The Cell Cycle: Carol's Experiences with Breast Cancer and Chemotherapy

Carol Killeen is a 57 year old woman who is a breast cancer survivor. She was diagnosed in December 2011. *The picture of her to the left is how she looked 1 year before her diagnosis*. She was kind and brave enough to share some of her cancer treatment experiences with me. Carol hopes that her story can illustrate some of the important aspects of the cell cycle to give students a lesson that they will remember. Though her battle with breast cancer was challenging she does not want pity or sympathy and states that the overall experience taught her how to appreciate life more fully and not to take anything for granted. Carol was leading an active life until she was diagnosed with a disease that if not treated would kill her. She knew that even if she was treated she would suffer greatly and could still face death.

Why is cancer so bad? How is cancer related to the cell cycle?

Mitosis is the process that most cells go through when they divide and replicate. When a normal cell goes through mitosis it is a good thing. There are many tissues in the body that are always going through mitosis –in fact it is required for you to be healthy. Think of your blood cells or skin cells. You never run out of them because they are always dividing. An important thing about mitosis is that it has to be controlled. The cells in your body should only divide when they are told to. It is very bad when cells divide whenever they want to. The rebellious cells that do this can become cancer cells.

Cancer cells divide constantly and invade other tissues to consume their resources and get the energy and materials necessary to continue spreading. Cancer cells typically start in one location before invading other organs. Once cancer cells have invaded an organ they progress through the cell cycle more frequently and replicate faster than the cells that are already there. Cancer cells can easily take over an organ and destroy it like weeds in a flower garden. This is why it is very bad when cancer cells spread throughout the body. Cancer cells can invade and destroy your organs one by one or all at once. When cancer cells spread it is known as "**metastasis**". When people say "your cancer has metastasized" it is a potential death sentence. Current cancer treatments have saved many people caught in this horrible circumstance but the treatments are still far from perfect. Many cancer treatments focus on controlling the cell cycle. If you can control the cell cycle and prevent mitosis then you can stop cancer cells from dividing, halt their progress, and maybe even destroy them altogether. Unfortunately cancer cells aren't the only cells in the body that frequently undergo mitosis which is why cancer therapy can be so nasty. Carol's breast cancer metastasized and her confrontation of this harsh reality is what defines her story as she experienced a situation where her life was dependent on the scientific control of the cell cycle.

Bill: When did everything start?

Carol: For about 10 months I had some pain in one of my breasts and I had an uncomfortable sensation under my armpit. It had bothered me for a while so I went to my doctor to have it checked out. They found a mass in one of my breasts. They told me that most masses were not breast cancer but in the back of my mind I knew it was cancer the whole time. They did some tests to get a closer look at the mass and they poked me with a needle to get a tissue sample of it. I recently lost my father, my aunt, and my very close friend to long battles with cancer. I had some idea of what I might be in for and I started mentally preparing myself for the worst.

Bill: How did you feel when you first got the diagnosis?

Carol: It was December 2011. I was driving to a ski trip in New Hampshire when I got a phone call from my doctor. I took the news in stride and was very calm on the phone. To everyone else in the car it probably seemed like nothing was wrong but on the inside I was terrified and shaken. Looking back on it I am lucky I did not drive off the road. When the news sank in, my first thought was that I was not going to be around for my grandchildren. The doctors were hopeful that the cancer could be completely removed by surgery. They did a few tests and it looked like the cancer cells were all in one place and had not spread to other organs. The good news was that if they got it all out then I would be cured. A few weeks later they did the surgery but I still felt like something was wrong.

After the surgery was over all of my friends and family met me in the recovery room and threw a big party. Everyone was so happy but I felt like something just wasn't right. About a week later the doctors contacted me and said that during the surgery they took some lymph nodes, which they said were structures that cancers spread to before they hit other organs, and that those lymph nodes were packed with cancer cells. This meant that the breast cancer had metastasized and could have spread to my other organs. If I didn't get treatment I knew I was dead. I was determined to fight it so my only real choice was to undergo chemotherapy. It is kind of a whole body poisoning where you hope you kill the cancer cells more than you hurt your own body. I had seen relatives go through it and I knew what to expect but seeing it and living through it were two totally different things. I completed chemotherapy in cycles. I went for a treatment once every three weeks for four straight months. Four weeks after chemotherapy ended I began radiation treatments.

Bill: Tell me a little bit about your chemotherapy and radiation treatments?

Carol: For my chemotherapy I was given **cyclophosphamide** and **paclitaxel.** Cyclophosphamide is a drug that damages DNA and prevents cells from using it. Paclitaxel is a drug which prevents cell division. They hooked me up to an IV and they would pump these drugs into my body for 2 hours every time I got a treatment. I got treatments every 3 weeks for 4 months. After chemotherapy was done I went for radiation(destroys DNA) treatment every day for 8

weeks. Although radiation left me fatigued and burned it was a piece of cake compared to chemotherapy. Since the treatments started I have been taking a drug called **anastrozole** every day which limits signals that tell breast cancer cells to divide. *The picture to the left is Carol after a few cycles of chemotherapy*.

Bill: What do you remember about chemotherapy?

Carol: I remember that it really knocked me out both physically and mentally. Losing part of my breast in the surgery was emotionally difficult. But I felt that the loss of my hair during chemotherapy would be more humiliating because it is such a large part of a woman's identity. It was not as devastating with eyebrow hair loss because you can paint those on but the loss of the hair on my head seemed like more of a personal wound. I felt the need to be in control of part of this process, to be prepared for some of it, so I decided to shave my head. I wanted to deal with my hair loss on my terms. I knew that it would be difficult for one of my family members to shave my head because it would be an admission that they might be losing me so I had a wig maker do it. It was a hard thing for my family to see but we all joked that we would laugh about it one day. A little while after my first chemotherapy treatment I was sitting at my computer and I noticed all of these little things that looked like dust all around the desk and the keyboard. It ended up being little hairs on my shaved head falling off. I was devastated! I thought that I had some control over my body when I shaved my head but I realized that I didn't even have that. That is what seeing those little hairs meant. I wore wigs so people did not know I was bald but this loss of my own hair was still hard to deal with because it was such a part of my identity.

Bill: It sounds like chemotherapy took a big toll on your daily life.

Carol: I felt that I was losing control of my life more and more each day. I worked in the health care field for nearly 30 years. I was used to caring for people, now I was the one who needed care. Before my treatments started I would get a hundred emails every day related to business. I loved it. I identified as a busy person and I took pride in that. Chemotherapy really knocked me out. My energy level crashed. After treatments I would come home and all I could do was rest in a chair. I would sleep for 48 hours sometimes. It was hard for me because I liked being busy. I couldn't work and it was killing me inside because that is who I was. I hated being a person who was too weak to move. There were times that I just wanted to die. It was a loss of identity and dignity on many levels. With my hair, it was my identity as a woman, with my energy level, it was my identity as a person. A major loss of dignity was my ability to eat. I couldn't eat or drink anything without throwing up a few minutes later or having horrible explosive diarrhea. I could not always even make it to the bathroom and I had to start wearing a diaper after my first chemo treatment. I never expected to be that sick. It was very humiliating and very humbling. It was a loss of identity as an adult. I felt that I became a child more and more each day. It was hard to feel such misery and keep going back for treatment when you knew you were just going to feel even worse after it was done. It was like going back to the torture chamber again and again. Fortunately, I have a great family and a lot of friends and I needed their emotional support to get through it.

Bill: It sounds like the support of your family and friends played a big role in surviving the stress of your cancer treatments.

Carol: I am so lucky to have the support that I do. Patrick, the man I am in a long term relationship with, was my primary caretaker and constant center of moral support. Sometimes I was too weak to cook for myself or drive a car. Patrick helped with both meal preparation and transportation to and from treatments. All of my children and grandchildren were extremely supportive as well. I began receiving emails, cards, food, and plants from friends and families. I continue to read the cards to this day, I saved each of them. I bought a pair of pink boxing gloves that were my symbol that I was going to fight until the end. I was fighting cancer but I needed my whole family in my corner. Treatments began to get easier, not great, but better. I began to think more positive thoughts due to the help of my family and friends as well as the physicians, staff, and fellow patients at the hospital and radiation center. The entire experience was tough but what I learned was that I was tougher, because I was surrounded by such a positive group of people and I will always feel blessed for their presence. The LIVESTRONG program sponsored at the local YMCA was also instrumental to my recovery. That is the point that I want to drive home with this interview, love and support matters when you are going through something like this.

Bill: I can imagine that you were happy when your treatments were over.

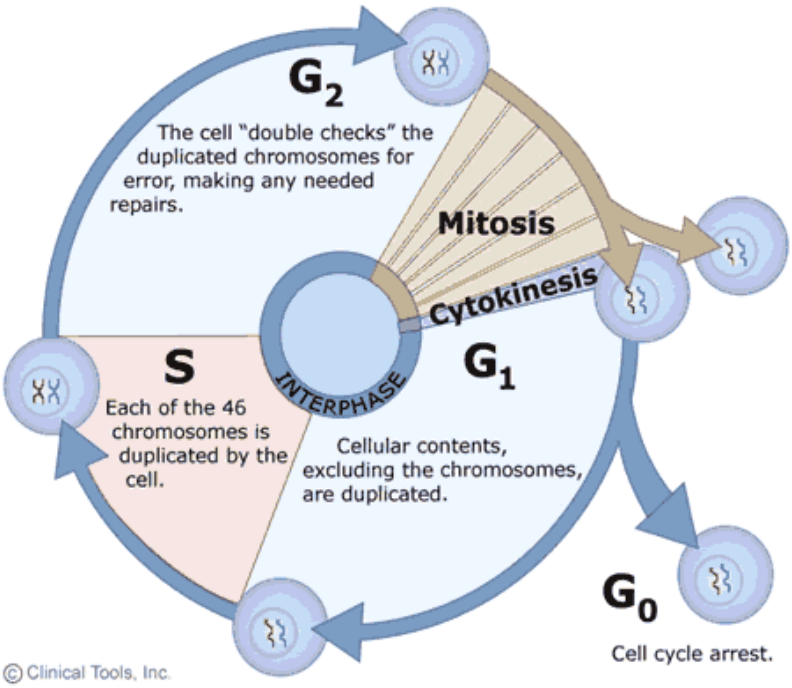
Carol: It was a great feeling. Patrick and I went on a vacation to Italy and really celebrated life. The whole experience really forced me to look at my life differently and in a very grateful way. Just prior to leaving for vacation my toe nails began to fall out! By that point, I had to be grateful for the ones I had left. So I got a pedicure for the remaining ones with the brightest polish I could find. I really get a lot out of life now and I enjoy the simple things. I see my cancer doctors (oncologists) fairly regularly and when they do tests they don't see any cancer. I hope that the chemotherapy and radiation killed anything that spread. I wish that I had an answer that the cancer was definitely gone but I am just so grateful to be alive and feel better. Although I endured a lot I have come out the other end with a sense of gratitude for my life, my family and for those who my life touches. *The image to the left is Carol after her treatments were over.*

Scientific Explanation:

Carol's story starts and ends with the cell cycle. **Mitosis** is a process where one cell divides and creates 2 identical daughter cells that have the same amount of DNA as their parent cell. Mitosis is the process of division used by all the cells of the body that do not become gametes(sperm or egg cells). Gametes are created by **meiosis** which leaves them with half as much DNA as the parent cell because the goal of a gamete is to combine with another gamete

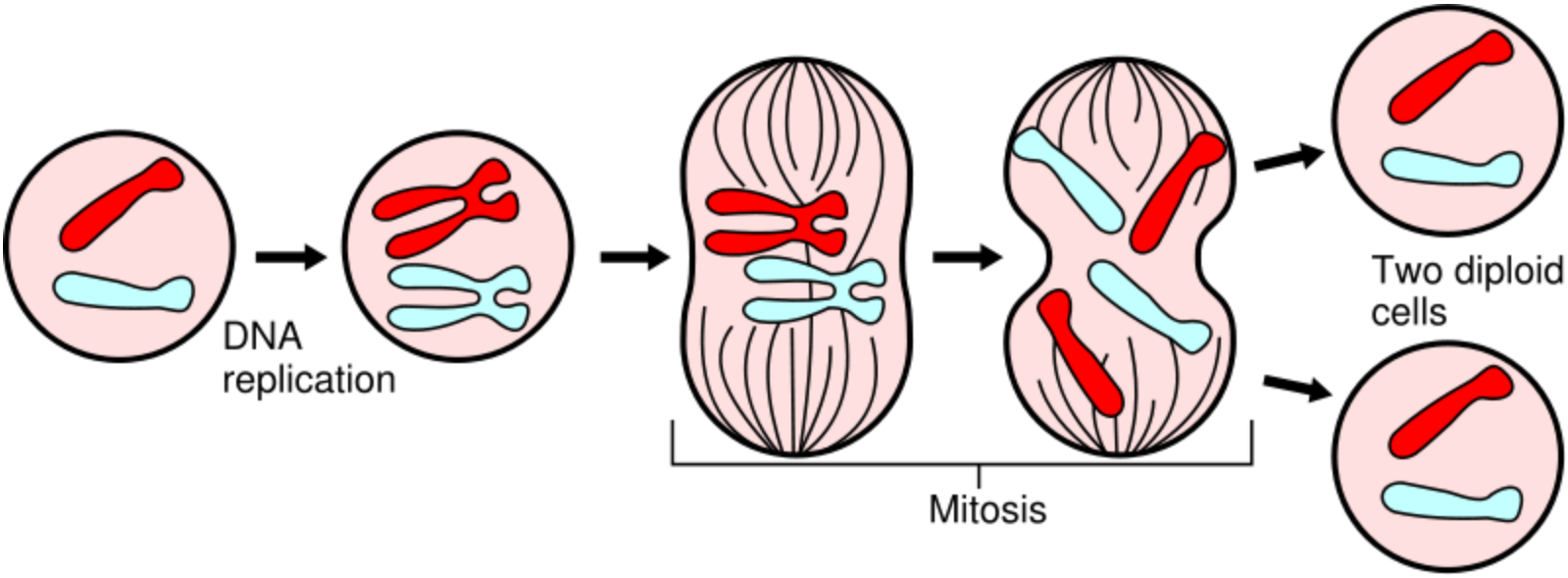
and make an entirely new parent cell that will undergo mitosis until it becomes its own organism(a baby). In between mitotic events there is a period called **interphase** where a cell grows and decides wether or not it wants to divide. Interphase has three phases: G1, S, and G2. Every phase has checkpoints to evaluate the quality of the DNA in the cell. If at any point the DNA seems like it is too damaged the cell cycle is stopped and the cell does not divide until the damage is repaired. Sometimes the damage is so bad that the cell kills itself. It is better to die than to produce damaged daughter cells. This act of cellular suicide is known as **apoptosis**. Sometimes the genes responsible for making proteins that check for DNA mutations and cause apoptosis are damaged and a cell will not kill itself when it should. These heavily damaged, defective cells can start to divide like crazy and and become cancerous. Proteins encoded by the BRCA1 and BRCA2 genes are responsible for repairing damaged DNA and encouraging apoptosis in cells with extensive DNA damage. When there are mutations in the BRCA1 or BRCA2 genes then the proteins produced can be really bad at their jobs and they actually allow horrifically damaged cells to progress through the cell cycle which predictably leads to cancer. People with mutations in the BRCA1 and BRCA2 genes develop breast cancer so frequently that young women who have these mutations occasionally have their breasts removed in their 20's and 30's so that they don't have to worry about developing breast cancer in the future.

In multicellular organisms(like humans) the cell cycle is tightly regulated. There are chemical signals that encourage cells to divide and signals that prevent cells from dividing. These two opposing forces live in a finely tuned balance. When an individual develops cancer the balance is severely tilted towards division. In Carol's case, a cell in her breast tissue developed damage or changes in its DNA that led to it becoming less affected by the signals that told it not to divide. The check points that would ordinarily stop this cell from dividing were no longer effective and this cancer cell did not undergo apoptosis like it should have. This cancer cell began to divide rapidly and with no control until it became a mass composed of millions and millions of cells. This mass put pressure on the surrounding tissue which caused Carol to feel the pain and discomfort that made her seek medical attention in the first place. When doctors took a sample of the tissue and examined it they found that the cancer cells had increased numbers of estrogen receptors. Estrogen is one of the chemical signals that encourages breast tissue to divide and if you have been reading any of this so far you know that those cancer cells should not get any encouragement to divide at all.. This is why Carol is taking anastrozole , a drug that prevents estrogen from being made in the body. Less estrogen in the body means that the cancer cells have fewer signals that tell them to divide and cell division slows down.



After M phase, also known as mitosis, the cell enters into a growth phase known as G1. During G1, a cell makes proteins based on the information in its DNA and those proteins go to work doing whatever that cell was designed to do. The cells that make up your muscles and your nerves basically stay in G1 forever. They are in G1 for so long that the phase is actually renamed G0 and these cells are called **quiescent** (don't undergo mitosis). This is why heart attacks and strokes are so bad because once these cells die there are no new cells that divide and replace them. If your muscle or nervous tissues die then they are not coming back, since the surrounding nerve and muscle cells will not progress through the cell cycle and divide to replace lost tissue. Some quiescent cells like those in the liver can re-enter the cell cycle if the liver has been damaged, hence the liver's reputation for regeneration. Once a cell progresses past a certain point in G1 known as the "**restriction point**" it has committed to dividing and only absolutely catastrophic events will prevent mitosis, usually resulting in apoptosis as a consequence.

During S phase a significant amount of DNA replication occurs, the goal is to double the amount of DNA in a cell so that when a cell undergoes mitosis each new cell has the appropriate amount of DNA. A human cell has 46 chromosomes, during S phase each chromosome is replicated so before mitosis a cell will have 92 chromosomes. When that parent cell splits in two then each daughter cell will then have 46 chromosomes. A chromosome that is duplicated becomes a pair of sister chromatids. During the G2 phase, proteins called microtubules are produced that latch onto the chromatids so that they can be pulled apart. The point on the chromatids that the microtubules hook onto is called the kinetochore. Microtubules also latch onto each end of the cell at points called centrioles so that the whole cell can get pulled in two. Microtubules supply the power to pull things where they need to go during the division process and are vital to mitosis.



Chemotherapy and radiation treatments are basically assaults on the cell cycle, some drugs act on specific parts of the cell cycle while others don't. Cyclophosphamide chemically alters DNA which leads to its damage and destruction. Ultimately this prevents a cell from

making proteins necessary to do essential work which can kill a cell. Proteins are the workers of the biological world and cell division is incredibly labor intensive, eliminating the workforce will halt cell division and maybe even kill the cell. It is like trying to build a skyscraper with no construction workers. The DNA damage could be so great that the cancer cell may undergo apoptosis as well. Cyclophosphamide does not have to act at any specific point in the cell cycle; it just runs through the body causing random terror to DNA everywhere. It inhibits the cell cycle at all points. Paclitaxel prevents the formation of microtubules during G2 so it is cell cycle specific and it impacts the M phase significantly. Without the power of the microtubules to pull the cell apart, division never happens, and the mitosis of cancer cells can be stopped. Radiation uses high energy light to destroy and damage DNA. This is most effective during S phase when the maximum amount of DNA is being made. If the damage to DNA is significant enough then the cancer cells will die. There are many other drugs available that act in different ways to disrupt the cell cycle and prevent cell division. If cancer cells stop dividing then they will stop spreading. Unfortunately as you might have seen through Carol's experiences, cancer cells are not the only cells in the body that undergo mitosis. Chemotherapy and radiation make no distinction between friend and foe; you have to be willing to scorch the earth to kill the enemy.

Hair is made up of cells that are constantly dividing which are why hair grows. If you mess with the cell cycle then the hair follicles pay the price as you can see in Carol's case. Without this persistent division no more hair can grow and it starts to fall out. Finger nails and toe nails are made of cells similar to those in hair and Carol's toe nails fell out as well. The cells that make up the lining of the digestive system have a rough life and frequently die due to the harsh conditions in the stomach and intestines. These cells need to be replaced continually through mitosis. Chemotherapy interferes with the cell cycle and prevents this replacement which leads to the nausea and diarrhea Carol experienced. Horrible nausea and uncontrollable diarrhea are so common in chemotherapy that they should be expected. Occasionally extremely painful sores can develop in the mouth due to cells dying and not being replaced. Red blood cells carry oxygen and are directly related to your energy level. The mitosis of cells in your bone marrow ensures that you have an endless supply of them. Chemotherapy can reduce the number of red blood cells in your body leaving you feeling extremely weak and tired like Carol did. White blood cells require a high level of production and are needed to keep the body safe from infection. Chemotherapy can make a person more susceptible to assaults from viruses and bacteria. If there are fewer police on the street then crime will increase. The DNA damage done by radiation and cyclophosphamide can also increase the risk of new cancers developing in the future but it is a future that would not be possible at all without treatment. The acceptance of these risks is what makes chemotherapy such a battle and the people that go through it very heroic. It is important to acknowledge that the side effects of chemotherapy are not just physical but also psychological as they produce losses to a person's independence, self esteem, and functionality. Hopefully this lesson showed you the other dimensions of care that a cancer patient or really any sick person needs beyond the science and medicine. Breast cancer is not uncommon and 1 out of every 8 women could have a story just like Carol's.

<u>Take Home Message</u>: When cells reproduce they have to progress through the cell cycle. Mitosis produces 2 daughter cells identical to the parent cells. Meiosis produces gametes and results in 4 daughter cells with half the number of chromosomes as the parent cell. Targeting the cell cycle is the basis of many drugs used in chemotherapy. Chemotherapy is a necessary but brutal process with side effects that are as damaging psychologically as they are physically.

Note: Quiescent cells like neurons have shown some capacity to re-enter the cell cycle but it is not clinically significant. This means that the division of these cells is something that happens in a lab but don't expect to grow new heart tissue after a heart attack or new brain tissue after a stroke. Sometimes cells like muscle cells and neurons that are viewed as permanently quiescent are also called post-mitotic. Most breast masses are not breast cancer but all breast masses need to be evaluated by a physician. Christoph Schorl is an expert in the cell cycle and spent much of his life researching the restriction point, he is delighted to answer further questions (Christoph_Schorl@brown.edu).

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Special thanks to Carol Killeen whose bravery and honesty are inspiring