A Snapshot of Breast Cancer

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Abstract

Breast cancer is the second leading cause of cancer related deaths in women. Risk factors for diagnosis include race, estrogen exposure, and alcohol consumption, among others. Women with a mutation in BRCA1 are 80% more likely to be diagnosed with breast cancer. BRCA1 pathways are not yet fully understood. Age and degree of risk determine screening practices, but yearly mammograms are recommended for women over 40. Treatment with Tamoxifen is exceedingly common, however problems with acquired resistance exist. Promising research of BRCA1 missense variations is in progress.

Introduction

This year in the United States, one in four deaths is cancer related (Siegel, Naishadham, & Jemal, 2013). While all four major cancer locations, prostate, lung, colorectal and breast, continue to see a decline in fatalities, an estimated 14% of all cancer deaths will be in women with breast cancer. Of an estimated 234,580 patients diagnosed with breast cancer this year, 2,240 will be male (Siegel et al., 2013).

Breast cancer originates in breast tissue. A malignancy beginning in the ducts that transport milk from the mammary glands to the nipple is called a ductal carcinoma. Invasive ductal carcinomas are the most common type of breast cancer in both men and women, occurring in 70-80% of all cases. Tumors that begin in the lobules that produce milk are termed lobular carcinoma, invasive lobular carcinoma accounts of 10-15% of breast cancers. Males, lacking lobules, have adenocarincomas that occur in glandular tissue where lobules would be (Breast Cancer, 2013). Much less common, occurring in only 1-5% of cases, is inflammatory breast cancer (Types of Tumors, 2013). Typically lacking a tangible lump, inflammatory breast cancer occurs when a lymph vessel becomes blocked with malignant cells (Breast Cancer, 2013). Separating it from other breast cancers, a breast with inflammatory cancer may swell to double its size within a couple of weeks, the skin may become reddened, pitted (having an orange peel appearance), feel warm to the touch, and frequently require more aggressive therapy (Giordano and Horotobagyi, 2003).

This article presents a review of the current understanding of breast cancers epidemiology, molecular basis and mechanisms, diagnosis and disease progression, current treatments, and future directions of breast cancer research.

Breast cancer is the leading cause of cancer deaths in women, but not all women are affected equally. Caucasian women have higher incidences than African-American women, but African-American women tend to be diagnosed before age 40. Breast cancer in African-American women is more deadly at any age; Caucasian women have an 88.8% survival rate, while African-American women have a 77.5% survival rate (see Table 1) (American Cancer Society, 2011). While differences in Non-Hispanic White and African American women may be due to varying socioeconomic and screening factors, more research is need to determine if molecular differences are present.

Risk factors vary from patient to patient. Age carries great significance. For women 70 years of age and older, 1 in 15 women will be diagnosed with breast cancer. Gender is another major factor as females are exposed to estrogen for decades. In an average woman's lifetime she has a 12.38% chance of developing breast cancer (Siegel et al., 2013). Family history has a major role. A first-degree relative (mother, sister, or daughter) with breast cancer about doubles risk for other first-degree relatives. Second-degree relatives (grandparent/child, aunt, niece, half sibling) face increased risks as well (Begg et al. 2008). While these familial mutations only cause about 5% of breast cancer cases, a woman who receives mutated DNA has a significant increase in her chances of breast and ovarian cancers (Yoshida & Miki, 2004). Genetic mutations in genes such as BRCA1/2, responsible for repairing DNA, TP53 (P53), PTEN, and STK11, and CHEK2 code for a tumor suppressor proteins, ATM, helps control cell growth, and CDH1 codes for a protein that controls cell adhesion. A relationship between increased lifetime exposure to estrogen and greater risk of breast cancer has been found, but is still poorly understood. While pregnant, women are not exposed to estrogen through menstruation. Women with multiple pregnancies and pregnancy at a younger age have been found to decrease the risk of breast cancer. There is thought to be a connection between breast-feeding and lower risk as well. Women with menstrual cycles beginning before age 12 or ending after age 55 are linked to greater risks, as they have greater exposure to estrogen and progesterone (What are the risk factors for breast cancer?, 2012). Being overweight, especially post-menopause, has been related to an increase in risks because adipose tissue produces significant amounts of estrogen. High consumption of alcohol is another known risk factor, the enzymes required for alcohol breakdown are the same enzymes used in the recycling of estrogen. Excess drinking can damage the liver, further inhibiting elimination of estrogen. Data from a current study suggests that as few as 3-6 glasses of wine a week is enough to cause a small increase in breast cancer risk; a 10% risk increase with each 10 grams of alcohol per day was also observed (Chen et al. 2011).

Breast Cancer Survival Rate: 5 Years

Ethnicity/Race	Survival Rate
Asian	90.7%
Non-Hispanic White	88.8%
Pacific Islander	85.6%
Hispanic	83.8%
American Indian/Alaska Native	85.6%
African American/Black	77.5%

Table 1: 5 year breast cancer survival rates based on race. African American women have a reduced survival rate than other ethnicities. Adapted from: American Cancer Society. Breast Cancer Facts & Figures 2011-2012. Atlanta: American Cancer Society, Inc.

Molecular basis and mechanisms

Role of BRCA1

One of the most significant genetic mutations related to breast cancer, shown to increase a woman's threat of breast cancer by 50-85%, is BRCA1/2 (Weitzel et al., 2007). Found on chromosome 17q2, BCRA1 is vital for embryonic development and has major roles in DNA repair, transcription, and cell cycle control (overview of processes in Figure 1). As mutations in BRCA1 are hereditary, they are nonspontaneous.

DNA damage and cell cycle arrest have been shown to cause an alteration of the phosphorylation of BRCA1, leading it to disperse to proliferating cell nuclear antigen (PCNA), a protein that encourages DNA replication. Immediately after dispersal, two other proteins, Rad51 and BRAD1 that are known for their role in DNA repair, join BRCA1. This suggests that BRCA1 is a substrate activated by kinase activity stimulated by damaged DNA (Scully et al., 1997). Supporting this, BRCA1 has been shown to be preferentially hyperphosphorylated during the S-phase (DNA replication) of the cell cycle and in response to DNA injury (Thomas, 1997). Other kinases related to BRCA1 include CHK2 and ATM, further indicating that phosphorylation is important in DNA repair (Yoshida and Miki, 2004). If BRCA1 was mutated and unable to participate in DNA repair, resulting genomic instability would likely lead to breast tumor formation.

BRCA1's major role in DNA repair takes place in double strand break repair and homologous recombination. Due to its ability to repair double strand breaks without causing deletions, homologous recombination is an important mechanism of DNA repair, failure of this process can lead to genetic instability and lead to tumorigenisis. Immunoprecipitation studies demonstrate coimmunoprecipitation of BRCA1, BRCA2, and Rad51 and co-localization of all three in the protein complex mediating recombination and chromosome pairing; indicating the formation of a complex involved in DNA repair (Chen et al., 1998). As the field of recombination and repair continues to grow, many pathways and mechanisms remain unknown. A recent study suggests BRCA1 is responsible for promoting homologous repair in single strand DNA breaks independent of replication checkpoint regulator ATM and end resection of double strand breaks during replication fork delay and collapse (Chen, 2012). While precise understanding of BRCA1 interactions with motif bound BRCA2 and Rad51 is still unclear, it has been shown that because BRCA1 and BRCA2 interact, any relationship between BRCA1 and Rad51 may be regulated by BRCA2. BRCA2 is believed to be required for Rad51 accumulation at sites of homologous repair as it prevents self-aggregation of Rad51 that would occur otherwise (West, 2003).

Vital to cell survival are cell-cycle checkpoints that ensure a cell is ready for the next phase of the sequence. As mentioned earlier, BRCA1 is phosphorylated when DNA damage is present. A similar process occurs in the regulation of G2/M and S-phase checkpoints; ATM, ataxia telangiectasia mutated, has demonstrated the ability to act as a kinase to BRCA1 when γ-radiation has damaged the genome. Mutated BRCA1 with missing phosphorylation sites lead to deficient G2/M arrest, indicating the importance of BRCA1 in this checkpoint (Cortez et al., 1999). This also implicates ATM in double strand break repair, it is believed to function as a BRCA1 regulator (ATM ataxia telangiectasia mutated, 2013).

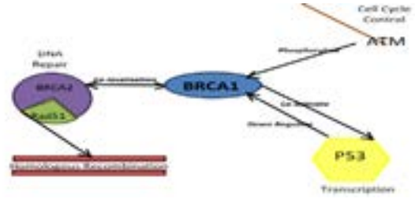

Figure # 1: BRCA1 involvement in DNA regulation in response to genomic damage. ATM phophorylates BRCA1 to regulate G2/M-phase. BRCA1 co-localizes with BRCA2 and RAD51 complex to repair double strand DNA breaks via homologous recombination. BRCA1 co-activates P53 to alter its transcriptional targets, P53 down regulates BRCA1 when no longer necessary.

BRCA1 is also involved in transcription. Closely associated with p53 (a tumor suppressor protein), BRCA1 and p53 levels increase concurrently when damaged DNA is present and both proteins are able mediate the expression of p21, a cell cycle inhibitor. BRCA1 has demonstrated physical link with p53 as well, array analysis of cells expressing identical levels of p53 demonstrate different transcriptional target preferences as determined by increasing levels of BRCA1 . While BRCA1 stabilizes p53, it has varied affects on the choice of transcriptional target by p53 when DNA damage is present. Test cells lacking functional BRCA1 showed favored apoptosis in comparison to control cells; apoptosis inducing gene PIG3 remained present upon genomic damage, despite exhibiting slightly reduced expression. In addition, Northern blot analysis indicates repression of these apoptosis promoting genes when functional BRCA1 is present, reduce apoptosis by as much as 75%, while genes promoting genome repair and cell cycle arrest, such as GADD45, see increased expression (MacLachlan et al., 2002). Continued occurrence of BRCA1 affects p53 transcriptional activity selection by encouraging the preference of growth arrest and DNA repair genes over apoptosis.

Association of p53 and BRCA1 also has a role in tumorigenesis. BRCA1 is highly induced in propagating mammary tissues; mutations can lead to abnormal breast development, amplified apoptosis, and genetic instability leading to tumorigenesis. Mice models show that when combined with p53 loss, tumor growth was enhanced (Xu et al., 1999). It is likely that genomic instability caused by BRCA1 mutations can lead to additional mutations in p53, creating a dangerous pathway promoting tumor growth. While many other factors play a role in tumor formation, understanding BRCA1 processes may provide insights into previously unknown cancer pathways and treatments.

Role of Estrogen

Exposure to estrogen begins during a female's first menstrual cycle at about age 13 and is vital for regulation of menses, maintenance of bones, and development of reproductive organs and breasts. In normal cells, estrogen receptors (ER) control binding with various ligands and the associated ER/ligand goes on to bind with a hormone response element (HRE). Transcription of the HRE is still poorly understood. Because estrogen receptors are found on most breast tumors, the body's estrogen may act as a tumor promoter; hormonal therapies will sometimes involve the removal of the ovaries: the body's main source of estrogen (Weinberg, 2007).

Diagnosis and Disease Progression

Early detection is vital for successful treatment of breast cancer. Screening methods and frequency should be determined with a physician.

Mammogram

The standard breast cancer detection procedure is a mammogram. Mammograms use a low powered x-ray to generate an image of the breast. As they are able to detect lumps in the breast at nearly any stage, they are typically recommended annually or biannually for women over the age of 40 (Patient Pages, 2003). While they do emit a small amount of radiation, they are inexpensive and typically generate an

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acceptable image. However, images are not perfect and false negative/positives are possible.

Magnetic Resonance Imaging (MRI)

An MRI typically produces the best image of all breast cancer screenings. Radio waves, not radiation, are used to capture the image of the breast, which may be injected with dye to increase contrast and examine blood flow. MRIs are superior at finding invasive breast cancer, but they too can create false negative/positive results. Cost-effectiveness for women considering MRIs is greatly dependent upon their age. Due to their high cost, MRIs are typically recommended for BRCA1/2 mutation carriers' ages 35 to 54. MRI screening in women outside this age group, even with BRCA1/2 mutations, is not recommended as younger age groups have a much lower incidence and older age groups have other risks of death (Plevritis et al., 2006). Mammogram imaging is recommended for those not in the 35 to 54 BRCA1/2 carrier group.

Ultrasound

Typically used in conjunction with mammograms, ultrasounds allow improved screening of the chest wall. An ultrasound may be recommended to follow up an abnormal mammogram or examine changes in a cyst (Breast Ultrasound, 2010). Breast ultrasounds may be used in women with denser breast tissue or implants where mammograms can produce a poor image. However, Deep imaging into the breast requires other examination.

Self-Exam

Recommended by clinicians as an additional screening method, self-exams were believed to increase the likelihood of detecting tumors at early stages. Meta-analysis of trials tracking self-examination results indicate that women who performed self-exams had twice the rate of biopsy; 3406 biopsies were performed in women who completed self-exams while the control group received 1856 biopsies (Kosters & Gotzsche, 2008). However, self-awareness of their breasts is recommended for all women.

Staging

Progression of breast cancer is divided into four main stages based upon the tumor-node-metastasis (TNM) system.

Breast Cancer Staging

Stage Name	Characteristics
Stage 0	Non-invasive; no metastasis, no spread to lymph nodes
Stage I	IA: Tumor less than 2cm, no spread to lymph nodes IB: Tumor less than 2cm, cancer cells groups present OR small groups of cancer cells present with lack of tumor
Stage II	IIA: No tumor in breast, growth to lymph nodes OR tumor less than 2cm with growth to lymph nodes IIB: Tumor in between 2-5cm, spread to 1-3 lymph nodes
Stage III	IIIA: No tumor in breast, spread to 4-9 lymph nodes IIIB: Tumor any size, tumor reached chest wall and/or skin, spread to 9 lymph nodes. Maximum for inflammatory breast cancer IIIC: Growth to lymph nodes near breastbone
Stage IV	Metastasis beyond lymph nodes and into organs

Table 2: Summarized Breast Cancer Staging. Stages have shared characteristics. Information summarized from: Singletary and Connolly, 2006 and How is breast cancer staged?, 2013

Common Chemotherapy and Hormone Therapy Drugs

Class	Target	Examples
Mitotic Inhibitors	Prevent microtubule formation	Ixempra, Navelbine, Taxanes
Antimetabolites	Acts as decoys for metabolites in DNA and RNA synthesis	Gemzar, Xeloda
Antitumor antibiotics	Inhibit enzyme allowing relaxation of DNA from supercoiled position	Anthracycline
Hormone therapy	Competitively inhibits estrogen receptors	Tamoxifen

Table 3 : Compilation of commonly used chemotherapy and hormone therapy drugs.

Primary tumor size (T), expansion to lymph nodes (N), and metastasis (M) are all believed to effect prognosis (Singletary & Connolly, 2006). Information about a breast tumor is collected via appropriate screening methods; when necessary, surgery may be performed to allow the physician a more complete inspection of tumor development (How is breast cancer staged? , 2013). Tumors are then classified by depth of T, N, and M phases and may be further distinguished based on pathology, clinical data, or autopsy (when patient is deceased) (Singletary & Connolly, 2006). These factors combined provide a stage grouping (summarized in Table 2). Shared categories tend to have similar projections for treatment and survival (How is breast cancer staged?, 2013).

Current Treatments

Treatment procedure is determined in part by cTNM (clinicalTNM) classification, based on clinical imaging and physical examination (Singletary & Connolly, 2006).

Radiation

Radiation therapy targets areas of malignant cells and repeatedly subjects them to DNA damaging radiation on a regular basis, disallowing them the opportunity to repair themselves. In early stage patients, tumors 4cm or smaller, non-metastasized tumors, and tumors spread to lymph nodes or skin are good candidates for radiation (When is radiation appropriate?, 2012). Treatment following surgery is common as well. Women who received a lumpectomy for DCIS and who had follow up treatment with radiation were shown to improve reoccurrence rates when compared to lumpectomy alone (Fisher, 1993).

Chemotherapy

Chemotherapy utilizes a series of drugs to kill cancer cells throughout the body. Typically administered to advanced stage patients and pre-surgery to shrink tumors.

There are many different classes of chemotherapy drugs that affect different pathways (Table 3).

Antimetabolites, such as Gemzar and Xeloda, interfere with DNA and RNA growth by replacing metabolites used in DNA/RNA synthesis. Both Gemzar and Xeloda are pyrmidine antagonists, meaning that they prevent synthesis of cytosine in DNA and RNA, thyamine in DNA, and Uracil in RNA. Xeloda is commonly prescribed with other chemotherapy drugs when tumors have ceased responding to antitumor antibiotics and mitotic inhibitors (Xeloda, 2012). Anthracyclines, antitumor antibiotics, are extremely effective at preventing DNA and RNA synthesis; these drugs inhibit the enzyme that allows the relaxation of DNA from its supercoiled state during transcription and replication. Despite their successful destruction of cancer cells, buildup of metabolites in the heart

can lead to cardiotoxicity. Another class of chemotherapy drugs, mitotic inhibitors, interferes with cell division processes rather than altering DNA expression. Mitotic inhibitors bind to tubulin monomers, preventing microtubule formation and thus cell division (Spindle Inhibitors, 2012).

Hormone Therapy

The most popular form of endocrine therapy, Tamoxifen is widely known for its highly effective results; it is the most commonly used treatment in male breast cancer and premenopausal women. However, it is also recognized for its ability to be made unproductive by acquired resistance. Endoxifen and 4-hydroxytamoxifen regulate the metabolism of tamoxifen, an estrogen receptor inhibitor. Response to Tamoxifen seems to be influenced by genomic variances in the enzyme forming Endoxifen, CYP2D6; because women with different CYP2D6 geneotypes have different Tamoxifen success rates. Women having two normal copies of CYP2D6 have half the risk of recurrence compared to women with a loss of CYP2D6 activity (Schroth et al., 2009). Further studies involving CYP2D6 expression could potentially allow patients with Tamoxifen acquired resistance to again be affected by the drug.

Future Directions

One of the most exciting research topics on the horizon is the continued development of highly personalized cancer treatments. In order to create these custom programs, understanding of molecular structures, pathways, and functions must be reached. A recent study takes a step in the right direction: three BRCA1 missense variants were identified as pathogenic. Transcription activation assay demonstrates decreased levels of reporter expression in variants Y1703S, W1718L, and G1770V is comparable to those shown in two known pathogens. Structural analysis with molecular visualization software demonstrates that the three newly suspected pathogens seem to impair BRCA1 structure in BRCT domains. Widespread investigation has recognized many novel variants of unknown significance since the identification of BRCA1 as the breast cancer gene. If these variants can be categorized, there is the potential for great changes in breast cancer diagnostics (Quiles et al., 2013).

Concluding Remarks

Breast cancer is the second most deadly form of cancer in women (Siegel et al., 2013). While understanding of breast cancer has come far since the revelation of BRCA1 ten years ago, there is much more research to be done. Understanding BRCA1 and estrogen pathways and functions may provide new avenues for treatment. Improving Tomaxifen effectiveness in patients that face resistance would allow continued treatment and potentially increased lifespan. No matter the avenue, researching solutions to breast cancer could change the lives of thousands of people.

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