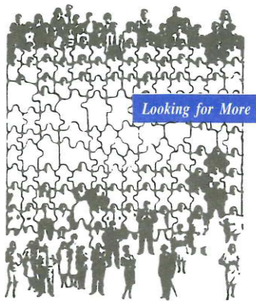

JOHNS HOPKINS RESEARCH CENTER
P.O. BOX 2067
HAGERSTOWN, MD 21742-2067

Address Service Requested

What more can you do?

Your continued participation is very valuable. With your help we can continue to find the clues to prevent cancer, heart disease, and other health problems. Please fill out the next questionnaire that should arrive in the mail within the next couple of months. Thank you for your help.

Establishment of the Community Research Review Committee

The Johns Hopkins Research Center has established a community advisory group to review genetic research protocols that involve participants from the community, and promote community awareness of the importance of our research in improving the health of individuals. Although all of our research must have prior approval from one of the institutional review boards of Johns Hopkins University, we would like to know whether a committee composed of a group of Washington County residents also agrees that the proposed research is useful and ethical. The Review Committee is composed of a representative from the following community organizations: Washington County Health Department Advisory Committee, Community Action Council, Washington County Bar Association, Washington County Medical Society, American Cancer Society, Washington County Ministerial Association, Y-Me of the Cumberland Valley, Washington County Health Systems and the Washington County Council of Churches. The committee has met twice and we are planning our next meeting later this winter.

John R. Marsh Cancer Center Seeks Volunteers for STAR Breast Cancer Prevention Study

The John R. Marsh Cancer Center is participating with Johns Hopkins STAR, the *Study of Tamoxifen and Raloxifene*. STAR is the second major breast cancer prevention study sponsored by the National Cancer Institute (NCI). It is the first research study being done to compare tamoxifen, a drug proven to reduce the chance of developing breast cancer, with raloxifene, another drug that holds promise for breast cancer prevention. STAR is being done throughout the United States and Canada and has enrolled over 14,300 women since the study began in July 1999. This number is 65% of the 22,000 participant number goal. The drug tamoxifen was proven in the first Breast Cancer Prevention Trial sponsored by the NSABP, to reduce breast cancer incidence by 49% in women at an increased risk for the disease compared to a placebo. In October 1998, the Food and Drug Administration (FDA) approved tamoxifen to reduce breast cancer risk in women at an increased risk for the disease. Raloxifene is approved by the FDA to prevent osteoporosis.

To be eligible for the STAR Trial, a woman needs to be 35 years of age or older, postmenopausal and have an increased risk for breast cancer. An increased risk for breast cancer is determined by many factors including age, family history of the disease and personal medical history. For example, women who have a strong family history of breast cancer or have had a breast biopsy that has shown atypical hyperplasia or lobular carcinoma insitu (LCIS) are at an increased risk.

The trial is limited to postmenopausal women because raloxifene has not been tested in premenopausal women. Only a few medicines or medical diagnoses make a woman ineligible.

Any woman contacting the John R. Marsh Cancer Center regarding STAR trial will receive a free assessment of her breast cancer risk and a written risk profile showing the potential benefits and risks of the study drugs. Eligible women receive the study drugs free.

Please call Debbie Smith, RN at 301-665-4680 for any additional information.

Health Letter

Johns Hopkins Research Center

January 2003

CLUE II FOLLOW-UP

Research Update

Thank you for continuing to participate in the CLUE study and providing us with the "clues " to prevent cancer and heart disease. Your response to the questionnaires has helped us greatly in our efforts to solve the puzzles of cancer and heart disease. Using blood samples and health information you have given us, we are able to study possible ways to prevent breast and prostate cancer, heart disease, diabetes and many other health problems. Some of the studies conducted at the Johns Hopkins Research Center since our last newsletter are:

Results from a study of micronutrients in the blood and the risk of breast cancer suggest that eating foods rich in carotenoids, found in fruits and vegetables such as carrots & tomatoes, may help lower the risk of getting breast cancer.

The toenail samples, which you provided, were analyzed to determine levels of cadmium and zinc that reflect the level in the body's tissues. We studied a group of men to see if cadmium or zinc could be associated with the risk of getting prostate cancer. Cadmium was thought to be a risk factor for getting prostate cancer. In our study there was no association between cadmium levels and the risk of prostate cancer. This study is important because it shows that with levels normally found in human populations, there is no risk with higher levels. Previous studies suggested a possible association with prostate cancer among men exposed to high levels in certain occupations. Zinc also was not associated with prostate cancer. Other studies had suggested higher zinc levels may protect against prostate cancer.

We also studied the effects of passive smoking on blood levels of antioxidant nutrients such as the carotenoids, which are thought to protect the body against oxidative damage. We had shown in an earlier study that people who smoke have lower levels of these antioxidant nutrients in their blood. We also found that people who are not smokers themselves, but are around others who smoke also have lower levels of these important nutrients in their blood. The message? Avoid smoking and eat plenty of fruits and vegetables.

We have an ongoing study to find out why some women who have had a benign breast biopsy may go on to develop breast cancer, while others don't. We are hoping to learn what we can do to prevent breast cancer.

How do we do these studies?

You are one of 32,987 people who participated in the CLUE II study, giving a blood sample, toenail sample, and filling out questionnaires. We stored the components of the blood (plasma, red blood cells, and white blood cells) so that years later we can take the blood and look at concentrations of nutrients, proteins or hormones in the blood that may give us clues to what protects us against certain diseases. While we measure the concentrations in the blood of an individual we really are looking at groups of people to understand the disease process. We look at groups of people who developed cancer or diabetes and heart disease and compare this group to groups of people (called controls) who remain healthy.

First we have to decide on the research questions. For example we are interested in whether or not higher levels of a blood marker for inflammation or a hormone called insulin-like growth factor are linked to cancer and heart disease. So we ask the question, do people who develop breast cancer tend to have higher levels of the marker of inflammation than people who do not get cancer? To answer this we go back and look at the questionnaire and find out who developed breast cancer. Then we pick a group of people who are of the same age and sex but have not yet had breast cancer. We go to the freezers where the plasma is stored

continued on next page…

...continued from page one,

and take out a sample from each person who got breast cancer and each of the controls that were selected for the study. The concentrations of the marker in the plasma are measured and all the data are grouped together for individuals who got cancer and those that did not. We look to see if the concentrations are higher or lower for those who got cancer compared to the control group. If we find out that people who developed cancer may have had some inflammation years before the cancer occurred, it is a clue to how we may prevent cancer. One of our doctoral students is beginning to do this study now. But it is only a clue.

These types of epidemiologic studies are called observational studies. They do not prove cause and effect. We like to see many studies showing the same association. In this case, finding an association between inflammation and cancer would suggest we may be able to lower the risk of cancer by using anti-inflammatory medications such as aspirin and other non-steroidal anti-inflammatory drugs (NSAIDS) such as ibuprofen. Another type of study would be needed to prove that taking aspirin could lower the risk of cancer, a clinical trial. The studies we do are the first step to finding ways to prevent cancer. Clinical trials are very expensive and we want to pick the most promising ways to lower the risk. Your participating helps us find those clues.

Once the blood samples are assayed, the data are analyzed to compare those with the disease and those without. The results are written in a formal paper for publication. The paper is then submitted to a scientific journal to be reviewed. Once the paper is peer-reviewed (reviewed by other experts in the field) and found to be a sound and valid study it is published. Other experts in the field of study can see the results and try to reproduce our results and take the findings to the next step, for example, a clinical trial. Research depends on this process of replication of studies. We have had over 60 papers published from results of the CLUE study.

Breast Cancer Study

We are in the midst of a study of why some women with benign breast disease go on to get breast cancer and others do not. The National Cancer Institute sponsors this study. Women who participated in the CLUE study and were told by their doctor they had benign breast disease or women who had a breast biopsy are included in the study. We are also studying any woman who developed breast cancer and comparing them to women who never had cancer or benign breast disease. Something we think may be important are hormones such as insulin-like growth factor and also differences among people in the way they metabolize carcinogens or repair damage to the DNA in the cells. To do this study we are going back to ask women who ever had a breast biopsy for permission to review the tissue slides and to examine the tissue blocks. Many women have agreed to help us with this study. For those women who sent back the consent form over 90 percent gave us permission to look at their breast tissue again. We thank you. Our goal again is to find clues that may help us find better ways to reduce the risk of getting breast cancer.

Cancer Screenings for Adults*

As one of eight centers established by the National Cancer Institute to develop, evaluate and validate biomarkers for earlier cancer detection, we are looking for ways to make simple screening tests for cancer. Current studies are focusing on using biological and genetic markers found in the blood. These biomarkers could signal that patients have certain cancers before symptoms arise, allowing for earlier intervention and treatment. Cancer that is detected early has a greater chance of being treated successfully. The best way to find cancer in its earliest stages is through regular cancer screenings.

	Ages 18-39	Ages 40-49	Ages 50+
Breast Cancer *(women)*	Monthly breast self-exam (BSE). Clinical breast exam by health professional every 3 years or more often if at high risk. (Discuss with your physician.)	Monthly BSE. Yearly mammogram. Yearly clinical breast exam near the time of mammogram.	Monthly BSE. Yearly mammogram. Yearly clinical breast exam near the time of mammogram.
Cervical Cancer *(women)*	Yearly pelvic exam. Pap test starting at age 18 (earlier if sexually active). After 3 consecutive normal tests, Pap test may be performed at the physician's discretion.	Yearly pelvic exam. Pap smear at least every 3 years (after 3 consecutive annual normals).	Yearly pelvic exam. Pap smear at least every 3 years (after 3 consecucutive annual normals).
Colorectal Cancer		Consider a colonoscopy if you have a family history of colon cancer.	Yearly fecal occult blood testing (FOBT) or sigmoidoscopy every 5 years or colonoscopy every 10 years.
Prostate Cancer *(men)*		Yearly prostate-specific antigen (PSA) blood test and digital rectal exam starting at age 45 if you are at high risk (African-American, or have a father or brother diagnosed with prostate cancer at a young age).	Yearly PSA blood test and digital rectal exam for all men.
Skin Cancer	Monthly self check. Familiar-ize yourself with any moles, freckles or skin abnormalities. Skin cancer check by a doctor every 3 years.	Monthly self check. Skin cancer check by a doctor every year.	Monthly self check. Skin cancer check by a doctor every year.

* *Source: American Cancer Society, www.cancer.org*

Diabetes

Ninety five percent of people over age 20 who have diabetes have type 2, commonly called non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes. If you have type 2 diabetes, your pancreas makes some insulin but not enough. Your cells can also become resistant to insulin's effects, keeping insulin from escorting enough glucose into your body's cells. By far the greatest risk factor for type 2 diabetes is being overweight. The exact role excess weight plays in type 2 diabetes is unclear, but it appears to increase insulin resistance. Your pancreas is then called on to produce more insulin to overcome the resistance and the insulin producing cells tend to become exhausted. Twelve percent of CLUE participants reported having been diagnosed with diabetes by 2000 up from 9 percent by 1996.

page

How do you know if you have diabetes?

Serious complications of diabetes can begin early, often before you know you have diabetes. The American Diabetes Association (ADA) recommends that all adults have a fasting plasma glucose test at age 45. If test results are normal, the test should be repeated every 3 years. If you have a family history of diabetes and are obese and inactive, you should be tested at a younger age and more frequently.

Some of the symptoms of diabetes are excessive urination, excessive thirst, excessive hunger, unusual weight loss, exhaustion, blurred vision, tingling in the hands and feet.

A fasting plasma glucose test is a simple, reliable test for diagnosing diabetes. After fasting overnight (or for 8 hours), a blood sample is drawn and the glucose level measured. Most people have a level between 70 and 100 milligrams of glucose per deciliter of blood (mg/dl). A level of 126 mg/dl or higher on two tests confirms a diagnosis of diabetes.

Preventing Diabetes

Maintain a healthful weight. Most people who develop type 2 diabetes are overweight. Aggressive efforts at achieving and maintaining a healthful weight may be beneficial, especially when combined with exercise.

Eat a healthful diet. How much you eat (keeping your total calories at an appropriate level) is more important than what you eat in reducing your risk. How much you eat ultimately determines your weight, and being overweight significantly increases risk. A diet low in saturated fat and sugar and high in complex carbohydrates and dietary fiber may also help.

Exercise-Exercise reduces insulin resistance and improves your body's ability to tolerate increased blood sugar. In one study, people at high risk for diabetes who exercised had a 50 percent lower incidence of type 2 diabetes.

Looking Towards the Future

We are currently looking at variations in the DNA of persons who gave us a blood sample and permission to store all components of their blood for research purposes.
We have completed genotyping for 50 genes on approximately 12,000 participants. We are not looking for persons who are carriers of disease associated specific genes but rather we are looking for differences in genes that code for enzymes that can process chemicals to be less harmful, repair damage to DNA or are involved in other ways to keep cells healthy. The genes we are studying have variations that are usually present in 10 to 50 percent of the population. These common genetic differences are called genetic polymorphisms. Because we all react differently to environmental factors, these differences make us more or less susceptible to beneficial or harmful exposures in the environment. Some people may be better than others at removing harmful chemicals from the body or repairing damage the chemicals may have caused to the cell structures. The removal and repair process is done by special proteins called enzymes. We may differ in how much of the enzymes are made, or how rapidly the enzymes work. One way to look at the differences in the proteins is to look at the DNA. DNA is the basic building block of life and makes up the genes that, in turn determine how much and how well our body's enzymes may work. Natural variations in our gene structure lead to difference in protein activity. Since we are just beginning these studies, we do not yet know if the genes or enzymes they produce are important in protecting us from getting cancer or other diseases. By building on the results of this study and others we hope we can get more clues on how the environment and our bodies work together to keep us well. Eventually we hope to find out who most needs help to prevent disease.

page