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 85% 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, Naslund, & Jemal, 2013). While all 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 the male (Siegel et al., 2013). While breast cancer is a disease that affects both men and women, it is more common in women than men. In 2010, breast cancer was the leading cause of cancer-related death in women. In 2010, approximately 39,620 women died of breast cancer (American Cancer Society, 2013). While breast cancer is a disease that affects both men and women, it is more common in women and is the most frequently diagnosed cancer in women worldwide (Siegel et al., 2013). Breast cancer is the most common malignancy in women between the ages of 40 and 50. Breast cancer is the leading cause of cancer death 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 needed to determine if molecular differences contribute.

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 increases the double risk for other first-degree relatives. Second-degree relatives (grandmother, aunt, niece, half sibling) face increased risks as well (Bogg 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). Genes associated with BRCA1, such as BRCA2, responsible for repairing DNA, TP53 (P53), PTEN, and STK11, and CHEK2 code for a tumor suppressor proteins, that help control cell division and proteins that control cell adhesion. A relationship between increased lifetime exposure to estrogen and breast cancer has been found, but is still poorly understood. While pregnant, women are not exposed to estrogen and breast cancer is decreased. 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 breastfeeding 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 linked to an increase in risk 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. Excessive 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 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).

Table 1: 5 year breast cancer survival rates based on race. African American women have a reduced survival rate than other ethnici- ties. Adapted from: American Cancer Society, Breast Cancer Facts & Figures 2012-2013, American Cancer Society, Inc.

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>5 Year Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian</td>
<td>90.7%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>89.8%</td>
</tr>
<tr>
<td>Pacific Island</td>
<td>85.9%</td>
</tr>
<tr>
<td>American/Alaska Native American/African Black</td>
<td>79.5%</td>
</tr>
</tbody>
</table>

Molecular basis and mechanisms
Role of BRCA1
One of the most significant genetic mutations related to breast cancer, shown to increase a woman’s breast of breast cancer by 50-85%, is BRCA1 (Weltz et al., 2007). Found on chromosome 17q21, BRCA1 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 strongly associated with breast cancer, they are not only deleterious or harmful and cancer control (overview of processes in Figure 1). As mutations in BRCA1 are strongly associated with breast cancer, they are not only deleterious or harmful and can either fail to function or be present in small quantities, leading to the increased risk of developing breast cancer (Weltz et al., 2007). Damaged DNA 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 participates in DNA replication (Kartner et al., 2009). Immediately after dispersed, two other proteins, Rad51 and BRAD1 that are known for their role in DNA repair, join BRCA1. This suggests that BRCA1 is responsible for the activity stimulated by damaged DNA (Scoully et al., 1997). Supporting this, BRCA1 has been shown to be preferentially hyperphosphorylated during the S-phase (phase of DNA replication) of the cell cycle and in response to DNA damage (Thomas, 1997). Other proteins related to BRCA1 include CHK2 and ATM, further indicating that phosphorylation is important in DNA repair (Yoshida and Miki, 2004). BRCA1 was mutated and unable to participate in DNA repair, resulting genomic instability would likely lead to breast tumour 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 tumorigenesis. Immunoprecipitation studies demonstrate communoprecipitation of BRCA1, BRCA2, Rad51 and co-localization of all three in the protein mediating recombination and chromosome pairing. Inducing the formation of a complex involved in DNA repair (Chen et al., 1998). As the first detailed description of recombination continues to grow, many pathways and mechanisms remain unknown. A recent study suggested that 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 motifs bound to 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. BRCA1 is known to control cell cycle checkpoint and accumulate sites of homologous repair as it prevents self-aggregation of Rad51 that would prevent homologous repair. 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 G2M y-radiation has damaged the gene. Mutated BRCA1 with missing phosphorylation sites lead to deficient G2M arrest, indicating the importance of BRCA1 in this checkpoint (Corlitz et al., 1999). This also implicates ATM in double strand break repair, it is believed to function as a BRCA1 regulator (ATM stevia telangiectasia, 2013).

BRCA1 is also involved in transcription. Closely associated with phosphorylation levels of 25-35, BRCA1 can move away from the DNA strand, and S-phase checkpoints; ATM, ataxia telangiectasia mutated, has demonstrated the ability to act as a kinase to BRCA1 when

Oxidative stress: Exposure to estrogen begins during a female’s first menstrual cycle, which is responsible for estrogen metabolism, maintenance of oocytes, and development of reproductive organs and breasts. In normal cells, estrogen is a protein that encourages DNA replication. Immediately after 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 participates in DNA replication (Kartner et al., 2009). Immediately after dispersed, two other proteins, Rad51 and BRAD1 that are known for their role in DNA repair, join BRCA1. This suggests that BRCA1 is responsible for the activity stimulated by damaged DNA (Scoully et al., 1997). Supporting this, BRCA1 has been shown to be preferentially hyperphosphorylated during the S-phase (phase of DNA replication) of the cell cycle and in response to DNA damage (Thomas, 1997). Other proteins related to BRCA1 include CHK2 and ATM, further indicating that phosphorylation is important in DNA repair (Yoshida and Miki, 2004). BRCA1 was mutated and unable to participate in DNA repair, resulting genomic instability would likely lead to breast tumour 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 tumorigenesis. Immunoprecipitation studies demonstrate communoprecipitation of BRCA1, BRCA2, Rad51 and co-localization of all three in the protein mediating recombination and chromosome pairing. Inducing the formation of a complex involved in DNA repair (Chen et al., 1998). As the first detailed description of recombination continues to grow, many pathways and mechanisms remain unknown. A recent study suggested that 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 motifs bound to 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. BRCA1 is known to control cell cycle checkpoint and accumulate sites of homologous repair as it prevents self-aggregation of Rad51 that would prevent homologous repair. 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 G2M y-radiation has damaged the gene. Mutated BRCA1 with missing phosphorylation sites lead to deficient G2M arrest, indicating the importance of BRCA1 in this checkpoint (Corlitz et al., 1999). This also implicates ATM in double strand break repair, it is believed to function as a BRCA1 regulator (ATM stevia telangiectasia, 2013).

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Table 2: Summarized Breast Cancer Staging. Stages have shared stages based upon the tumor-node-metastasis (TNM) system. Progression of breast cancer is divided into four main stages.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Tumors are small and localized to the breast.</td>
<td>Early stage patients, tumors 4cm or smaller, non-metastasized.</td>
</tr>
<tr>
<td>II</td>
<td>Tumors have spread to lymph nodes but not to distant sites.</td>
<td>Tumors have spread to lymph nodes or skin are good candidates for radiation.</td>
</tr>
<tr>
<td>III</td>
<td>Tumors have spread to distant sites.</td>
<td>Tumors are then classified by T, N, and M.</td>
</tr>
<tr>
<td>IV</td>
<td>Tumors have spread to distant sites and metastasized.</td>
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Stage I
- Tumors are small and localized to the breast.
- Early stage patients, tumors 4cm or smaller, non-metastasized.

Stage II
- Tumors have spread to lymph nodes but not to distant sites.
- Tumors have spread to lymph nodes or skin are good candidates for radiation.

Stage III
- Tumors have spread to distant sites.
- Tumors are then classified by T, N, and M.

Stage IV
- Tumors have spread to distant sites and metastasized.
- Tumors are then classified by T, N, and M.

References


Concluding Remarks
- Breast cancer is the second most deadly form of cancer in the United States, affecting both men and women. Understanding the biology of breast cancer is crucial for developing effective treatment strategies.
- While we have made significant progress in understanding breast cancer, much more needs to be done to improve outcomes and reduce the burden of this disease.

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