methods have therefore been used to estimate the prevalence of MBC. The duration of survival of patients with MBC (itself an estimate based on data from clinical trials involving highly selected patients), multiplied by the annual number of breast cancer deaths, has been used to approximate MBC prevalence. Estimating survival duration is complicated by significant variability related to the type of MBC and the treatment received. With good access to care and favorable tumor biology, some MBC patients can live for a decade or more. Using more sophisticated techniques, Australian biostatisticians have modeled the prevalence of MBC using the New South Wales cancer registry, estimating the prevalence as 3 to 4 times the number of annual deaths from breast cancer[100]. This approach is based on the fact that at least 90% of breast cancer deaths occur as a result of complications related to MBC.

Treatment Options

In large part, MBC remains incurable because the cancer is able to acquire resistance to each treatment given, as mutations occur and some cancer cells die but other more deadly ones remain and reproduce. Thus, MBC is controlled through the use of sequential "lines" of treatment that work in different ways.

Targeted therapies focus on genes that play dominant "driver" roles in the growth of ER+ and/or HER2+ MBC. Use of drugs that successfully target these key drivers controls cancer growth and extends survival. Sooner or later, however, MBC almost always acquires resistance to a given treatment, and a treatment change is necessary. Beyond tamoxifen, aromatase inhibitors (Arimidex, Femara and Aromasin) and fulvestrant (Faslodex) have offered further lines of treatment for MBC patients with ER+ disease. Trastuzumab (Herceptin) has slowed the spread of this aggressive form of MBC in the 25% of patients whose cancer is HER2+. Continued use of drugs targeting HER2 throughout treatment results in better control of HER2+ MBC. Newer agents targeting the HER2 pathway need to be studied further but may extend survival, as indicated in a recent small study showing a median survival of 45 months in patients with HER2+ MBC [101].

It's important to ask whether all MBC patients whose cancers are ER+ and/or HER2+ have equal access to the multiple lines of expensive targeted treatments appropriate for their subtypes and to the supportive follow-up care now considered standard that can greatly improve quality of life. Cytotoxic chemotherapies in combination with HER2-directed treatments are important to those patients with HER2+ breast cancer. Chemotherapy is the sole effective approach so far in triple-negative (TN) MBC treatment. Over the past 2 decades, newer chemotherapy agents have undergone reformulation and refinement to improve tolerability and therefore improve quality of life as well, even if they do not significantly extend survival. Improved tolerability is especially important for patients with TN MBC, for whom chemotherapy remains the only treatment option. These kinds of quality of life improvements are not reflected in studies that look at survival alone..

Survival

It has been suggested that outcomes of those with de novo MBC could be used to model duration of survival for all patients with MBC, because mortality data for de novo MBC patients are captured in the SEER registries.

However, de novo MBC patients are not necessarily representative of the entire MBC population. This is shown in a study[102] comparing the outcomes of de novo and recurrent MBC patients by analyzing an MD Anderson Cancer Center database of MBC patients who received chemotherapy from 1992 to 2007. Overall, patients with recurrent MBC had a 1.75 increased risk of death (median survival, 27 months) compared with de novo MBC patients (median survival, 39 months). In the recurrent MBC group, several factors predicted longer survival: initial diagnosis at stage I, presence of HER2+ disease, low-grade tumors, no prior chemotherapy, and a longer disease-free interval after adjuvant treatment. It should be noted that survival was longer for patients who were white (vs. other race or ethnic group), premenopausal (vs. postmenopausal), had ER+ MBC (vs. other types), or had only 1 (vs. >1) bone metastasis.

One reason for the difference in survival may be that the patients with de novo MBC had not been exposed to any breast cancer treatments at the time of diagnosis, and consequently had not acquired resistance to therapy, leading to better and longer responses to treatment as compared with the recurrent MBC patients.

Survival Benefit of New Treatments

It is generally believed that, as new treatments have been introduced for MBC, the duration of survival in the MBC population has increased. A number of studies have examined this hypothesis, with data from 1975 through 2008. Some studies have involved de novo cases from SEER and other registries; others, hospital-based populations with available recurrence and outcome data. Typically, the studies have examined successive periods over a number of years to see whether duration of survival has improved over time (see **Table 8**).

Over the past few decades, the duration of survival after a diagnosis of MBC has increased modestly—by months, not years.

Dawood et al. examined survival among more than 15,000 patients with de novo MBC in the SEER registries from 1988 to 2003[103]. They found modestly improved median survival over time (from 20 months to 27 months) among non-Hispanic white women, but not in black women, whose median survival remained constant at 17 months. SEER data for many types of cancer have revealed disparities between non-Hispanic white and black populations.

Chia et al. examined data for 2150 MBC patients referred to the British Columbia Cancer Agency from 1991 through 2001, a decade during which 7 new MBC treatments became available in Canada[104]. At the earliest time point, median survival was only 14 months, but it increased to 22 months by the end of the decade.

Giordano et al.[105] analyzed data from the MD Anderson Cancer Center database for patients with recurrent breast cancer from 1974 to 2000. The median survival was 15 months for the earliest cohort to 58 months for the most recent cohort. However, the sample included women with locally advanced recurrence, which has a better prognosis than distant metastatic disease.

Ruiterkamp et al. studied 8000 patients with de novo MBC in the Netherlands Cancer Registry diagnosed between 1995 and 2008, finding an improvement in median survival from 17 to 23 months, with the largest increase occurring among patients under 50 years of age[106]. An earlier (2007) population-based study in northern Holland by Ernst et al.[107] found similar results: an increase in median survival from 18 months in 1975 to 21 months in 2002.

Finally, Andre et al.[108] analyzed 724 consecutively enrolled patients with de novo MBC, from 3 French cancer centers, diagnosed between 1987 and 2000. Overall, the median survival improved over time from 23 to 29 months. Among patients with ER+ MBC, median survival improved from 28 months to 45 months, whereas patients with hormone-insensitive MBC (TNBC or ER– MBC), median survival was unchanged.

The apparent lack of a survival benefit seen in the Andre et al. study with the use of new cytotoxic chemotherapy agents in TN or ER– MBC was confirmed by Pal et al., who analyzed 274 patients with de novo MBC patients in the City of Hope, California, registry between 1985 and 2004, to ascertain the possible contribution of newer chemotherapy agents[109]. The authors concluded that, although overall survival had improved slightly over 20 years, "the contribution of conventional cytotoxic agents to this improvement is minimal."

Overall, these studies suggest that improvements in survival duration are due to targeted treatments for hormonally sensitive and HER2+ breast cancers. Of note, the survival estimates in these studies could reflect not only evolution of available care but also changes in imaging, earlier detection of metastatic disease, and changes in the definition of distant metastases.

Table 8. Changes in Median Survival of MBC Over Time, According to Study

Authors, Year	Population	Database	Time Frame	Median Survival Change over Time
Dawood et al. 2008 [103]	>15,000 de novo MBC	NCI SEER Registries, US	1988–2003	▶ Increase from 20 months to 27 months among non-Hispanic white women ▶ No change (from 17 months) among black women
Chia et al. 2007 [104]	2150 MBC patients	British Columbia Cancer Agency, Canada	1991–2001	Increase from 14 months to 22 months
Giordano et al. 2004 [105]	834 patients with recurrent MBC*	MD Anderson Cancer Center, US	1974–2000	Increase from 15 months to 58 months
Ruiterkamp et al. 2011 [106]	8000 patients with de novo MBC	Netherlands Cancer Registry	1995–2008	Increase from 17 months to 23 months
Ernst et al. 2007 [107]	1089 patients with de novo MBC	South-East Netherlands Registry	1975–2002	Increase from 18 months to 21 months
Andre et al. 2004 [108]	724 patients with de novo MBC	3 French cancer centers	1987–2000	Increase from 23 to 29 months overall ▶ Increase from 28 months to 45 months among patients with ER+ MBC ▶ No change among those with ER– MBC

Abbreviations: ER = estrogen receptor, MBC = metastatic breast cancer, NCI = National Cancer Institute, SEER = Surveillance, Epidemiology, and End Results program, US = United States.

* Sample included patients with locally advanced relapse.

Disease-Free Interval

Patients with de novo MBC are used in studies of prognosis, despite the difficulty of extrapolating results from this population to the entire MBC population, because the disease-free interval—the time between the initial diagnosis and the metastatic diagnosis—doesn't exist in this subgroup and need not be considered. Because the length of time before breast cancer recurs has been confirmed as an independent predictive factor known to impact duration of survival, studies relying on these data can be misleading.

Tevaarwerk et al.[110] demonstrated the effect of the disease-free interval in their 2013 analysis of long-term patient outcomes across 11 phase 3 adjuvant chemotherapy trials completed by the Eastern Cooperative Oncology Group over approximately 30 years (1978–2010). In this study of 13,785 breast cancer patients who received adjuvant chemotherapy, 3447 patients (25%) developed distant MBC; the overall median survival after relapse was 20 months. The factor that best predicted duration of survival was disease-free interval, which was 2.44 times higher among patients with relapse 6 or more years after initial diagnosis as compared with those with relapse after 3 or fewer years. By contrast, TN or ER– tumors (vs. ER+ tumors), any involved lymph nodes (vs. none), and black race (vs. other) were much weaker (but statistically significant) predictors of survival.

Modest increase in survival has been observed mainly in ER+ and/or HER2+ MBC and is attributable to the wide use of targeted therapies. No survival benefit has been found in TN MBC.

In fact, when this study's results were stratified to take disease-free interval into account, the increased survival benefit over time all but disappeared—except among ER– MBC patients who had relapse within 5 years after adjuvant treatment. The exception was probably due to the approval of trastuzumab (Herceptin) in 1998.

Summary

Recent studies on duration of survival of de novo and recurrent MBC generally demonstrate 3 findings:

The disparity between survival among black women with MBC and non-Hispanic white women with MBC appears to be increasing as treatments improve.

- Over the past few decades, the duration of survival after metastatic diagnosis has increased modestly—by a matter of months, not years. Hospital-based studies generally report a larger survival benefit than population-based studies.
- The modest increase in survival has been observed mainly in ER+ and/or HER2+ MBC and is attributable to the wide use of targeted therapies. No survival benefit has been found in TN MBC.
- The disparity between survival among black women with MBC and non-Hispanic white women with MBC appears to be increasing. According to SEER data, non-Hispanic white patients with de novo MBC have a survival benefit that is not found in black patients. It is unclear how much of the observed disparity in outcome is related to access to care and related socioeconomic concerns and how much is related to the greater incidence of TN MBC among black women.

Conclusions

Information about the epidemiology of MBC is currently lacking.

- **Prevalence and incidence of MBC.** The prevalence and incidence of patients with MBC is unknown. Also unknown is whether the number of recurrent MBC patients is increasing, decreasing, or staying the same. Without this information, we cannot accurately and effectively demonstrate the need for services or plan and fund the application of services.
- **Disease course by population and MBC subtype.** Disease trajectories, outcomes, and patient experiences for the different subtypes of MBC have not been well characterized.
- **Impact of MBC treatment.** Many critical questions regarding the optimal treatment of MBC remain unresolved. It is imperative that the use, effectiveness, and impact of MBC treatments on the overall MBC population be understood.
- **Length and variability of MBC survival.** Despite existing research, we have no accurate estimate of how long MBC patients are likely to live. The factors underlying observed variability in median survival across studies are unknown. Among the potential factors are differences in access to newer drugs (especially targeted therapies) and multiple lines of treatment, access to careful follow-up and expert palliative care to preserve optimal quality of life, and the presence of co-morbidities.
- **MBC disparities.** Despite research demonstrating poorer outcomes for disadvantaged, underinsured populations overall, we don't know the true impact of socioeconomic factors on what treatment and care are available for MBC patients and, in turn, how this may affect duration of survival and quality of life.

For the past 30 years, the breast cancer community has been a leader in patient support, advocacy, and research. Advocates have a pivotal role to play in the planning and implementation of future research. The MBC Alliance can continue to lead the way by helping policy makers and other MBC stakeholders to establish the blueprints for collection of epidemiologic data that will allow patients with MBC to be followed, to be visible, and to finally count.

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