40 Years

of Breast Cancer

and predictions
for the future

by

Dr. Deborah Axelrod

DEDICATED EXPERIENCED SUPPORT
SHARE 40 YEARS
for women facing breast and ovarian cancers

I started medical school in 1978; that was 38 years ago. Though my training was in general surgery, I gravitated to endocrinology — and surgery involving thyroid, parathyroid, adrenals, pituitary and of course breast. If you think about it, the breast is chock full of hormones and the ultimate end endocrine organ.

When you are diagnosed with breast cancer, you don't need a hobby. Breast cancer will consume your thoughts, energies, plans and relationships. It's a full-time job and there's little time to do anything else but work towards amassing information and getting well. Our knowledge changes continually.

It has been a whirlwind of progress and not…..We still have to break very sad news to patients. Not everyone will survive.

Our understanding about breast cancer has evolved. Our treatments are different for different breast cancers. Although it may seem that two tumors are the same — same size, hormone positive and no lymph node involvement — these two women may have totally different diseases that will require drastically different treatments because their prognoses differ tremendously. We have learned much about how cancers behave differently yet on "face value" look the same.

In 1977, tamoxifen was approved for use in women with advanced breast cancer. In 1990, the FDA approved the use of tamoxifen to help prevent the recurrence of cancer in "node-negative" patients.

In 1985 an NIH Consensus development conference led to the following systemic treatment recommendations: (1) premenopausal women with positive nodes, regardless of hormone receptor status,

should be treated with combination chemotherapy (remember for a long time preceding these recommendations, single agent chemotherapy was the treatment of choice); (2) premenopausal women with negative nodes should generally not be offered adjuvant (chemo) therapy unless considered “high” risk; (3) postmenopausal women with positive nodes and hormone positive cancer should be offered tamoxifen as the treatment of choice; and (4) postmenopausal women with negative nodes regardless of hormone receptor levels should not be offered adjuvant therapy unless they are considered “high” risk, in which case adjuvant therapy could be considered.

Across the United States, the uptake of the 1985 recommendations for adjuvant therapy in women with node-positive disease was already high. It reached 80% in 1987.

Then in 1990, the NIH panel issued another consensus statement, this time recognizing the impact women had on insisting on local disease control with lumpectomy vs mastectomy and based on the maturation of the NSABP local trials. The panel took note of and recommended: (1) breast conservation treatment as an appropriate method of primary therapy for the majority of women with Stage I and II breast cancer and, in fact, preferable because of equivalent survival to total mastectomy with axillary dissection while preserving the breast; (2) there is clear evidence that the rate of local and distant recurrence is decreased by both adjuvant combination cytotoxic chemotherapy and by adjuvant tamoxifen; (3) the decision to use adjuvant treatment should follow a thorough discussion with the patient regarding the possible risks and toxicities of therapy and its impact on quality of life; and (4) patients with tumors less than or equal to one centimeter have an excellent prognosis and do not require adjuvant therapy outside the clinical trials.

The result was that the use of adjuvant therapy for node-negative disease which was slightly less than 13% in 1987 increased markedly to 57% by 1995.[1]

We started to see more public figures including politicians, actors and activists come out as “survivors.” The breast cancer political movement, embodied by the National Breast Cancer Coalition (NBCC) and spokesperson, Fran Visco, set out to deliver 175,000 letters to Congress and the President in October 1992 (“Do the Write Thing” campaign), representing one for each women diagnosed with breast cancer that year. The number ballooned to 600,000 letters. The women authoring the letters made demands. They demanded more research to end breast cancer, more money to be allocated for research and advocates to sit on the boards that decide the allocation of those funds. This was an extraordinary demonstration of grassroots power. The Department of Defense (DOD) Breast Cancer Research Program was established. Since that time, almost 3 billion dollars in federal funding has been earmarked for breast cancer research, not enough if you ask any of us.

The activist, founding feminist and beloved politician in New York, Bella Abzug (July 24, 1920 – March 31, 1998), said whether you are one-breasted or two-breasted, this is a two-fisted fight. She was a breast cancer survivor with lymphedema. I remember bringing bagels and coffee to her apartment and examining her edematous arm, which seemed to bother her the most about her treatment.

In the 70’s and 80’s, women would sign a standard pre-operative consent form for a surgical biopsy with an overnight stay and possible mastectomy. They would then be anesthetized and go into surgery not knowing whether they would wake with their breast intact, or completely removed in a far more aggressive surgical

procedure (mastectomy) than what women currently undergo. These one-step procedures would later be shunned as barbaric since a woman would go to sleep with two breasts and possibly wake to find they had only one breast, often with a seriously deformed chest wall. With the recognition that staged procedures would prepare a woman psychologically for the ultimate procedure, the two-staged procedure became the standard for surgical care with a biopsy, discussion of the results and next steps with the woman, then a mastectomy if needed. We have now come full circle – striving for a one-step procedure for the definitive surgical treatment of breast cancer.

The Hippocratic Oath, a 500 BC Greek text, was the first set of Western writings to deliver guidelines for the conduct of medical professionals. It advised containment and concealment of information given by physicians to their patients for their patients' own best care.[2] The rationale is a beneficence model of care—the doctor knows better than the patient, and therefore should direct the patient's care. The concept of "informed consent" was technically first used in the United States in a medical malpractice court case in 1957. It wasn't until the 1980's and 1990's, however, that women were advised of their choices and asked to make an "informed decision" about a health intervention based on a balanced discussion and dialogue with their doctor. Lee Miller from SHARE trumpeted the belief that the medical establishment and patients needed to communicate. Shared decision making, dialogues and balanced discussions were a product of her endeavors.

At the beginning of the millennium, women woke overnight to find that hormone replacement therapy (HRT) for symptoms of menopause was no longer recommended. The Women's Health Initiative (WHI) reported in several publications that for the 16,608 women in the study who took a combination of estrogen and progesterone, the risk of breast cancer increased by 26%, heart attack by 24% and stroke by 41%.[3] With the decline in HRT came

the decrease in the numbers of new hormone positive cancers diagnosed.

The US government immediately issued new guidelines stating that HRT is justified only while taking the patient's individual risk factors into consideration and should be prescribed at the lowest possible dose and for the shortest possible amount of time. For most physicians and patients, HRT was no longer considered a 'lifestyle' drug for women, but a choice that came with considerable risk. This potentially affected 50 million postmenopausal women in the US. I think that this report single handedly augured and presaged the power of the media to wreak havoc and cause mistrust in the community, creating fear and confusion in interpreting these results. Physicians had a hard time catching their breath counseling women about the study.

SHARE was the first group in the United States to offer peer-led support groups to women with breast and ovarian cancers. They served such diverse populations as Latinas, African Americans, lesbians and those with metastatic breast cancer. This at a time when these communities were at best marginalized and clearly had fewer resources and information than the mainstream population even when their cancers were more advanced.

We quoted Dr. David Spiegel a lot then particularly since he was doing groundbreaking research at Stanford and published a study in The Lancet which found that women who had metastatic breast cancer and were randomized to support groups lived 18 months longer than those who weren't in a support group. Spiegel started his research in the 1970s, when virtually no cancer patients were in support groups. His subsequent publication in 2007 failed to sustain that observation, but he concluded that psychosocial support and stress management to augment medical treatment improves cancer outcome and quality of life.

Though pink ribbons still abound, SHARE has remained grounded in providing hotline advice, support groups, workshops and programs that are always informative and not sugar coated. SHARE is always well represented at national organizations and our volunteers train in Project LEAD® (the National Breast Cancer Coalition's premier science training program for activists). There are the old-timers at SHARE who give us young'uns a shot of reality when we talk about the good old days. And of course there's nothing that beats experience in understanding the chronicity of breast cancer.

So in considering how things have changed — let me illustrate the last 40 years (hmmm, well the last 38 for me) of progress and what is still needed.

Risk

From 1992 to 1997, 13,338 women were enrolled in the NSABP Breast Cancer Prevention trial ("P-1 trial"). The National Surgical Adjuvant Breast and Bowel Project (NSABP) and the first prevention study of its kind in the United States for breast cancer resulted in a statistically significant reduction in the risk of invasive estrogen positive breast cancer. These results were published in 2005. The STAR trial (Study of tamoxifen and raloxifene) followed, demonstrating that raloxifene (evista) was also as effective as tamoxifen in reducing the risk of invasive breast cancer.

There have been remarkable advances, thanks to the Human Genome Project, in mapping out the genes in one's body. Though we are many years away from understanding and identifying the interactions that can cause significant diseases and cancers, we have identified most of these genes.

Based on specific genetic mutations, different types of breast cancer may occur with particular traits and characteristics. This is called the "phenotype." For instance, a woman who tests positive for the BRCA1 mutation has an increased risk of developing a triple negative breast cancer (one that does not have surface receptors for estrogen, progesterone or the Her 2 protein). Triple negative breast cancers are more aggressive and are not treated with hormones but with different types of chemotherapies.

We have recently developed new technology that allows us to use multi-gene panel testing for a throughput of various mutations that we can do all at once. We have an increased understanding of which mutations are the "bad ones" — the ones that significantly increase your risk of breast cancers or other cancers, such as ovarian, colon, melanoma, brain, thyroid and prostate.

In addition to known mutations in our underlying DNA, there are some changes found in breast tissue itself on biopsy that we know increase the risk of developing an invasive breast cancer. These cellular changes include atypias and lobular carcinoma *in situ* (LCIS). Double mastectomies were performed for "therapeutic" reasons in the 70's and 80's for LCIS. We know that this is not cancer but a "marker" for risk. Some in our community want to reclassify ductal carcinoma *in situ* (DCIS) as "indolent" lesions of epithelial origin (IDLE) not requiring treatment but close observation. Most of us do not embrace this philosophy but a number of papers have been published lately concluding radiation after lumpectomy for DCIS does not improve survival as it does with an invasive breast cancer. Clearly DCIS is felt to be overtreated. A study of DCIS in the UK is looking at observation alone.

This topic of overdiagnosis and overtreatment of breast cancer is an important issue and an opportunity for improvement.

Hand-in-hand with understanding issues of overdiagnosis is appropriate and improved use of screening techniques. Decades ago, MRI use in breast cancer was limited to detection of implant rupture (the “linguini” sign). We now use MRI as a screening tool in mutation carriers and in those who have a lifetime risk of 20-25% of developing an invasive breast cancer.

Screening

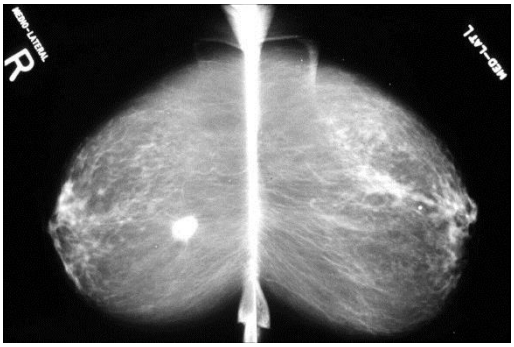


Figure 1 right breast with dense spiculated mass and a fatty breast

Recommendations for screening have changed with each decade. The pendulum has swung back and forth many times towards each end.

Currently the recommendations are to start later and end earlier. Much of it has been driven with economics in mind, though this is “unsaid.”

Women should understand that less screening may represent a missed opportunity to appreciate a better outcome.

The Right screening tool needs the Right technology, the Right radiologist and the Right breast. We are limited by breast density still. Women will be called back for additional testing, one of the reasons the “later screening advocates” recommend mammograms at later ages (when the breast has time to atrophy and is less dense), with an age limit and decreased frequency.

We haven’t heard the end of this for sure.

Diagnosis

The needle is in and the knife is out. We would always prefer to biopsy a lesion or calcification with the needle — either thick or thin — but surgery (unless it’s definitive) should be avoided.

Though over the decades, surgeons and breast imagers have looked at ways to remove the “entire” piece of questionable tissue whether it be a small mass or cluster of calcifications; the image guided biopsy is diagnostic and **not** therapeutic.

What’s new is that from a small core of tissue we can tell a lot about the primary characteristics of the tumor — including the biomarkers like the Her 2, estrogen and progesterone receptors and Ki67 rate, or growth pattern. We may know just from this birdseye view who will be likely to benefit from chemotherapy and who won’t.

The preoperative use of breast MRIs has not translated into improvement in survival in women who are diagnosed with breast

cancer as part of their work up. There are more mastectomies being performed because of increased use of MRI.

MRI is useful for women with locally advanced cancers who are getting chemotherapy before surgery, in those where it is essential to see how far the tumor extends and how they respond to the drugs, and at times, for surgical planning.

Deborah Axelrod with her son Ben (first row on the right) at a SHARE walk in Central Park in 1995.

Treatment

The overall survival in those treated with breast conserving therapy vs. mastectomy are equivalent. These remain the mainstay of surgical management -- lumpectomy or mastectomy. For invasive cancer, axillary staging (sentinel node biopsy) is required.

Oncoplastic techniques have created more flexibility when larger amounts of tissue need to be removed or surgery would create a significant physical defect. Oncoplastic surgery is an innovative approach which combines plastic surgery with surgical oncology resection of tumors.

Recently, many articles and position statements by national organizations have reported that the margins on invasive cancer needed are much less than the 1cm surgeons strived for in the past.

The use of the margin probe™ significantly decreases the rates of re-excision.

Needle or wire localization of non palpable cancers continues to be the main method in directing surgeons to the precise area. Recently, the utilization of different pellets has been introduced. The benefits are that they can be placed weeks before the surgery, thus alleviating scheduling issues and women do not have to have the wire placed just before surgery, which requires a trip to the radiology suite, and then a trip to the OR with the wire “hanging” out of the breast.

Women who are mutation carriers and elect to undergo prophylactic mastectomy may be offered nipple sparing mastectomies. Though the nipple is insensate, it spares “the identity” of the breast. That autologous reconstruction (using one’s own tissue) has been around for many decades. Different techniques have been introduced which spare tissue volume thus minimizing donor site tissue removal with improved aesthetics. Some reconstructive surgeons are working on increasing sensation to the nipples.

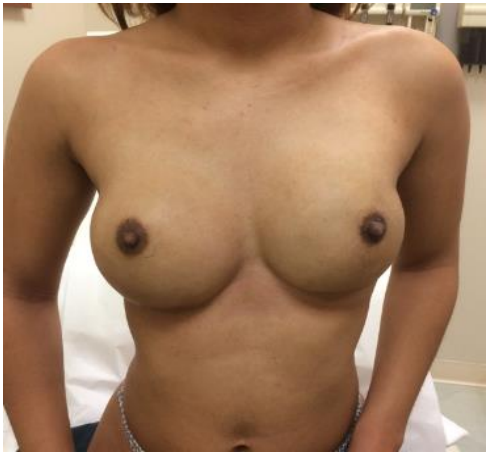
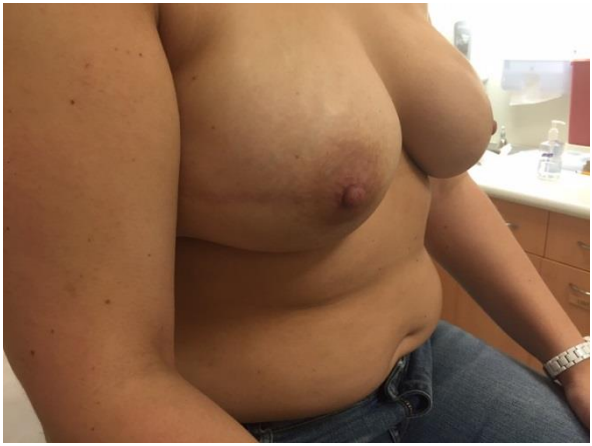


Figure 2 nipple sparing mastectomy with implants and inframammary incision

I've always said, they're sisters, not twins, but we don't want them to be distant relatives -- aesthetics is important.



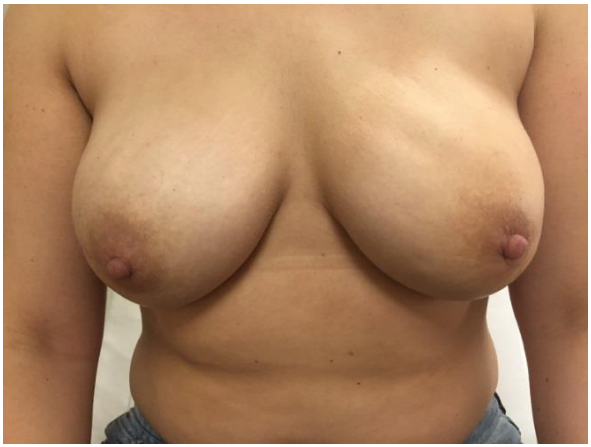


Figure 3 nipple sparing mastectomy with implants and lateral extension

Axillary node surgery has also changed. With the advent of the sentinel node procedure, taken from the melanoma model in the late 90's, came the adaptation to clinically node negative breast cancer. The complication of lymphedema or the accumulation of fluid in the arm and hand is significantly decreased with this procedure.

Based on the study by American College of Surgeons Oncology Group Z0011 (ACOSOG Z0011), clinically node-negative patients who underwent lumpectomy and sentinel node (SN) biopsy and had 1 or 2 SN with metastases were randomized to either axillary treatment or no further axillary specific treatment. There was no difference in overall survival. Women who have undergone lumpectomy with up to 2 positive sentinel nodes are now not undergoing completion axillary dissection.

Lymphedema management and understanding of factors that exacerbate this condition have evolved greatly. When I was in Prague in the 90's, with SHARE advocates, women who had mastectomy followed by radiation were "put on disability" and not allowed to work. They had lymphedema. *Lymphedema is still a major underlying reason for unemployment for affected women in the United States*. There are many myths that were circulated based on lack of scientific evidence such as (1) avoiding venipuncture (blood drawing), (2) wearing compressive garments for air travel and (3) avoiding exercise.[4] New studies conclude that exercise should be encouraged and that it does not cause lymphedema.[5] Compressive garments are probably not necessary for air

travel and still to be determined is whether blood drawn from the affected arm needs to be discouraged. It is however clear that in those at increased risk for lymphedema (having had any axillary surgery), it is important to maintain a normal body weight and avoid weight gain.

Radiation techniques have also changed. More accelerated radiation is being offered and so too is partial breast instead of whole breast radiation. More recently women who are over age 70 with favorable tumors may be offered observation without radiation.
We live in the era of personalized medicine. Not all tumors are alike. For instance we know that tumors that express the Her 2 proto-oncogene are more aggressive tumors. A monoclonal antibody such as Herceptin® will be included in the chemotherapy regimen. The FDA originally approved trastuzumab (Herceptin®) to treat breast cancer in September 1998. Approval was limited to use in patients with metastatic breast cancer who had tumors that were HER2-positive and was later approved in 2006, for early stage patients who had not developed metastatic disease but for use in the prevention of disease recurrence.

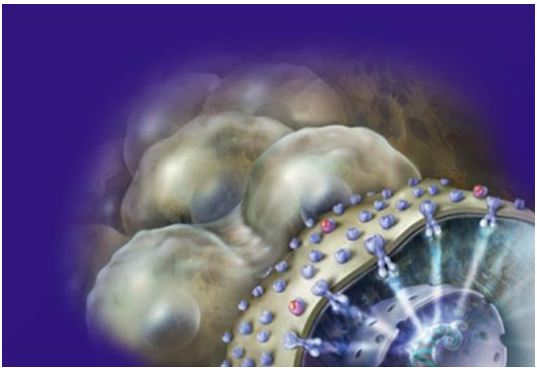


Figure 4 when Her 2 is overexpressed, the amount of HER2 protein on the cell surface increases by 10- to 100-fold. This can lead to excessive cellular division and formation of tumors.

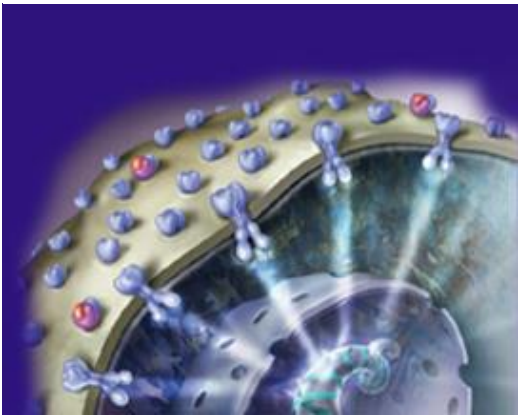


Figure 5 HER2 amplification is seen in up to 20% of breast cancers

Excised tumor tissue taken can be sent to specific laboratories for genomic profiling. Based on these results, there is added knowledge about the prognosis of the cancer and a prediction of the magnitude of response to treatment. There are many different assays or tests that exist and they include to name a few, Oncotype DX® , ProSigna (PAM50)® and MammaPrint®.

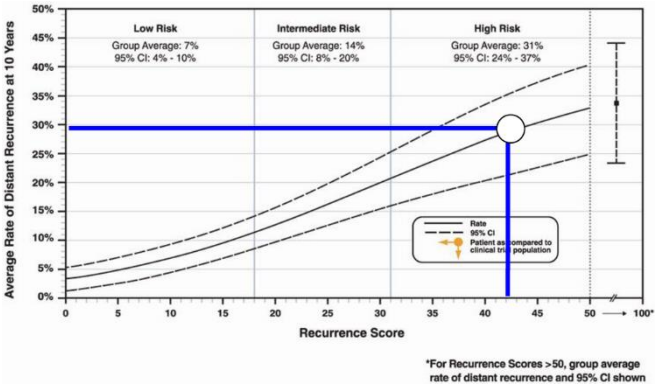


Figure 6: the oncotype DX assay shows a high risk of recurrence at 10 years. Based on this information, this patient will be offered chemotherapy.

Survivorship

The number of cancer survivors is steadily increasing. In 2015, the estimated number is 3.4 million breast cancer survivors. By 2050, there will be more cancer survivors than those newly diagnosed with cancer.

In 2006, the Institute of Medicine (IOM) mandated that by the year 2015, each cancer survivor be provided a summary of diagnosis, treatment received (treatment summary), future follow-up care plans, and healthy lifestyle recommendations.

The American Society for Clinical Oncology (ASCO) recommends regular physical breast examinations, breast self examinations and mammography (waiting 6 months after the completion of radiation for the mammogram on the radiated breast). Routine scans such as chest x-ray, bone scan, CT and PET scans, MRI and other tests such as blood tumor markers **are not** encouraged.

In 1996, the NCI created the Office of Cancer Survivorship (OCS) in recognition of the growing population of cancer survivors in the United States. Few current cancer therapies are benign, and widely used cancer treatments (surgery, chemotherapy, radiotherapy) are known to carry substantial risk of adverse long-term (persistent) or late effects (occurring months to years after treatment has ended).

SHARE was formed to address the psychosocial aspects of the disease when support was not readily available. Tens of thousands of women and their families have relied on us for support over 40 years. We are a second family to many, forming bonds that provided immeasurable assistance in times of a crisis. SHARE has embodied the meaning of what it is to be a survivor.

Predictions (my laundry list)

- Cancer behavior based on a core of tissue will direct the treatment phase
- Less cancer surgery
- Less chemotherapy
- Less radiation
- Redefine cancers that are more indolent and less likely to progress
- More targeted therapies
- More targeted therapies based on a better understanding of pharmogenomics[6]/genetics
- More genetic mutations identified
- More sharing of genetic database
    - Mutations classified that are variants of uncertain significance will be BENIGN
- More risk reducing surgeries with better cosmesis
- And finally, another 40 for SHARE !

[1] Harlan et al. Adjuvant Therapy for Breast Cancer: Practice Patterns of Community Physicians. Journal of Clinical Oncology, Vol 20, No 7 (April 1), 2002: pp 1809-1817.

[2] Faden, Ruth R.; Beauchamp, Tom L.; King, Nancy M.P. (1986). *A history and theory of informed consent* (Online ed.). New York: Oxford University Press. ISBN 0-19-5036867.

[3] Wassertheil-Smoller et al. Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. JAMA. 2003 May 28; 289(20):2673-84.

[4] Cemal et al. Preventative measures for lymphedema: Separating fact from fiction. *Journal of the American College of Surgeons*. 2011;213(4):543-551. doi:10.1016/j.jamcollsurg.2011.07.001.

[5] Schmitz et al. Weight lifting for women at risk for breast cancer-related lymphedema: a randomized trial. JAMA. 2010 Dec 22;304(24):2699-705. doi: 10.1001/jama.2010.1837.

[6] An example of how patients respond to drugs in relation to their genetic makeup includes women who have CYP2D6. This is an enzyme. This enzyme changes tamoxifen to a form that is more active. If someone on tamoxifen has low levels of CYP2D6, then it is possible this person may not derive benefit from tamoxifen and could be offered an aromatase antagonist.

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