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Malignant Melanoma

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Topics in Biology

Abstract

Malignant melanoma is a cancer of melanocytes. It is caused by environmental (mainly UV light) and hereditary factors. Melanoma has the ability to spread rapidly to nearly every organ in the body. The incidence of melanoma has been rising steadily in Caucasian populations since the 1900s. Fortunately, the disease is completely curable with little chance of recurrence if caught early enough. Treatments for melanoma include surgically removing the melanoma, lymphadenectomy, immunotherapy, and chemotherapy. The goal of this research paper is to explore the causes and treatments of melanoma as well as to call attention to this rapidly prevailing cancer.

Melanoma is the most deadly type of skin cancer, and is also one of the fastest growing types of cancer in Caucasian populations. Since the early 1900s, there has been an alarming rate of increase. In 1935, the lifetime risk for developing melanoma was 1 in 1500 (Figure 1). In 2002, the risk had increased to an astonishing 1 in 68 (American Academy of Dermatology). Melanoma is a cancer found in melanocytes, which are cells that produce melanin, although it can spread to other parts of the body if not treated promptly. Melanin is the pigment that gives our hair, skin, and eyes color. It also protects our skin cells by absorbing harmful ultraviolet rays (Schofield & Robinson, 2000).

Melanocytes are located in the dermal-epidermal conjunction in our skin, and become cancerous when overexposed to UV rays. When UV rays causes a mutation in the gene which controls the production of a protein that regulates melanocyte cell division, the melanocytes began to proliferate uncontrollably (Schofield & Robinson, 2000). This is how melanoma begins. According to the American Cancer Society, there will be 68,130 estimated new cases of melanoma and an estimated 8,700 deaths resulting from the disease in 2010. From 2003-2007, the median age at diagnosis for melanoma was 60, and the median age at death was 68 (National Cancer Institute). In North Carolina alone, the incidence rate of melanoma is expected to rise 4.8% this year (National Cancer Institute). This increased incidence of melanoma is mostly due to lifestyle changes. Society as a whole is spending more time outside and covering up less skin than in the past. Ozone depletion is also a possible cause for the increased incidence of

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melanoma but many experts believe that it has had minimal effects (Haas, Hogle, Moore-Higgs & Gosselin-Acombs, 2007)

It is widely agreed that overexposure to UV light is the primary cause of melanoma. There is strong evidence to back this up. When melanocytes are exposed to more UV light than they can absorb, the photons of the UV light penetrate the cell and break bonds in the DNA, which results in mutations. Melanoma begins on parts of the body that have received intense intermittent exposure to the sun. Researchers found that melanoma is most common on the backs of men and legs of women, both areas that receive intermittent exposure as opposed to constant exposure. Melanocytes on these parts of the skin are not accustomed to high levels of UV light and are therefore more susceptible to overexposure. In addition, most melanoma cases occur in Caucasians because there melanocytes produce lesser amounts and lighter forms of melanin than do those of darker skinned people, which results in less protection from UV rays. Moreover, it has been found that the incidence of melanoma increases proportionately with the amount of UV exposure in a given geographical area. For example, the most cases of melanoma occur in Northern Australia, where people receive an intense amount of UV light because they live near the equator. On average there are 2000 new melanoma cases each year in Australia (Figure 2), which is more than any other country (Cancer Council Victoria). Also, several population migration studies suggest that when people who reside in temperate climates migrate to tropical climates, their risk of melanoma increases (Schofield and Robinson, 2000). For example, if a person moves from Alaska to Florida, they will be at a greater risk of developing melanoma because their melanocytes are not used to the high levels of UV exposure.

Though excessive sun exposure may be the leading cause of melanoma, it is not the only cause. A person's genes play a role in their risk for melanoma as well. The p16 gene, a

tumor suppressor gene, was the first gene identified to be associated with regulating melanocyte growth. If a person is deficient of the p16 gene through hereditary means or some other reason, they could develop melanoma with even a little exposure to UV light. According to the "Multiple Hit Theory", several of the genes that regulate cell growth (including the p16 gene) must be damaged for a cell to become cancerous. When UV light damages one of these regulatory genes, the cell begins to proliferate uncontrollably. When the cell divides, the new cell's DNA is identical to that of the original cancerous cell (Schofield & Robinson, 2000).

A mole is a cluster of melanocytes that are all clones of a single melanocyte. Most melanomas start in moles. Moles are formed when regulatory protein making genes are partially damaged, resulting in lesser amount of regulatory protein to restrain the proliferation of the melanocytes. Because of this, a mole is more susceptible of developing melanoma (Schofield & Robinson, 2000). A person with greater than 50 moles on his or her body has a much greater risk of developing melanoma. If a mole is **a**symmetrical, has irregular **b**orders, **c**olor variation, a **d**iameter larger than that of a pencil eraser, and is **e**volving (ABCDE); there is a high chance that it could have cancerous cells (Poole, 2005).

In 1967, Dr. Wallace Clark devised a system that rated melanomas based on how deep they invade the skin. Clark's level I (also known as melanoma in situ) is when melanoma is present only in the dermal-epidermal conjunction. Over time, the melanoma cells grow downward. When they invade the papillary dermal layer, they are said to have reached Clark's level II. In Clark's level III, they have completely filled the papillary dermal layer. In Clark's level IV, the cells have invaded the reticular dermal layer and Clark's level V is when the melanoma has reached the subcutaneous fat (Figure 3). As Clark's level increases, so does the probability of the melanoma reoccurring (Poole, 2005). Also, after Clark's level II, the cancer

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becomes much more difficult to treat and the ten year survival rate of patients decreases (National Cancer Institute).

Once the melanoma has reached the dermal layer, they are considered invasive because they can enter the lymphatic system and the bloodstream. Most melanoma cells are not capable of doing this, but it takes just one cell to enter the lymphatic system for the cancer to spread to other parts of the body, a process known as metastasis. After melanoma enters the lymphatic system or bloodstream, it can invade various body organs, such as the brain, lungs, and liver. In metastasis, the melanoma cells stick to a blood vessel in an organ. Next, they make their way into the tissue of the organ, where they then release cytokines, which brings new blood vessels to them so they can be nourished (Schofield & Robinson, 2000). Melanoma is unlike any other cancer in that it can spread to any organ in the body. Metastasis can be classified as regional or distant. As the names imply, regional metastasis is when the melanoma is restricted to being between the primary site and the lymph nodes that drain the primary site, and distant metastasis is when the melanoma spreads to other organs, such as the brain or lungs (Poole, 2005).

Melanoma is a tragic disease, as is any other cancer. Fortunately, however, it is completely curable if caught early enough. The first step in the treatment process is being diagnosed with melanoma. If a doctor suspects a cancerous mole, he or she will take a biopsy of it and send it to a pathologist. The pathologist then examines it under a microscope and determines whether cancerous cells are present and what stage they are in.

Regardless of what stage the melanoma is in, surgery is usually always involved in the treatment (figure 4). A wide local excision is used to remove the melanoma and tissue around the primary site. How wide the excision is depends on the depth to which the melanoma has invaded.

When a large piece of skin is removed, the adjacent skin flap is used extended and stitched over the excision to cover the wound. If it is suspected that the cancer has metastasized, then a lymphadenectomy may be performed. In a lymphadenectomy, the lymph nodes are removed and analyzed to see if they contain cancer. However, in many cases, this treatment is unnecessary. A relatively new technique known as a lymphoscintigraphy allows doctors to inject a small amount of radioactive tracer into the skin where the melanoma first occurred. Doctors can then use nuclear medicine scans to detect the presence of radioactive tracer in the draining lymph nodes (Poole and Guerry, 2005). Another technique, known as the sentinel node biopsy, involves removing the sentinel lymph node, which is the first lymph node that the cancer is likely to spread from the tumor (National Cancer Institute).

In many patients, the melanoma reoccurs after surgery because they may have some microscopic cancer cells that were not removed. When this happens, doctors turn to adjuvant therapies. One adjuvant therapy is immunotherapy, which uses the body's immune system to attack melanoma cells. Normally, the immune system for patients with melanoma does not recognize melanoma cells as foreign. The goal of immunotherapy is to make the immune system recognize these cells as being abnormal or foreign. Researchers have developed melanoma vaccines against tumor specific antigens. However, all melanoma cells do not make the same antigens; so many melanoma cells are often missed. Tumor specific vaccines are still only available in clinical trials (National Cancer Institute).

Another approach to immunotherapy is the use of cytokines. Alpha interferon and interleukin 2 are two cytokines that have been found to be most effective in the treatment of melanoma. When alpha interferon is injected into the body, it changes the surface of melanoma cells by making them more easily recognizable by the immune system. A study conducted in the

1990s found injections of alpha interferon after surgery slightly more effective in reducing recurrence than no treatment after surgery. However, a more recent long term study found that there was not a statistically significant difference overall. Both studies found that the injections were effective when the melanoma had only spread regionally, but not when it had metastasized to other organs. All in all, the studies found that injections of alpha interferon actually helped approximately 20% of the people injected (Schofield & Robinson, 2000). Also, patients reported side effects such as chronic fatigue and depression. Interleukin 2 (IL-2) is a cytokine similar to alpha interferon, but has a different effect on the cells of the immune system. IL-2 increases then number and fighting power of T-cells and other cells in the immune system (Schofield & Robinson, 2000). Several trials were conducted to find the effectiveness of IL-2, and much like alpha interferon, it helped less than 20% of patients. IL-2 is still being studied and has not been approved as an adjuvant therapy yet.

Another type of adjuvant therapy is chemotherapy. The most commonly used drug to treat advanced melanoma is DTIC (Dacarbazine). There is no other single drug that has been proven more effective and consistent. Doctors' and researchers' knowledge of how the drug works is limited. It is known that it randomly kills cells that are dividing more rapidly than others; however, there are other drugs with that ability that have no effect on melanoma. Like any metastatic melanoma treatment, only 20 to 25% of patients are affected by the drug. Side effects include severe nausea, muscle aches, and lowered blood cell counts. Temazolamide and fotemustine are two other chemotherapy drugs that have similar effects and have are effective in about 20% of patients. There are also several other drugs that may be used in combination with each other. The most common combination is called the Dartmouth regime. "It combines the chemotherapy drugs DTIC, cisplatium, and BCNU with a commonly used breast cancer pill

called tamoxifen." (Schofield & Robinson, 2000). The Dartmouth regime is effective in approximately 30 to 35% of patients, with 10% having complete remission and 20 to 25% having partial remission.

Currently, there is a lot of research being conducted on melanoma treatments and cures.. Large strides are also being made in identifying which genes are associated with melanoma, so a gene based therapy may be in sight. Hopefully, by informing the public of the dangers of UV light, the increasing trend of melanoma incidence will finally come to a halt.

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Appendix

Figure 1



Lifetime Risk of Developing Melanoma in the U.S.

(www.medscape.com/.../03/470300/470300 fig.html)



National Cancer Institute

Figure 3



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Clark's Levels



Melanoma Workup:

Chest radiography, complete blood count, and liver function tests for AJCC Stage I/II +

Magnetic resonance imaging of brain, computed tomography of chest/abdomen, or positron emission tomography scan for AJCC Stage III

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