On the Cutting Edge of Prostate Cancer

By Emily Disbrow

Reigning as the second leading cause of cancer death in men, prostate cancer will affect approximately one in six men over the course of a lifetime, causing upwards of 25,000 deaths each year in the United States. Yet many men endangered by this disease remain reluctant to “go under the knife” and have their prostate removed in a radical prostatectomy. Drs. Anna Bill-Axelson and Lars Holmberg, primary authors of a recent study, may have shown that surgery is the most beneficial option for these patients...

In the United States, about 60,000 men undergo radical prostatectomies each year; this procedure is being increasingly more common in many Western countries. However, exceedingly few attempts have been made to calculate the true benefits of this surgery. As a result, patients are too frequently misinformed, leading to possible incorrect decisions about treatment and opening the door for further progression or metastases of cancerous cells as time moves forward. This study furthers our understanding of the benefits of radical prostatectomy as a potential cure for one of the most prevalent cancers plaguing society today.

In its early stages, prostate cancer does not usually produce many symptoms. A little more than a third of prostate cancers are not diagnosed until the cancerous cells have spread outside the prostate. The earlier that the cancer is detected, the higher the chance of a successful treatment and recovery with little or no side effects. When choosing treatments, patients must consider multiple factors, including how quickly the cancer is spreading, how much it has already grown, and their own age and health status. Historically, once diagnosed, prostate cancer patients have been offered various options for treatment, the three most prominent being radical prostatectomy (to remove the prostate altogether), intensive radiation or hormonal therapy (to shrink or contain the existing cancer cells), and watchful waiting (where treatment is deferred until the tumor grows larger).

In Bill-Axelson and Holmberg’s study, 695 men were recruited from 14 centers in Sweden, Finland, and
Iceland. In order to be eligible to participate in the study, each potential subject had to be under 75 years of age, maintain a health status that would allow for radical prostatectomy, have a life expectancy of more than ten years, and exhibit the “presence of newly-diagnosed, untreated, localized prostate cancer”\(^1\). The men were randomly assigned to one of two groups – one group of 347 undergoing radical prostatectomy, and one group of 348 assigned to watchful waiting. This study involved statistical analysis of the resulting status of each subject after ten years of participation. Bill-Axelson and Holmberg presented two primary hypotheses: first, that the risk of death due to prostate cancer decreases over time as a result of the initial tumor being removed in radical prostatectomy, and second, that radical prostatectomy has a significant positive effect on overall survival.

The participants were given regular clinical examinations throughout the course of the ten-year study, with their medical records being intensely reviewed during this time. As participants died, their files were released to an independent committee to determine the exact cause of death; this committee was blinded, as they did not know which treatment group each deceased patient belonged to. The committee determined four main end points: death due to prostate cancer, distant metastasis, local progression, and death from any cause. Distant metastasis involves the emergence of cancerous cells in other parts of the body; local progression includes symptoms such as recurrence of tumors localized to the prostate gland or urinary obstructions indicative of prostate problems.

Relative risks and differences in cumulative incidence were computed (with 95 percent confidence intervals) as measures of effect for each end point.

Bill-Axelson and Holmberg used Gray’s test to disprove the null hypothesis, with a p-value of less than 0.05 showing statistical significance. All figures were compiled from the ten-year follow-up (there was an initial follow-up approximately five years, or halfway, through the study). The results of the statistical analysis confirmed both hypotheses. Initially, 347 men were assigned to radical prostatectomy; after ten years, thirty died of prostate cancer and fifty-three of other causes. Of those fifty-three patients, seven of them showed signs of recurrence of prostate cancer.
Similarly, 348 men were assigned to watchful waiting; however, fifty died of prostate cancer and fifty-six died of other causes. Of those fifty-six participants, twenty-one indicated that prostate cancer had re-emerged in some form. With regards to overall occurrence of metastases after ten years, approximately 14% (50 of 347) of the men in the radical prostatectomy group had distant metastases, much less than the 23% (79 of 348) of men in the watchful waiting group exhibiting metastasis. The incidence of local progression showed a similar contrast much sooner. After five years, 8.1% of the radical prostatectomy group showed signs of local progression, as opposed to 27.2% of the watchful waiting group – this difference increased over time to respective cumulative incidences of 19.2% and 44.3% at the end of the study. Remarkably, the trends in overall mortality showed a statistically significant difference by the end of ten years: 83 of 347 men in the radical-prostatectomy group had died compared to 106 of 348 men in the watchful-waiting group.

What do all these statistics mean? It means that patients who choose to undergo radical prostatectomy, to risk “going under the knife”, reduce their risk of dying from prostate cancer by 44% in this study. Furthermore, according to this example, local progression is 67% less likely to occur and metastasis is 40% less likely to occur. Most importantly, in this instance, death is 26% less likely to occur over the ten-year period following surgery. Bill-Axelson and Holmberg also reiterated that over the first five years of this particular study, radical prostatectomy cut the risk of dying from prostate cancer in half, and reduced the risk of further cancerous growth by a full 37%.

How accurate are Bill-Axelson and Holmberg’s findings? Should future physicians be herding prostate cancer patients into the operating room routinely? Bill-Axelson and Holmberg maintain that while radical prostatectomies do reduce the occurrence of all the end points investigated, the absolute difference in survival rates is moderate. Thus, decisions about treatment options will most likely remain painful and difficult. However, with this data, patients can now weigh the risks associated with the surgery (namely possible varying degrees of impotence and incontinence) against the now-quantified and increasing recurrence of prostate cancer and higher death
rate in those who participate in watchful waiting. This study, and its potential replications, could lead to a much higher number of patients desiring to undergo radical prostatectomies. This increased demand should inspire a second look at prostatectomy techniques, with the goals of facilitating the procedure and attempting to eliminate the side effects. This study suggests that radical prostatectomy is the more effective choice to wipe out the cancer over time; the individual decision is still left to the patient, as is outlined in the principles of medicine.

Personally, I would like to see this study replicated with a larger, more geographically diverse population. Furthermore, the nature of the methods of this study encourages another follow-up of these patients, perhaps at a time of fifteen or twenty years after treatment. I believe that another follow-up study would further confirm Bill-Axelson and Holmberg’s long-term hypotheses, or at least give researchers a clearer picture of the long-term effects of the various treatment options. I think the age parameters of this study are acceptable, since the results are based on statistical analysis of causes of death and prostate cancer tends to affect older men. Another interesting angle would be to examine subgroups within the experiment population, i.e. age, racial, or ethnic subgroups. Do younger men have a better chance of recovery? Is prostate cancer race-selective in any sense? Regardless, Bill-Axelson and Holmberg have decidedly taken the first step to quantify the benefits of surgery to correct prostate cancer; perhaps their technique and analysis can be applied to other populations or other types of cancer in order to glean more knowledge which may help society curb the harmful influence of cancer on our world.

Reference:

The Mystery of the Molecular Clock

By Ryan Reynolds

Many researchers believe the molecular clock can be calibrated using metabolic rate—a notion Dr. Robert Lanfear believes he has thoroughly discredited.

By analyzing the amount of evolutionary divergence between two homologous genes, biologists can infer approximately how much time has passed since their divergence. This can be used to date many types of evolutionary events, most frequently speciation. Despite its great utility, this technique is notorious for its wide margin of error. As such, many researchers aim to find a way to accurately predict rates of molecular evolution and make the clock more reliable. One popular hypothesis holds that high metabolic rates correspond to rapid evolution. To test this notion, Dr. Robert Lanfear of the Australian National University and colleagues collected data on the metabolic and microevolutionary rates of more than 300 animals, but they found no significant correlation between the two.

Unfortunately, the picture is complicated by wide variance in mutation rates, contributing to great uncertainty in the estimates of time passed. This variation was observed early on and is well documented, but scientists have yet to find a clear explanation for what causes it. Among the possible contributing factors that have been suggested are selective pressure and body size. Selection could augment any mutation rate, whether sequence conservation or diversity was required, but it is not immediately obvious why many parts of the genome would be subject to such effects.

Many studies have observed that smaller animals tend to have greater substitution rates, to the extent that this trend is largely accepted. One explanation is the generation time hypothesis: smaller animals tend to go through more generations in a given time span, so more mutations can accumulate. Others have suggested metabolic rate as the primary cause. It is known that rapid metabolism would result in greater production of intracellular oxygen radicals that can damage DNA; the assumption is that this radical production will lead to more heritable mutations. While some studies have noted a correlation between metabolic rate and molecular evolution, most of them had smaller sample sizes than others that noted no such trend. Is it possible that the observation was entirely spurious?

Lanfear’s group took extra precautions to avoid the shortcomings of previous studies. They compared 12 different genes, including some coding for both RNA and proteins found in both the nuclear and mitochondrial
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The species examined comprised a wide variety of animals, including a large number of invertebrates. Totaling more than 300 species, this allowed for generous sample sizes. Although this wide comparison was sufficient to ensure that its conclusions were applicable throughout the metazoa, they did not attempt to test members of other kingdoms.

This study compared pairs of closely related species. In each case, information on the metabolic rate and body size of each species was collected from the literature, as well as available genetic sequences. The authors calculated the “branch length” for each species, which is how much it has diverged from the pair’s common ancestor (based partly on comparison to outgroups). It is assumed that the longer branch length corresponds to the faster rate of molecular evolution. These data were utilized in sign tests that ignored magnitude and looked only at direction: did the population that had been evolving faster also have a greater metabolic rate or a smaller body? This test allowed for a comprehensive comparison without the need to determine how long the pair had been diverging. A second set of tests compared this distribution with what would be expected for constant or varying substitution rates, and linear regressions were calculated comparing the different variables.

In spite of the battery of tests performed, not one iota of direct evidence was found for a correlation between metabolic and substitution rates. As expected, they did see plentiful variation in evolutionary rate, as well as a trend between that and body size—in mammals. They also found evidence of a significant effect in some genes when using a proxy of metabolic rate. This variable was a predictor of metabolic rate based upon size and environmental temperature that had been used in previous studies.

Lanfear devotes a significant portion of his article to criticism of the metabolic rate hypothesis, in an attempt to explain its observed insufficiency. He notes that metabolic rate is not the only significant factor in the production of oxygen radicals; differing efficiency could drastically alter it. He also points out that radicals tend to be short-lived, so those produced in mitochondria would not be able to reach the nuclear genome. If this were the main reason, however, we would expect to still see a correlation in the mitochondrial genes. We do not, so there must be more to the story.

Another proposition is that mitochondria in germ cells could be less active than those found elsewhere. If this were the case, metabolic rate may indeed correspond with mutation, but not the sort that would be passed on. It is also known that efficiency of genome repair varies between organisms, which could severely obfuscate any mutation trend that may have developed. Improving DNA repair is one way natural selection could slow down the molecular clock. Additionally, there is the possibility of adaptive substitution resulting in increased rate.

Assuming all the statistical tests were performed correctly, this study indeed strikes a hefty blow to the metabolic rate hypothesis. Even if there is a relationship, it is too heavily obscured to be used for calibration of the molecular clock. That much has been amply demonstrated, but there is still plenty about the situation that is unclear.

It seems particularly difficult to decouple the many variables involved in molecular evolution. If metabolic rate and generation time are related, then how can we be certain which one is responsible for an observed trend? Lanfear believes that other
experimenters found positive results with metabolic rate as a side-product of body size, but why wasn’t this effect seen in his analysis? Why did they find positive results with the metabolic rate proxy?

It is regretful that the bulk of data on molecular evolution is limited to the animal kingdom. One wonders if the same principles could be applied to plant or bacterial genomes. Microbes could be particularly useful, as their rapid reproduction might allow for measurable amounts of molecular evolution over the span of an extensive research project. This would allow for investigation of substitution rates in a controlled environment. There would certainly be a few differences in such a system; the direct contact of bacterial cells with the surroundings likely raises the significance of environmental factors. Also, the effects of the separate germ cell line present in most animal species would not influence it.

This writer, for one, expects selection to win out as the dominant factor in varying rates of molecular evolution. It is already well established that some genes, such as those for immunity and smell, are under pressure for diversity and therefore mutation. Most of the genes in this study are essential for cellular function, so they would likely be under conservative pressure, if anything. One way to eliminate this complication is to only consider substitutions that have no functional significance. This would unfortunately not eliminate the effects of differing molecular repair rates. If correct, it will be quite difficult to attempt to predict which lineages would have stronger pressures. Perhaps certain survival and reproductive strategies, such as K and R selection, will be found to determine their significance. In any case, the complexity of biological systems and sheer number of factors that might affect substitution rates would seem to indicate that it will take some time and clever experiment before a clear picture comes into view.

Reference:
1 Lanfear, Robert et al. 2007. Proc Natl Acad Sci USA. 104(39), 15388-15393.
Coffee: Four Cups a Day Keeps Breast Cancer Away?
By Catherine Nezich

Many Americans consume more than one cup of coffee or tea each day. There is new evidence that these beverages may reduce the risk of benign breast disease for premenopausal women.

From college students to doctors, coffee and tea are frequently consumed for their stimulatory effects. These beverages are complex mixtures of active biochemical compounds, such as caffeine and polyphenols, which scientists have begun to associate with cancer. Many studies have analyzed the effects of caffeine on the development of benign breast disease (BBD), a risk factor for breast cancer, but results are limited and contradictory. Black tea polyphenols have been recently linked to the prevention of various cancers, but its link to breast disease has not been directly studied. This is why Baker et al. investigated whether there was a relationship between breast cancer risk and the consumption of regular coffee, decaffeinated coffee, and black tea. Because these beverages are consumed so habitually worldwide, their findings give new hope for effective prevention of BBD in premenopausal women.

Baker and colleagues conducted a hospital-based, case-control study of individuals who received medical attention at Roswell Park Cancer Institute (RCPI), a large regional cancer treatment center, between 1982 and 1998. In their study, they interviewed a case group of 1932 women (98% Caucasian) who had been diagnosed with invasive breast cancer within a median time of 19 days of participation. The control group included 1895 women, again mostly Caucasian, who had gone to RCPI with a suspicion of breast neoplasms, but had not been diagnosed for such. All participants answered a Patient Epidemiology Data System (PEDS) questionnaire that collected information regarding menopausal status, reproductive experiences, demographic background, occupational and environmental exposures, medical and family history, and other lifestyle factors.
such as diet and daily consumption of regular coffee, decaffeinated coffee, and black tea. Trend tests and regression analyses took into account several variables, including residence inside or outside of western New York, menopausal status, and age at birth of first child.

The study found that breast cancer risk was 40% lower in premenopausal women who consumed four or more cups of regular coffee per day. However, this protective effect was not seen in premenopausal women who drank decaffeinated coffee or black tea. The study also did not find any association between consumption of any of the three beverages with breast cancer risk among postmenopausal women.

Baker et al. also searched for a connection between coffee, decaffeinated coffee, or black tea and either of two histologic subtypes of breast cancer: ductal and lobular. There were 46 cases of premenopausal women with lobular carcinoma who experienced an increased risk of lobular breast cancer by consuming one cup or less of coffee per day. Furthermore, this study reports a tentative observation that by drinking any amount of black tea, these same 46 women experienced a reduction in lobular risk.

Baker and colleagues systematically and meticulously generated revealing statistics and trends. They considered different effect modifiers for each beverage because each one presents a different exposure to a person. If they calculated a factor to significantly affect breast cancer risk for a beverage, that factor was then included in the final trend analysis. They even considered consumption of the other two beverages for each drink. Most importantly, unlike any other previous study, Baker et al. stratified their data via menopausal status. In short, this study is legitimate and offers sound statistics and conclusions that should be followed up with a similar study to test their replication.

This current study was strengthened by its large sample size, which allowed a good comparison between pre- and post-menopausal women. However, because the research had a case-study design, it is probable that some selection bias may have occurred in order to compose a group of patients specifically treated at RPCI. Also, this group probably did not represent the general population of women in the nation with or without breast cancer. Yet, their self-reported daily consumption of coffee or tea is probably representative since these drinks are either consumed regularly or not at all.

A major problem with studies such as this one is that “benign breast disease” is actually a broad category of nonneoplastic breast cancer subtypes. There are three main subtypes: nonproliferative, proliferative without atypia, and atypical hyperplasia. As Baker et al. recorded an increase in lobular breast cancer risk with consumption of black tea in a subsample of 46 cases, another recent study revealed that coffee consumption significantly increased the incidence of only atypical hyperplasia in a small group of women. These findings indicate that certain effects of caffeine and polyphenols may be limited to certain histological types. Past research has not considered this aspect directly, but the study by Baker et al. warrants the increased consideration of this variable in future research.

BBD is a condition that implicates many complex factors in its risk analysis. The methodology of Baker et al. accounted
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for several of these confounding variables extremely well, providing reliable statistics. However, future research calls for a study that composes the case and control groups randomly from the general population rather than from a specific hospital. The “general population” should also include an equal number of women from several different racial backgrounds, rather than being composed of mostly Caucasian women, as in this study.

The next step is to examine the association of beverage consumption with women who have different histological types of breast cancer. It would also be interesting to investigate whether other widely consumed caffeine-containing beverages, such as Coca-Cola, have any effect on breast disease. New questions must be asked, such as: Does caffeine or polyphenols alone affect BBD, or is it their combination that produces the effects observed in this study? Scientists need to unearth the mechanisms of the benefits from coffee and tea. Yet, maybe other studies need to focus more on the women’s diets: Do coffee drinkers eat healthier than non-coffee or tea drinkers? Do coffee drinkers get more regular check-ups? If this research is pursued, the future may hold personal treatments for women with different subtypes of breast cancer, utilizing compounds that most people are exposed to daily.

Reference:
Breast Cancer & Pregnancy: Is Race A Factor?

By Erica Richards

Many studies have revealed that reproductive factors such as the number of pregnancies a woman has and whether or not she breastfeeds affect how likely she is to develop breast cancer, but few have investigated how race could impact risk.

African American women have the highest death rate for breast cancer in women under 70. In light of this statistic, it would seem that studies of breast cancer would involve large numbers of African American women. But in fact, the opposite is true.

Past studies of the relationship between reproductive factors and risk of breast cancer have been conducted primarily with white women, and these factors were highly indicative of how likely a woman was to develop a tumor. But studies involving African American women have been limited. Studies that were done seemed to indicate that number of pregnancies and age at first pregnancy had the same impact on all women, regardless of race, but that the effects of breastfeeding may differ. So how much does race really affect breast cancer, and why are African American women more likely to die from it? By conducting a study that involved both white and African American women, as well as women of different age groups, Ursin and colleagues\(^1\) came to the conclusion that risk of breast cancer decreased significantly with each pregnancy in all age and race categories, but since African American women were less likely to breastfeed and usually breastfed for a shorter time period than white women did, they were less likely to benefit from the decreased risk of breast cancer that breastfeeding provided.

Scientists believe that women who have one or more complete pregnancies have a lower risk of breast cancer because of the dramatic hormonal changes pregnancy causes in the body, and especially in the mammary glands. It has also been shown that the more menstrual cycles a woman has in her lifetime, the more likely she is to develop breast cancer, because breast cancer risk is associated with lifetime exposure to estrogen. The number of times a woman is pregnant, and the length of time she breastfeeds after each pregnancy, will affect the number of menstrual cycles she has during her lifetime and therefore her risk of developing breast cancer. Other factors that may also lower risk because of decreased number of periods are late menarche (age at first period) and early menopause.

In their study, Ursin et al. interviewed a case group of 4,567 women (2,950 white and 1,617 African American) who had been recently diagnosed with invasive breast cancer, as well as a control group who had never been diagnosed with cancer. They collected information about reproductive history, medical history, family history of cancer, and other lifestyle factors such
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as smoking, alcohol use and exercise, up to the date of the cancer diagnosis. The reproductive factors that were considered were whether a woman had ever been pregnant (gravidity), whether she had ever had a full-term pregnancy (parity), number of pregnancies and full-term pregnancies, and years since last full-term pregnancy. Other factors that were considered included whether a woman breastfed and the duration of breastfeeding. Odds ratios (ORs) were calculated based on responses, and data was analyzed separately for women older than 50 since risk factors appear to have greater affects in older women, possibly as a result of the onset of menopause.

The study found that, compared with women who had never been pregnant, young white women who had a full-term pregnancy had a 28% reduction in breast cancer OR, and older white women had a 23% reduction. The corresponding values for African American women were 10% and 11%. However, the study also found that the decrease in risk per pregnancy was virtually identical across racial groups. And as number of pregnancies increased, a woman’s risk continued to decrease in all age and racial groups. But late age at first birth was associated with an increased risk for breast cancer in white women only.

In addition to studying how pregnancies affected the women, the study also found that the protective effect associated with breastfeeding was greater in women who had given birth within the past five years. If they had breastfed for over 21 months, these women had a breast cancer risk decrease of 62%. Lactation may reduce the probability of developing breast cancer because it postpones the resumption of normal menstrual cycles after pregnancy. This study also found that on average, white women breastfed twice as long as their African American counterparts, and this may be an explanation for the decreased breast cancer incidence rates among young white women.

Finally, the study also found that older African American women had more children than older white women, as well as a decreased occurrence of breast cancer, but younger African American women were more at risk than younger white women. Ursin and colleagues concluded that if having a large number of children was a factor in lowering the occurrence of breast cancer in the older women, there may be an increase in breast cancer in older African American women over time since younger African American women had fewer pregnancies and also breastfed for shorter periods of time. They recommended that breastfeeding for a longer duration should be encouraged, especially among young African American women.

Overall, the study only found slight differences between the two races. But it was one of very few that actually involved a large number of African American women and compared them with white women, so it may pave the way for more studies involving different races and how pregnancy and lactation affect the risk of developing breast cancer.

While this study and others speculate on why pregnancy and lactation help lower the risk of breast cancer.
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cancer, the specific reason has not yet been pinpointed. And even though it is widely known that having more pregnancies and breastfeeding help protect against breast cancer, many women do not have the option of having many children or even breastfeeding for a long period of time. The good news is that this study finally showed that there is little difference between the two races regarding how much pregnancy and lactation can help prevent breast cancer, and it could help African American women lower their risk by breastfeeding for a longer period of time. But more studies need to be done to find the exact reason for the decrease in risk, and that may lead to a better understanding of treatment and prevention of breast cancer.

Reference:
Chocolate: From candy to skin care
Megan Hoban

For years women have been searching for good excuses to eat pounds upon pounds of chocolate guilt-free. Well, it seems that scientists have finally found a legitimate excuse to do just that – chocolate can protect women’s skin. There is new evidence that a special chemical that is prevalent in chocolate can help improve skin condition in women, which just might revolutionize the way people think about skin care.

Scientists, as well as the cosmetics industry, have long been searching for ways to protect and improve skin condition. More recently, the two have been specifically interested in the damaging effects of the sun on skin and overall health and its prevention. Previous studies have shown that skin protection from the sun (or photoprotection), through topical and dietary approaches, is both effective and readily available. Yet it is the dietary approach that continues to intrigue many as it may be a simpler, more effective answer to sunburn and skin damage from UV rays. This is why in the current study, Heinrich and associates investigated the effectiveness of special chemicals found in cocoa (called flavonols) and their ability to protect women’s skin from harmful UV rays as well as improve overall skin condition.

Skin care has become one of the nation’s top industries as today’s women constantly fuss over wrinkles, loose skin, sunspots, roughness, pale complexion, and much more. They are willing to try cream after cream or poisonous injection after poisonous injection in an attempt to look younger and healthier. Society demands smooth, healthy, tan skin for a woman to be beautiful and yet provides only a few, expensive ways to obtain that high standard. Sunlight is the main cause of most undesirable skin conditions and is the reason scientists have been investigating ways to combat the sun’s damaging effects. It has long been known that micronutrients and vitamins provide effective systemic and topical photoprotection, including such nutrients as Vitamin C, carotenoids, tocopherol, and Vitamin E. These not only help prevent sunburn (or, as its known in the scientific world, UV-induced erythema) but also act as good antioxidants to prevent the photo-oxidation of lipids, proteins, and DNA within the body and thus prevent erythema, early aging, photodermatosis, and even skin cancer. In addition, these nutrients have the ability to interfere with signaling between cells in the UV-dependent responses of tissues to protect against damage.

The nutrients studied by Heinrich et al. are flavonoids, which are present in many common fruits and vegetables and have chemical properties similar to those stated above of Vitamin C, carotenoids, tocopherol, and Vitamin E. Therefore, flavonoids are also good antioxidants, which accounts for the antioxidant efficiency of many fruits and vegetables. Yet not only do flavonoids benefit the body as antioxidants, they can also
regulate enzyme activity, effect anti-inflammatory pathways, and influence cell division. It is here that the chocolate aspect of the current study comes into play; for flavonoids are also abundant in tea, red wine, and of course, cocoa.

In numerous past studies, flavonoids (known similarly as flavonols) have proven to be beneficial in decreasing harmful UV effects on the skin. Tea flavonols, when consumed orally or applied topically, have shown in animal studies to reduce skin damage, erythema, and lipid peroxidation. Similar results have been found when green tea polyphenols, a class of micronutrients under which flavonoids fall, were applied to human skin, including a decrease in sunburn cells and the protection of epidermal cells from UV damage. These previous findings make Heinrich et al.’s suggestion that repetitive intake of a flavonol-rich cocoa product will reduce skin sensitivity to UV exposure, improve skin structure, and refine skin texture a reasonable one.

In the current study, Heinrich et al examined 24 females between the ages of 18 and 65 years who were in good health, were not pregnant, and did not smoke, sunbathe, breast-feed, or consume medication that would effect the outcome of the study. These 24 women were randomly distributed into two groups under double blind conditions – a high flavonol group (HF) and a low flavonol group (LF). The women in both groups were required to consume a cocoa drink every morning at breakfast with the HF group consuming about ten times more flavonols. The study lasted 12 weeks and skin condition, including sensitivity to UV irradiation, cutaneous blood flow, hemoglobin concentrations, skin structure and texture, skin hydration, and transepidermal waters loss was monitored and analyzed at 0 weeks, 6 weeks, and finally 12 weeks. By monitoring all aspects of skin condition, Heinrich et al. was able to establish a solid basis upon which to test their hypothesis.

Upon completion of the study, Heinrich et al. found that the HF group did indeed provide improvement in all tested aspects of skin condition. Testing sensitivity to UV irradiation found that, when compared to initial tests, the reddening of skin 24 hours after UV exposure was nearly 25% less in the HF group while there was no change in the LF group, showing that flavonol in the diet can help protect against sunburn. In addition, cutaneous and subcutaneous blood flow increased significantly in the HF group while it again did not change in the LF group. The study found that hemoglobin concentrations did not change in either group, but did not note this as being significant. It is the skin structure and texture that showed the most interesting results as the women in the HF group showed increases in skin density, thickness, and hydration, while they showed a decrease in roughness, scaling, and transepidermal water loss. It is believed that this improvement in skin condition is seen because of the increase in blood flow as blood flow contributes significantly to skin appearance. While all of these changed after the 12 week duration in the HF group, the LF group showed no change in any of the factors, again showing that flavonols have a significant, positive effect on skin condition in women.
This new information has the potential to drastically change how women care for their skin. Yet perhaps the risks of this new treatment do not outweigh the benefits of healthy skin. The study does not consider the possible side effects of consuming such a large amount of cocoa on a daily basis: in order to match the amount of total flavonols present in the HF beverage, one would have to consume 100 grams of dark chocolate – naturally not a healthy daily eating habit. So how could the flavonols be administered so as not to cause women more harm than good? Perhaps a supplement or pill of some form would be an efficient way to administer the nutrients, but this would again take away from the ease of sun protection which Heinrich et al. was attempting to establish. In addition, is this only beneficial for women? What about men? Can this be administered to the entire population to protect everyone? Is there a low-cost answer – supplementing everyday food with extra amounts of flavonols to provide this to everyone?

So with this new knowledge, the next task is to find a way to provide this protection to women easily, inexpensively, and efficiently. This data could lead to a whole new way of protecting against the sun and improving skin care. Yes, sunscreen is a sure answer in skin protection from sunburn and damage, but people tend to use sunscreen only when going to the beach, and that certainly is not the only time they come into contact with UV rays. This new information offers people a way to protect their skin from the everyday stresses of the sun that are not protected against through the use of sunscreen. In addition, this can provide women with a great way of preventing aging and protecting their skin from damage while improving its overall health and beauty. The solution is easy and best of all, it tastes good. Yet above all of these beneficial aspects of flavonols, the most intriguing is that it may have a noteworthy effect on the fight against skin cancer. Could this be the answer to preventing UV-induced skin cancer? Further studies would have to be done to prove whether this could be true, but Heinrich et al. has certainly taken the first steps in that process.

Reference:
Sudden Infant Death Syndrome raises questions with every death. Dr. David S. Paterson, lead author of a recent study, may have found an answer.

Sudden Infant Death Syndrome (SIDS) is the leading cause of death in the United States for infants\(^1\). The reasons behind SIDS remain unknown, but Dr. Paterson and his fellow researchers have found a new direction for research. The authors have confirmed the hypothesized differences in SIDS victims’ brain chemistry, and have proposed a new model to predict just when SIDS will occur. The 5-HT system of the brain was abnormal in SIDS cases. This difference, a probable cause of SIDS, is one part of the proposed triple-risk model. Future research now can focus on discovering this difference in a living infant, so parents can know if their child is at risk.

Advice to new parents has changed radically in just three decades. In the 1970s, it was recommended that all babies sleep on their stomachs. In the 1980s, parents were told that babies should sleep on their sides. Now, the American Academy of Pediatrics recommends that all infants less than six months old sleep on their backs to prevent SIDS. The little-understood syndrome has been a source of shame and grief for generations, as blame is often given to parents. There are no full explanations to give parents. Wives’ tales still recommend countless ways to prevent a cause of death that science has yet to understand.

Previous studies showed a connection between abnormal function in the medulla’s neurotransmitters and SIDS. The medulla’s serotonergic system is a part of the brain thought to control such vital functions as heart rate and breathing. The medulla also is believed by researchers to control protective instincts such as arousal from sleep when there is not enough oxygen. Babies with SIDS were shown to have abnormalities in this section of the brain.

The presence of other risk factors, such as the baby sleeping on his stomach or sharing a bed with parents and being less than six months old, could cause SIDS when present with the brain irregularities. The authors tested this hypothesis when they began a new study to draw more definite conclusions.

Paterson et al. hypothesized that 5-HT dysfunction would be observed in the medullae of infants that had died from SIDS. To test this, they obtained from the San Diego Medical Examiner’s Office the frozen medullae of infants that had died from SIDS and from other acute causes. No cause of death was under investigation. The infants that had died from non-SIDS causes were studied as a control group. In all samples, the medullary 5-hydroxytryptamine (5-HT) system, better known as the serotonin system, was examined. Examiners testing samples were unaware of the cause of the infant’s death. The study gathered data on the 5-HT neuron count and density, 5-HT\(_{1A}\) receptor binding density, and 5-HT transporter binding density.
The data was found using several tests. The number and density of 5-HT neurons was found using immunocytochemical testing. This complicated method of staining solutions and then using a computer to calculate the count and density was made more accurate by the use of two trials. The mean was used for statistical analysis. 5-HT$_{1A}$ receptor and 5-HTT binding densities were found through another long process used to gather data from produced digital autoradiographic images. DNA isolated from brain tissue was prepared using standard methods. The resulting DNA bands were identified under UV light, and the genotype was determined.

Data about conditions such as sleeping position at the time of death was also collected and sorted into risk factors. This data analyzed for a correlation with brain abnormalities. Risk factors included birth position, minor illness within one week of death, and age. $t$ tests were used to compare data. In all analyses, $P < .05$ was considered significant. The probability of finding their results by chance was always less than one in twenty.

SIDS cases had a higher 5-HT neuron count and density, proved significant with a $t$ test. 5-HT$_{1A}$ density was lower in SIDS cases. The ratio of 5-HTT binding density to 5-HT neuron count was lower in SIDS cases. Male SIDS cases had lower 5-HT$_{1A}$ binding density. No association was found between the brain abnormalities and other risk factors.

The study showed through these results that there is a connection between medullary 5-HT pathology and SIDS. The abnormalities potentially make the 5-HT system of the medulla have abnormal 5-HT neuron firing, synthesis, release, and clearance. Based on data collected, Paterson et al. developed a triple-risk model of SIDS and its occurrence.

The triple-risk model proposed suggests that sudden death results when three factors affect the infant at the same time. The abnormal composition of the brain gives the infant an underlying vulnerability, the first part of the model. The second part is an environmental or physical stressor, such as sharing a bed with parents or the infant sleeping on his belly or side. The third risk is the age of the infant; infants in the critical developmental period, the first six months of postnatal life, are at the greatest risk for SIDS.

The conclusions of the target article are sound. The authors have found the beginning of the solution to a problem. Their hypotheses are based on implications from previous research, and they accepted no hypotheses not supported by numbers and statistical value. Their methods are all supported by previous example and research, and are far too much like brain surgery for this author to criticize some part of the procedure. The next step, however, goes farther than simply confirming that errors in serotonin transmission are a cause of SIDS.

Finding the cause of SIDS is not the sole aspiration of such research. Finding the cause would explain much about the disease, but the important next step is to develop a test that can be performed on living baby. The results of this test could give parents information...
they need. A baby known to be susceptible to SIDS would require more careful attention. Parents could work closely with doctors to know why their baby should sleep on his back. Knowing the cause is only a part of the goal. Saving just one family, infant from death and parents from grief, will make all research worth the years of work.

Reference:
Beyond Beauty: Can Botox® End Migraine Pain?

By Edita Klimyte

Botox® has become a household name for its effects on facial wrinkles. Now it stands to take on a new role in preventing pain caused by migraine headaches. Recently researchers investigate the mechanisms behind migraines and what Botox could do for those who suffer.

Migraine headaches are a recurring pain endured by millions of Americans. Currently we do not have an effective, preventative therapy. Recently, researchers experimenting with Botulinum Toxin type A (BoNT-A), the same toxin that is used in the cosmetic Botox, demonstrated that there might be hope for a more efficient way of treating this common, and often severe, pain.

Migraine has been a recent target of medical investigation because of its effect on the quality of life, the limited efficacy of current treatments, and the huge number of people the disorder affects. Migraine pain is caused by pain receptors in the muscle known technically as cutaneous nociceptors that activate peripheral sensitization, which in turn activates central sensitization, creating the perception of pain. BoNT-A, the toxin produced by the bacterium Clostridium botulinum, was first observed to prevent this pain when patients were treated with Botox for cosmetic purposes, i.e. facial wrinkles, and reported the beneficial results. While research has been done since this initial discovery, in conditions such as low back pain, neoropathic pain, and even migraine, how BoNT-A works to reduce pain remains unexplored. In addition, previous research concentrated on animal models, and the few experimental studies on humans failed to demonstrate significant effect of BoNT-A on pain.

So can Botox really help prevent the pain that is associated with migraine headaches? In their experimental study, Gazerania et al. ¹ injected the treatment group with Botox and recorded the pain, flare, and secondary hyperalgesia (pain sensitivity that occurs in surrounding undamaged tissues) that each subject experienced after creating a physiological pain stimulus with an injection of capsaicin, a pain-inducing chemical found in peppers. The researchers hypothesized that BoNT-A suppresses the release of neuropeptides from peripheral nociceptive nerve endings and reduces the capsaicin-induced sensory reactions; simply put, they predicted that Botox injections would prevent the subject from experiencing the pain that he usually would from future migraines. The results showed that the subjects that received the Botox injections had significantly reduced pain, flare, and secondary hyperalgesia after capsaicin inoculation.

In their experiment, Gazerania et al. treated thirty-two healthy male volunteers randomly with either BoNT-A or saline injections in four regions of the face. In subsequent visits, one, four, and eight weeks after the treatment, the subjects were injected with capsaicin in the forehead. Specific responses, including pain intensity (measured using a conventional pain-intensity scale), visible flare, surface skin temperature, blood flow, secondary hyperalgesia, and
the pressure pain threshold (all measured using standard equipment), were observed and recorded before the capsaicin injections and at different intervals afterwards. To establish a reference, these were all also measured at a baseline visit before the Botox or saline injection.

The results of the experiment supported the researchers’ hypothesis. The mean pain intensity area was larger in the saline group than in the BoNT-A group by about 60%. The visible flare area was also bigger in the saline group by about 33%. The differences in both of these responses were found to be statistically different. Also, the assessment of surface skin temperature revealed similar results; the mean temperature rise in the saline group was nearly twice as high as in the BoNT-A group. In addition, a significant suppressive effect of BoNT-A was observed on the increase in facial blood flow and secondary hyperalgesia, by about 35% and 60% respectively. Lastly, the pressure pain threshold revealed that the capsaicin made all of the subjects more sensitive to pain, but less so in the BoNT-A group. The positive effects of BoNT-A seemed to wane, however, over the course of the eight weeks.

The design of the experiment seemed to be foolproof, as long as the assumptions that were taken are true. The experiment was placebo-controlled, double blind, and randomized; the subjects of the experiment were randomly selected to either receive the treatment, an injection of BoNT-A, or the placebo, an injection of saline. Neither the subjects nor the injection administrators knew which treatment the subject was receiving; the saline treatments were disguised in BoNT-A vials. This removed the possibility of skewed results from a placebo effect or researcher bias. The statistical tests were relevant, and as long as they were done accurately, raised no red flags.

Certain key assumptions taken by the researchers troubled me, since it was not made clear whether these are known facts. Firstly, it is important that the capsaicin-evoked sensitization is the same as that which results from migraine pain; otherwise, there is no connection from the model in the experiment to the real condition. As long as the physiological response is the same to both stimulants, as is implied by the fact that they both involve the trigeminovascular system, this does not jeopardize the validity of the study.

Secondly, most of the physical responses measured by the researchers, such as the visible flare and blood flow, were recorded specifically five minutes after the capsaicin injection, which is based on the assumption that it is the best time to read the response. This is a large assumption that required some explanation behind its reasoning. Is five minutes enough time for the body to respond to the injection? This postulation is not nearly as important as the first since the researchers did end up finding a significant difference in reactions at the five-minute mark; it would have been a more controversial assumption if no difference would have been measured. I still think, however, that this is something that deserves attention. It should be indicated whether this is the peak of the body’s reaction to the capsaicin so the reader can be sure that the point of maximum difference was measured.
Finally, a large sample size is important in an experiment to get an average that is very close to representing the true population; in their experiment, Gazerania and his colleagues had only 32 subjects. They were also all males. While I am unsure what impact this had on the results, if any, it is troubling to me because this is obviously not representing the true population.

According to numerous studies, women are even more affected than men by this condition, and the researchers should have included female subjects to see if BoNT-A has an effect on their pain as well. Thus, to improve on this experiment the sample size should be increased and also should be an equal mix of males and females.

The researchers initially predicted that BoNT-A reduces central sensitization by inhibiting peripheral sensitization of nociceptive fibers. This hypothesis was tested by an injection of BoNT-A on an experimental human model of trigeminal sensitization induced by capsaicin injection to the forehead. The results supported their hypothesis; the treatment group, which received the Botox injection, had a significantly less severe reaction to the capsaicin than the group that received the saline.

More than 28 million Americans — three times more women than men — suffer from migraine headaches, a type of headache that is often severe. Currently, only over-the-counter pain medications are available to treat this neurological disorder, but they are effective after the migraine has set in and often have disagreeable side effects. The study done by Gazerania et al. showed that Botox has potential to prevent migraine headaches; since none of the subjects reported any side effects from the injections, this would be a great way to treat patients suffering from recurring migraines. While this study hasn’t put the final say on the subject, it has opened up a can of worms. With more experimental studies like this one, all doubts will be able to be ruled out, and the medical community could get closer to making this preventative treatment available to the public.

Reference: