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Breast Cancer: Research and Treatment

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HONORS THESIS

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We seek to understand and treat cancer to reduce a major source of human suffering. Cancer is a plague of our generation, one of the last incurable diseases. It is interesting to note that past generations did not generally live long enough to suffer from cancer. Infectious disease drastically limited the human life span. In recent history, western medicine has been able to control infection and life expectancy has risen dramatically. Cancer is the next hurdle. Modern research slowly gains insight with the hope of finding new ways to control cancer.

This paper provides information about the process by which cancer develops and how the disease can be treated. The paper begins with a discussion of the plausible causes for cancer. Then, explanations of how cancer works at a cellular level will help the reader think about cancer in the same framework as modern cancer researchers. Next, some of the current pursuits of cancer research are explored. In order to provide more specific information, the focus narrows to breast cancer. New discoveries and experimental pursuits are discussed. The last section of this paper explains the process a breast cancer patient might go through as breast cancer is diagnosed and treated.

I. Causes of Cancer

A search of the literature will reveal countless studies that correlate a variety of foods, chemicals, and lifestyle choices to increased or decreased rates of cancer. The list of options that may relate to the frequency of cancer is long, and studies often conflict with one another. Correlation studies are the only method for tracking the frequency of cancer in a population, but correlation studies have their problems. Correlation does not equal causation; A third factor may cause both elements in question, especially when the supposed cause is a broad parameter. Nevertheless, there are a few major trends of correlation studies that have stood up to hundreds of studies.

Tobacco is an undeniable cause of cancer. Smoking can cause cancer in the lung, upper respiratory tract, esophagus, bladder, pancreas, stomach, liver, and kidney. It has also been implicated in cancers of the colon, rectum, and leukemia. 30% of cancer fatalities are due to smoking (Trichopoulos, 1996). Risk increases with the frequency that a person smokes and the tar content of the cigarettes. Starting to smoke at a younger age also increases the risk for cancer. The most important factor of all, however, is duration. The longer a person smokes, the higher the risk for cancer. It is always beneficial for people to quit smoking, regardless of age or number of years they have smoked.

Diet is an equally serious predictor of cancer. A diet high in saturated fat and red meat is associated with colon and rectal cancer. A poor diet and a smoking habit are so often confounded that it is difficult to quantify the separate effects of these factors, but together they are responsible for up to 60% of all cancer fatalities (Trichopoulos, 1996).

Many other factors in the diet are responsible for certain types of cancer. Alcohol has been shown to cause cancer in the upper respiratory tract, digestive tract, and liver, and it may contribute to cancer of the breast, colon, and rectum. Excess salt has been shown to cause stomach cancer. Also, populations of children in Southeast Asia who eat salty fish have a high occurrence of cancer in the nasopharynx (Trichopoulos, 1996). Coffee and artificial sweeteners, however, have not been linked to cancer in humans. Experiments have shown the artificial sweeteners can induce tumors in lab animals, but only in doses so high that no human could consume a dangerous amount.

Environmental and work related causes have also been proven. Asbestos, benzene, formaldehyde, diesel exhaust, and radon are most toxic offenders. Workplace regulations have successfully curbed cancers caused unsafe working conditions.

People often wonder if some races are more prone to cancer than others. The current consensus is that there is *not* a racial predisposition that is due to genetic difference. Many studies have compared the rate of cancer in separate races of people and found that people of one race get cancer more than another race. However, these results can always be explained by other confounding factors. For example, if many members of a race live below the poverty line, they have an increased risk of dying from cancer. The reason is poor medical attention, not anything pertaining to race. Diet and lifestyle are other common factors that skew data. A study comparing women with breast cancer found that women in Japan are one-fourth as likely to get breast cancer as Americans. However, that same study showed that Japanese-Americans living in the United States do not have a significantly different risk for breast cancer. The racial difference was not the causative factor.

All types of radiation have been tested for the possibility of causing cancer. Studies conclude that electric and magnetic fields from power lines and household appliances do not cause cancer, no matter how close a person lives to a generator. Cell phones are another item that has come into question in recent years. Cell phones, microwaves, wireless systems, and even living creatures emit electromagnetic radiation at a higher level than power lines, but the photon energy is still several orders of magnitude less than is necessary to ionize a molecule and possibly cause a mutation that could lead to cancer. However, it is difficult to assess the compound effect of all of these factors.

Nuclear materials easily surpass the energetic threshold necessary to cause mutations. Residents of Hiroshima and Nagasaki during World War II were exposed to the most intense amounts of radiation ever observed in humans. One percent of the victims who survived more than one year after the initial blast developed cancer (Trichopoulus, 1996). This may be less than the general public expected, but considering the body's ability to correct mutations and the rare collection of mutations that are necessary to cause cancer, this is an alarmingly high statistic. Nuclear energy plants, on the other hand, do not pose the same risk to those nearby. Leukemia in not higher among those who live next door to nuclear plants and children of nuclear plant workers do not show a higher a higher rate of leukemia than the general public. The final example of exposure to radiation is chemotherapy treatments for cancer. Ironically, medical treatments that use radiation account for 1% of cancer fatalities. This is not an adequate reason to shy away from a treatment that could save a patient's life, but there is a risk. Chemotherapy patients should actively screen for other types of cancer.

Despite the many causes that can be correlated with cancer, some cancers are not due to external influences. A very rough estimate suggests that nearly one-fourth of all cancers occur independently of any of the above causes. Carcinogens within the body and genetic mistakes that are not repaired also cause cancer.

II. Cancer at a Cellular Level

Cellular Growth

Cancer is the uncontrolled growth of a single cell. It is helpful to look at the process of cell growth and division in normal cells to see how problems occur. In normal, cellular growth, cells proceed through four stages of the cell cycle. The first stage is G1 (Gap 1), a resting stage between growth. Next is S-phase, when the cell synthesizes DNA, doubles all the organs, and grows. This is followed by G2 (Gap 2), a second rest phase. The fourth stage is M-phase, when mitosis occurs and the cell divides into two daughter cells. There are checkpoints in the cell cycle at G2, after M-phase, and before S-phase begins. At each checkpoint, the cell can go back to the preceding stage to correct or complete a step (Bailey, 1998). The cycle ensures that the cell won't divide before DNA has been properly replicated and the cell has grown.

A cell divides when chemical signals reach the outside of the cell and bind to protein receptors on the surface of the cell. The signal gets relayed to the nucleus, which begins to transcribe DNA into a protein. When *growth factors* bind to surface receptors, the message for growth is received in the nucleus, and the DNA will transcribe a protein to initiate cell growth. When *growth-inhibiting factors* bind to other surface receptors, a different message is received in the nucleus, and DNA transcribes a protein responsible

for inhibiting cell division. A cell only divides when messages from growth factors outweigh messages from growth-inhibiting factors.

A cancerous cell has lost control of these constraints and divides indiscriminately. Mutations in the receptors cause them to change so that the wrong messages are received. Receptors are proteins with a signature shape and electrical charge. Only one type of protein with the exact shape and charge will fit together with the receptor, like a key in a lock. Problems occur when a mutation changes the shape or charge of the receptor. The appropriate proteins will not bind and the wrong proteins may be able to bind in their place. For example, a receptor for growth factors may change so that many different kinds of protein are able to bind to it. The cell will be inundated with messages promoting cell division. It will divide as fast as possible as long as proteins continue to bind to the surface of the cell and send growth signals to the nucleus. The cell has become cancerous. Receptors for growth inhibitors can also mutate to cause cancer. Any change to these receptors would have dangerous implications. If growth-inhibiting factors can not bind to surface receptors, the cell never receives any messages to stop dividing. Recall that the nucleus receives a balance of positive and negative messages for growth. If receptors for growth factors are normal but receptors for growth inhibitors malfunction, the nucleus constantly receives a positive message for growth. The cell will divide without limit.

Genetics

Cancer is ultimately due to changes in DNA that cause proteins to be translated incorrectly. Proteins controlling initiation and inhibition of cell growth are not functioning correctly, due to misinformation from genes. Several specific mutations on

certain genes are necessary before a cell actually loses control of growth regulation. In fact, most cancers require six or seven mutations before abnormal growth begins. The first several mutations may cause a slight increase in cell growth that results in a benign tumor. Additional mutations will cause more problems in growth regulation and ultimately cause the cell to progress into a full-blown cancerous cell that is likely to spread.

Scientists have classified genes that affect cancer into three categories: oncogenes, tumor suppressor genes, and mutator genes. Oncogenes stimulate cell proliferation. In cancer cells, they are more active than usual. Tumor suppressor genes have lost their ability to inhibit cell division in cancer cells. Mutator genes are part of a system to ensure DNA fidelity. They are involved with DNA replication and also correct mistakes that are present after replication. DNA polymerase is an example of a protein that corrects mistakes in the DNA as the DNA replicates. This system only leaves one mistake for every 10^7 or 10^8 base pairs. Other proteins correct mistakes after DNA synthesis. These proteins can remove a mismatched base pair and replace it with the correct nucleotide. They recognize the older of the two DNA strands and use it as a template. Methyl groups attach to DNA over time, so proteins recognize the older strands of DNA as the strand with methyl groups attached. If the newer DNA strand does not match the older strand corrections will be made. With this system in place, the body only leaves one mistake in every 10^9 to 10^{10} base pairs. Problems in the genes that cause these proteins to malfunction make the cell more prone to mutation errors. More mistakes get made and mistakes are left uncorrected.

Mutator genes will not correct against mutations that have been inherited. The correction system uses older (more methylated) DNA as a template to correct mistakes, but would not alter DNA from these blueprints. The body would not identify hereditary mutations as mistakes. As long as DNA replicates properly and the newly formed strand of DNA is the same as older strands of DNA, the body will not identify a problem. Harmful genes are often called mutations because they are different from others and they cause a damaging condition, but they are an integrated part of a person's genome. The word "mutation" is sometimes used in this paper to denote a *change* in DNA, but other times it refers to a problem that is hereditary.

When one mutation occurs in the cell's DNA, it appears to increase the likelihood that more mutations will occur and go uncorrected. This may be evidence that repair systems become less efficient with age. Or, perhaps the cell receives so many signals to divide that it rushes through checkpoints in the cell cycle and more mistakes happen this way. It may also reflect damage to a gene that controls mutations, a mutator gene.

One example of a mutator gene is p53. When DNA is damaged, p53 brings the cell cycle to halt and gives the cell time to repair DNA. If the DNA has been damaged beyond repair, the cell will die in a process called *apoptosis*, or *programmed death*. The p53 gene is instrumental in initiating programmed death. The function of the p53 gene is supported by an experiment with genetically altered mice. Mice who were missing the p53 gene on both alleles were viable and had no problems with growth. However, 75% had cancer after six months and 100% had cancer after ten months (Russell, 1998). The experiment showed that p53 is not necessary for growth, but has a definite role as a tumor suppressor. If both alleles of the p53 gene have been inactivated, cells won't stop to

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repair DNA and cells won't die, no matter how much damage has been done to the DNA. There are many ways that the p53 gene could be inactivated. At least seventeen proteins interact with p53. Mutations in the p53 gene itself or in any of these proteins could stop the activity of p53.

Mutations are random, rare events that build up in DNA over the course of a lifetime. It is an incredibly unlikely occurrence when the six or seven specific mutations that are necessary to produce a certain type of cancer occur in a single cell! In addition, the body's DNA repair systems must fail for each mutation. It takes time for mutations to accrue until one cell contains the unlucky combination. For this reason, cancers tend to occur later in life.

Cancers that occur in younger patients tend to involve fewer genes. A cancer that can be caused by only one or two mutations is a more likely event than a type of cancer that requires six or seven mutations. When looking at general trends in a population, not as much time passes before the unfortunate mutations occur when fewer genes are involved. Retinoblastoma, cancer of the eye, is the most common cancer in young children. True to the theory, retinoblastoma can be induced by a mutation in a single gene. It is the only known cancer that involves only one gene. The gene responsible for retinoblastoma, called RB+, is a tumor suppressor gene. When both alleles of the RB+ gene mutate, the cell loses control of growth regulation (Russell, 1998).

Heredity

It is possible to inherit one or more genes involved with cancer. A person receives the mutated form of the gene in place of the normal form. Heredity is a strong factor for retinoblastoma and it further explains why retinoblastoma occurs in young

people. Many children inherit a recessive allele, RB, which does not operate properly. They are healthy as long as the other allele for that gene functions correctly, but they have a strong predisposition for cancer. RB, the mutated form of the gene, is present in *all* of their cells. A mutation could occur in *any* of the cells to make the remaining allele of the RB+ gene inoperable. The cells will begin to proliferate without limit and become a tumor.

Some families pass along several genes that predispose people to cancer. For example, a person could receive two or three of the mutations that cause *familial adenomatous polyposis* (FAP), a type of colon cancer that requires at least six mutations before the cell becomes a tumor that will spread to other parts of the body (Russell, 1998). A genetic predisposition for cancer is not a death sentence. There are still several rare mutation events that must occur over the course of this person's lifetime before the cell becomes cancerous. Some members of the family will never suffer from cancer. However, people who inherit mutations clearly have a head start toward acquiring cancer and they tend to accrue all the necessary mutations earlier in life. When data is analyzed for populations, the hereditary link of some cancers can be seen when *younger* patients suffer from cancer.

III. Breast Cancer

Breast cancer is a common disease of out time. 185,000 new cases of breast cancer are diagnosed each year. Over 46,000 women die each year from breast cancer. In developed countries, women have a one-in-ten chance of being diagnosed for breast cancer and the risk increases with age. The average age of onset is fifty-five (Russell,

1998). Most statistics refer to breast cancer in women, but men suffer from breast cancer as well.

Types of Breast Cancer

The anatomy of the breast consists of fifteen or twenty lobes arranged in a daisy shape underneath the nipple. Each lobe has smaller lobules attached. Lobules end in bulbs that produce milk. Ducts connect bulbs, lobules, and lobes to the nipple for nursing. Lobes are surrounded by fatty tissue with lymph nodes dispersed throughout.

The lymphatic system is part of the immune system. A network or lymphatic vessels and lymph nodes make, store, and disperse cells that fight infection. Intruding cells get trapped in the lymphatic system and removed from the infected area. Lymph nodes are found under the arms, behind the ears, in the abdominal cavity, in the groin, behind the knee, and many places throughout the body.

There are two major types of breast cancer. *Ductal carcinoma* is cancer of the ducts and *lobular carcinoma* is cancer of the lobules. If cancer reaches a lymph node and metastasizes, or spreads, lymph nodes may carry it to the underarm, the area above the collarbone, or many other sites in the body.

Hereditary Breast Cancer

It is possible to have a hereditary predisposition for breast cancer. If a first-degree relative (mother or sister) has breast cancer, the patient is two to three times more likely to get cancer. Cancer is likely to have a genetic factor when patients have cancer early in life, if several family members have cancer, or when the disease affects both breasts. The average age for patients with a genetic predisposition is forty-five to forty-seven, compared to age fifty-five in the general public. However, the prevalence of

hereditary breast cancer should not be overstated. Only 5-10% of cancers may be due to genetic inheritance. *Most* cases of breast cancer are sporadic (unrelated to hereditary).

Breast Cancer Genes

Two breast cancer genes have been discovered. The BRCA1 gene was discovered in 1994, followed by BRCA2 in 1995. One study showed that 80-90% of people who have mutations in the BRCA1 and BRCA2 genes will develop cancer (Thorlacius, 1998). A population study in Iceland tried to assess the commonality of mutations to the two breast cancer genes. One mutation in the BRCA2 gene occurred in as much as 0.6% of the population (Thorlacius, 1998). These two genes are quite large and many mutations are possible. Of course, only certain mutations to the BRCA1 and BRCA2 genes cause breast cancer. Most mutations that have been observed result in a protein that is shorter than usual, suggesting a loss of function mutation. Studying these two genes could provide information for other types of cancer. Mutations in these two genes may cause ovarian, prostate, and colon cancers. Mutations in the BRCA2 gene could also cause pancreatic cancer, laryngeal cancer, and malignant melanoma. The link between each of these types of cancer is not understood at this time.

The Link to Estrogen

A collection of correlation studies provides evidence for the theory that overexposure to estrogen causes breast cancer. Estrogen controls growth of secondary sex characteristics, so it follows logically that overexposure to estrogen is associated with abnormal growth in the breast. Young people who have excessive growth (height or weight) at an early age have been correlated with a higher risk for breast cancer. Obesity

at a young age also increases the risk. The most probable explanation for these two phenomena is that these women menstruate earlier in life and are exposed to their body's own hormones for a longer duration. Obesity in adults does *not* cause a propensity for breast cancer. (However, it does increase the risk for cancer in the endometrium, colon, kidney, and gallbladder.) This suggests that early menstruation, or the exposure to estrogen at a younger age, is the true culprit, not obesity. Early menarche and late menopause are both predictors of breast cancer. In addition, women who receive supplemental estrogen after menopause also have a higher rate of breast cancer.

Some environmental pollutants may cause cancer by a similar mechanism to estrogen. Organic compounds that are ring shaped and contain chlorine have been shown to cause cancer. These compounds are called xenoestrogens because of their structural similarities to estrogen. Researchers propose that they mimic estrogen and stimulate cell division in the breast and reproductive organs. These compounds are found in pesticides like DDT. DDT, or Deet, is now illegal in the United States, but it is still used in many other countries.

All this evidence led to the conclusion that estrogen is the growth factor that is being over-expressed in cancer cells. As early as 1952, Nobel laureate Charles B. Huggins showed that hormone deprivation brings some types of breast cancer into remission (U.S. Dept. of Health and Human Services, 1984). The new strategy to fight breast cancer became finding a way to stop estrogen from binding to receptors. Researchers have identified the estrogen receptor on the surface of cells that regulate transcription (Eng, 1998). They have developed a strategy to stop estrogen from binding to those receptors. If a substance very similar to estrogen is pumped into the system, it

can bind to the estrogen receptor and take the place of estrogen. These dummy estrogen molecules do not send any kind of signal to the cell's nucleus and they block the receptors, preventing real estrogen from sending a signal. Chemists alter the chemical structure of estrogen molecules by adding hydroxyl, amino, nitro, or iodo groups to the ring structure of estrogen (Brooks, 1997). Recall that DDT contains a molecule that was so similar to estrogen that it actually sent a signal and caused the problem. The molecules created by scientists had to be carefully tested to insure that they would bind to the estrogen receptor but not actually cause a signal to be sent.

Hormone therapy using chemicals that mimic estrogen has been quite successful with some types of breast cancer. However, not all tumor cells have estrogen receptors on their surface. In tumors that have estrogen receptors, or estrogen-positive breast cancers, hormone therapy causes more than half of breast cancers to go into complete remission. Tumors with cells that do not contain estrogen receptors, estrogen-negative cancers, are completely unaffected by hormone therapies (U.S. Dept. of Health and Human Services, 1984). Research involving estrogen receptors has made more progress than any other pursuit in breast cancer research, but there are clearly other types of breast cancer and other explanations.

The p53 Gene and Apoptosis

A rare disorder called Li-Fraumeni syndrome has provided important clues for another type of breast cancer. Li-Fraumeni is a rare genetic disorder found in only one hundred families worldwide. Members of these families are prone too several types of cancer, but breast cancer is the most common (Russell, 1998).

Families with Li-Fruameni syndrome pass along a mutation in the p53 gene. This mutation is present in healthy cells as well as tumor cells for those with this rare hereditary difference. Studies of these patients may be key to solving the cause of cancer in other patients. Some unrelated cancer patients suffer from the same type of cancer, a tumor due to the same mutation in the p53 gene. It is important to note that people with Li-Fraumeni syndrome have the p53 mutation in every cell in every organ of their body, but they are not prone to every type of cancer. The mutation causes a problem with programmed death, or apoptosis, that is specific to breast cells (Russell, 1998).

As discussed earlier, the p53 gene plays an instrumental role in apoptosis for cells with a great deal of DNA damage. A new focus in cancer research revolves around finding a way to cause cancer cells to continue into apoptosis. New compounds called retinoid antagonists induce apoptosis. They have been found to be effective against all types of breast cancer, irrespective of whether the tumor is estrogen-positive or estrogen-negative (Fanjul, 1998).

An interesting twist in reproductive health is that women who have children earlier in life have a reduced risk of breast cancer, endometrial cancer, and ovarian cancer. Many women in the developed world postpone childbirth to pursue career and education. Postponing the first pregnancy has actually been identified as a risk factor. Researchers suggest that this is because having children causes breast tissue cells differentiate for a specific function. Differentiated cells are much less prone to abnormal growth. As cells differentiate, they lose their ability to proliferate. Cells eventually reach "terminal differentiation" and die. They are then replaced by stem cells and the pattern continues as stem cells progress toward terminal differentiation (Russell, 1998). Proteins

that trigger differentiation are may be signals to help the cell proceed through the cell cycle normally, followed by apoptosis. Genes that regulate terminal differentiation may be another source of DNA error that can contribute to problems with apoptosis.

IV. Detection and Treatment for Breast Cancer

Diagnosis

Patients are their own first lines of defense against breast cancer. Self-examinations can be the key to early detection and a better outcome. Cancer may take the form of a lump or thickening in the breast or underarm area, or a change in size or shape of the breast. Any change in color or feel of the skin should be checked as well. Discharge from the nipple is also a dangerous predictor. It is still important to be checked regularly by a health care professional, especially over age fifty. Simply being a woman over the age of fifty is the best predictor of breast cancer.

A primary care physician or a physician's assistant should provide information to patients and encourage patients to get regular mammograms. Women often neglect getting regular checkups because of fear, fatalism, cost, procrastination, or they are simply unaware of the risks. Health care professionals may detect a problem by simple palpation. It may even be possible to distinguish a benign tumor from a malignant tumor by feel alone, although one would not rely on this method alone.

A mammogram is a much more reliable test. Mammographic imaging technique is simply an X-ray of the breast that will show any abnormalities. All sites that offer mammograms must comply with the Mammography Quality Standards Act, a set of federal regulations to insure quality. Some physicians prefer to use ultrasonography, or ultrasound. High frequency sound waves enter the breast and bounce back, creating a

picture of the tissue. Ultrasound tests can be used to show whether a lump is solid or fluid.

If the mammogram shows calcifications or any abnormalities, the patient needs further tests. It is necessary to remove tissue to get an accurate diagnosis. A fine needle aspiration, or needle biopsy, is the least intrusive procedure. A hollow needle draws out fluid or a small amount of tissue. The specimen is sent to the pathology lab and a pathologist sends back a diagnosis the next day. A surgical biopsy extracts more tissue. A physician removes part or the entire suspicious lump. This tissue is also sent to the lab for diagnosis by a pathologist.

Treatment

Surgery is usually the first treatment when breast cancer is detected, but it may be used in conjunction with other methods such as chemotherapy, radiation therapy, or hormonal manipulation. Chemotherapy uses drugs to kill cancer cells whereas radiation therapy uses X-rays. These two methods can be a great aid for cases of very large tumors. They can shrink the tumor so that the tumor can be removed more easily by surgery. Hormone therapy attempts to combat the effects of estrogen and stop the progression of tumors.

Progress in Treatments

At the end of the nineteenth century, Dr. William Halsted performed he first mastectomies in the United States. He developed the procedure known as the radical mastectomy, or Halsted procedure. The surgeon removes the breast and muscles of the chest wall in order to remove the cancerous cells. The outcome was successful and patients survived longer, but there were problems with the procedure. Removing muscle

sometimes caused disability and swelling in the arms. Also, the procedure required large incisions and some mastectomies left a large enough gap to necessitate skin grafts. The radical mastectomy is considered outdated and is rarely used. Modern methods allow surgeons to *partially* remove pectoral muscles if the cancer has reached the muscle, but the disabilities caused by the Halsted procedure can be avoided.

Throughout the twentieth century, the trend in breast surgeries is to conserve breast tissue and move toward a less intrusive procedure. The modified radical mastectomy is a similar procedure developed in the 1960s. Surgeons remove breast tissue and axillary lymph nodes but leave chest wall muscle intact. The incision is smaller and the procedure is less disfiguring to the patient. The modified radical mastectomy has the same success rate as the radical mastectomy. A simple mastectomy is an even less imposing procedure that removes breast tissue but leaves muscle and lymph nodes. This procedure is not common and can only be used in cases of very early detection. By 1983, the National Surgical Adjuvant Breast Project developed the procedure known as the lumpectomy, or quadrantectomy, which removes only the cancerous part of the breast tissue and leaves the nipple and some breast tissue. Axillary dissection, removal of the lymph nodes, is paired with a lumpectomy to remove all traces of cancer.

Newer methods greatly improve the quality of life and psychological wellbeing of the patient, but there are limits to their success. The new surgical procedures have not actually lessened to number of people dying from cancer; they simply provide options for cancer patients. Furthermore, a modified radical mastectomy is necessary in many cases. A woman in her first of second trimester of pregnancy would not choose radiation

treatment that could harm the baby. A lumpectomy can not be used when more than one tumor is present in different quadrants of the breast. In cases where the mammogram shows calcifications which appear to be malignant, it is likely that cancerous cells are dispersed throughout the breast and a modified radical mastectomy is the best choice to ensure that all cancerous cells have been removed. The recurrence rate after a mastectomy is 8 %, whereas surgeries that conserve part of the breast have a 10-15 % recurrence rate after ten years (Mercy Health Services, 1999). However, if breast cancer does return, a patient who still has breast tissue can always have a modified radical mastectomy. A patient who had a mastectomy at the first occurrence of breast cancer will have cancer recur in the pectoral muscles, which is more difficult to remove.

The Role of the Pathology Department

Unfortunately, surgery is not the end of the story for cancer victims. Once a surgery has been performed, the hospital must confirm that the test has been successful. If the surgery has not done a satisfactory job of removing cancerous cells, further treatments are available (see Additional Treatments, below). In many cases, cancer returns, especially when it has not been detected and treated early enough. Pathologists give a prognosis for the likelihood that cancer will reappear. They may recommend frequent checkups in the future if the results are questionable.

When the pathology laboratory receives tissue specimens from surgery, pathologists conduct gross observation and dissect the tissue to collect information. They note the size and shape of the tumor and the number of tumors if there are more than one. The number of lymph nodes and the presence or absence of extracapsular lymph nodes is

recorded. It is important to observe whether the tumor has invaded the lymphatic space. This helps predict whether cancer has entered the lymphatic system.

Pathologists must make a judgement for how far the cancer has progressed. The most popular system, developed by the American Joint Committee on Cancer Classification, classifies the patient as stage 0, I, II, III, or IV. A cancer in the earliest stages is referred to as a carcinoma in situ. It is non-invasive and is limited to a confined area. Cancers that are confined to a small part of a duct, for example, may remain dormant for years or it may never become invasive. If detected and removed during this stage, cancer is considered to be cured and it is very unlikely to return (Altman and Sarg, 1992). Stage I cancer is confined to the breast area with a tumor no more than one inch in diameter. Stage II cancer has spread to the underarm lymph nodes and has a slightly larger tumor. In stage III cancer patients, cancerous cells have spread to lymph nodes or nearby breast tissues and the tumor is more than two inches in diameter. Stage IV cancer is *metastatic* and has already spread to other organs (Cook and Dresser, 1996).

Metastasis is the stage when cancerous cells break off from the original tumor and travel to other sites in the body through the blood or lymphatic systems. Common sites for secondary tumors include the chest wall, local lymph nodes, brain, lungs, liver, bones and central nervous system (Skarin, 1992). When a secondary tumor develops in another part of the body it is still considered breast cancer because it consists of cells from breast tissue (Cook, 1996). A pathologist must identify the type of cell that the tumor came from. If the tumor is a secondary tumor from another part of the body, careful identification of the type of cell can identify another cancerous site in the patient's body.

When the pathologist finishes these observations, he or she dissects the tissue and removes representative samples for testing. A sample directly on the surgical margin will be tested to determine if all of the cancerous cells have been removed. The hope is that the tissue on the surgical margin is normal tissue, free of cancerous cells. Tissue samples are removed at intervals throughout the tissue to find out the extent and multitude of cancerous cells. Each lymph node must be removed for tests. Presence or absence of cancer in the lymph nodes illustrates whether cancer has traveled to other parts of the body. It is an important gage of the patient's future health.

Tissues that the pathologist has chosen are processed overnight in the pathology lab. Tissues are fixed in formylin and a series of alcohols, then permeated with wax. The wax makes the tissues solid so that it can be sliced. The small block of wax with tissue embedded in it is placed in a machine called a myotome, which slices the block into strips that are four microns thick. This is thinner than the width of a red blood cell and gives the doctors an excellent view of the tissue. This very thin strip of tissue is placed on a glass slide. The slide goes through a series of stains. Different stains adhere to different types of tissue, depending on the chemical properties of the tissue. The different colors help distinguish one type of cell from another. The next morning, the pathologist can look at a cross-section of the tissue under a microscope. This view of the cells under the microscope gives all the information a pathologist needs to diagnose the cells as cancerous or healthy.

The pathology lab may want to make extra slides of the tissue for special stains. Histologists run special tests for estrogen or progesterone receptors. They use the different chemical properties of each type of cell to determine if the cells are estrogen-

positive or estrogen-negative. If the cells are estrogen-positive the patient has a type of cancer that has been studied more, and the patient has more options for treatment.

Additional Treatment

Physicians use the observations and recommendations made by the pathologist to plan further treatment. The report from the pathologists may reveal that cancerous cells remain in the body even after surgery. Even if the cells appear to be free of cancer, pathologists may recommend further treatment for severe cases when the cancer had progressed through the stages to a dangerous level.

If physicians decide further treatment is necessary, they must decide whether they are treating a patient who can be cured. In some patients, the cancer reaches an incurable stage and the goal is simply to prolong life and sooth the symptoms. Chemotherapy may not be worth it if the patient is too weak to handle the side effects. Hormonal therapy may be a better option.

Other patients are curable, but they need additional therapy to exonerate all traces of cancer. Treatments after surgery are known as *adjuvant* treatments. They may be recommended for severe cases when there is a high risk that cancer will return. Patients have adjuvant treatments tailored to their needs, but a typical treatment would be chemotherapy for four to six months, hormonal therapy for five years, or possibly both. Adjuvant treatments intend to permanently rid the body of cancer.

Radiation therapy is commonly used after surgery to get rid of remaining cancer cells and prevent the return of cancer. Treatment is recommended when the pathologist reports a tumor greater than five centimeters, a tumor that has invaded the skin or chest wall, surgical margins that are cancerous, and multiple metastatic lymph nodes.

Radiation treatment allows surgeons to perform surgeries that conserve more of the patient's breast, then follow up with radiation treatment. It is especially preferable when cancer has invaded muscle in the chest wall. Removal of that muscle could leave the patient with limited arm movement, while radiation will leave the muscle intact. Radiation treatment can begin as soon as surgical scars have healed. A common radiation treatment program is thirty to thirty-five daily treatments over a seven-week period.

Bone marrow transplants attempt to conserve bone marrow stem cells that could be killed by the chemotherapy or radiation therapy. Stem cells are removed before chemotherapy begins and replaced after the treatments are over. The procedure is very dangerous and a few patients die of the procedure. Bone marrow transplants are actively being researched and may become more common in the future.

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