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The Impact of Colonic Microbiota on Breast Cancer



Subject Information Sheet and Consent Document

Introduction

This form provides you with information so you can understand the possible risks and benefits of participating in this study; so that you can decide whether or not you want to be a part of this research study. Before deciding whether to participate in this study, you should read the information provided on this document and ask questions regarding this study. Once the study has been explained and you have had all your questions answered to your satisfaction, you will be asked to sign this form if you wish to participate.

Why are you invited to participate in this study?

You are being asked to take part in this study because either

1. you have been diagnosed with breast cancer within the last 6 months, you are between the ages of 50 to 70, you have never received chemotherapy and have not received radiation or antibiotics within the last 4 weeks and ARE willing to undergo the research flexible sigmoidoscopy GROUP 1
2. you have been diagnosed with breast cancer within the last 6 months, you are between the ages of 40 to 50, you have never received chemotherapy and have not received radiation or antibiotics within the last 4 weeks and are willing to undergo the research flexible sigmoidoscopy GROUP 2
3. you are a completely healthy person undergoing a routine check up for colon cancer because you are over the age of 50 and you have had a mammogram in the last 9 months that was normal. GROUP 3
4. you have been diagnosed with breast cancer within the last 6 months, you are between the ages of 50 to 70, you have never received chemotherapy and have not received radiation or antibiotics within the last 4 weeks and ARE NOT willing to undergo the research flexible sigmoidoscopy GROUP 4

Research studies include only people who choose to take part. Please take your time to make your decision and discuss it with your friends, family and/or physician. Remember that your participation is completely voluntary. There is no penalty if you decide not to take part in this study or decide later that you want to stop participating in this research study. Your care at Rush University Medical Center will not be affected if you decide not to participate. The sponsor for this study is the U.S. Department of Defense, Congressionally Directed Medical Research Programs on breast cancer.

What is the purpose of this study?

The purpose of this study is to find out the types of bacteria that normally live in your large intestine and their metabolic activity (i.e. the ways in which bacteria process food, hormones or drugs). Normally, as human beings, we all have large amounts of bacteria that live in our large intestines (also called our colon). In fact, we carry about 2 pounds of bacteria in our intestines and it is estimated that the number of bacteria in our intestines outnumber our own body's cells by 10 to 1. As humans, we also have a close relationship with these bacteria through the inner lining of our intestines and there is a cross talk between the bacteria and our body through the intestines. In fact, it is estimated that the surface area of intestines that comes into close contact with bacteria is about 3 football fields in size. Medical researchers estimate that the bacteria that live in our intestines have a metabolism (ability to break things down) that is just as much as our own liver. Despite the billions of bacteria that are in our intestine, we know little about them or how they metabolize drugs and other substances such as female hormones.

One of the most important factors that have been thought to play a role in breast cancer development is female hormones called estrogens. Estrogens can be made by the human body itself. They can also be given in the form of birth control pills or as a medication or taken into the body from the outside environment. Both types of estrogens (those that are made naturally and those that are taken in) may impact the development of breast cancer in some women. Estrogens that are not made naturally in the body may increase the risk of breast cancer in some women. Estrogens are easily absorbed in the intestine and circulate between the intestine, the liver and other tissues of the body and blood. They get absorbed over and over through the intestinal tract and this absorption of estrogens and female hormones is dependant on the presence of bacteria in the intestines. For example, people in whom the large intestine (also called the colon) is removed, have lower blood and urine levels of female hormones. In general, for breast cancer development, having high amounts of female hormones is not good and is considered a risk factor. There are interesting reports that bacteria in sewage treatment plants can break down estrogens and female hormones or make them into more active forms.

Because the intestinal bacteria affect the circulation and absorption of female hormones such as estrogen, bacteria and the systems that metabolize female hormones in the bacteria may hold clues as to why certain people develop breast cancer and others do not. Furthermore, some research has shown that high amounts of fat in the diet may increase the risk of breast cancer. Such higher amounts of fat can also change the types of bacteria that reside in the intestines. This is the reason why the researchers for this study want to look at the type of bacteria and the way they metabolize female hormones and other hormones. Specifically, the researchers want to compare the bacteria that are in the intestines of patients who have breast cancer to those who do not have breast cancer.

How many people are expected to take part in the study?

We hope to have a total of 90 women enrolled in this study (60 females diagnosed with breast cancer and 30 healthy women who will be comparable to the breast cancer patients in terms of their age and race).

What will you be asked to do?

If you agree to participate in this study, you must sign and date this consent form. You will be required to come to Rush University Medical Center for one screening visit to be enrolled in the study. If you elect to undergo the research procedure you will then return for a limited flexible sigmoidoscopy visit or have the procedure done on the same day. This applies to the

groups who have elected to undergo the research procedure, Groups 1, 2 and 3. If you do not wish to undergo the research procedure, Group 4 you will ONLY have the one screening visit.

Screening visit (All groups): This visit is only done for research purposes and will be free of charge. During your screening visit, you will have the following done:

1. You will meet with one of the study doctors (Drs. Mutlu, Quander or Keshavarzian) for approximately 30 minutes. The study doctor will perform a history of your medical illnesses and do a physical examination and will ask you questions about medications, allergies, past surgeries etc.
2. The doctor will also evaluate you to see if you need to be checked out for colon cancer. Colon cancer is a leading cause of death in the United States and the United States preventative task force requires that everyone over the age of 50 (even if they are healthy and have no digestive issues or have no family members with colon cancer) be offered a colon cancer check up. The doctor will ask you questions about whether you have had any colon cancer check up tests in the past. These past tests that you may have had include a flexible sigmoidoscopy, colonoscopy or barium enema. They are described below:

A colonoscopy is a procedure where a flexible telescope like thin tube is inserted from your rectum (the part of the body where stool comes out of). It is pushed into your large intestines (also called your colon) gently for about 3-5 feet depending on how long your colon is. The flexible telescope has a video camera at its tip. With this camera, the doctor is able to see the lining of your colon where tumors and cancers usually start on a video screen. The doctor usually also puffs some room air inside your colon to make the video pictures clearer. Colonoscopy is generally done after you receive heavy dose laxatives that clean out your colon of all stool the day before. This is called a bowel preparation or bowel prep. During the test, you are given medications that make you sleepy and drowsy- you are awake but do not remember much about the test. This is called sedation. A colonoscopy usually lasts about 30-60 minutes.

A flexible sigmoidoscopy is a similar test to the colonoscopy. Again a flexible telescope with a video camera at its tip is inserted to the rectum and pushed in by about 2 feet. This test looks at only the lower 1-2 feet of your colon. Typically, no medications are given to make you sleepy and drowsy. Typically, you will have to take several enemas to clean the left side of your colon for this test. This test lasts about 15 minutes.

Another option to check for colon cancer in the past was an X-ray test of your colon. This is called a barium enema. Before this test, you also take heavy dose laxatives to clean your colon of any and all stool. The day of the test, a small finger-thick tube is put into the rectum. Through the tube, the doctor (an X-ray specialist also called a radiologist) puffs both air and about ½ of a gallon of chalky white liquid into your colon; and takes x-ray pictures looking for cancer in the inner lining of your colon or early growths that may be related to cancer called polyps.

Colonoscopy and flexible sigmoidoscopy and barium enema tests are routine approved tests that are used in clinical care of patients to check for colon cancer and polyps. The doctor will ask whether you have had any one of these tests before and explain them to you and give you educational pamphlets about colon cancer check-ups and these tests.

If you have not had a colonoscopy within the last 10 years after age 50; or if you have had not a flexible sigmoidoscopy after cleaning out your bowels within 5 years after age 50; or if you have not had a barium enema within 5 years after age 50, then you will be recommended routine colon cancer check up. Specifically, the doctor will recommend that you undergo one of these tests or their alternatives as normal clinical care. If you wish to undergo these tests, you will be scheduled to do them at a later date of your choice, outside of this study.

3. On the day of the screening visit, you will also be asked to fill out some questionnaires. These are as follows:

- a) New patient database questionnaire: This questionnaire asks about your past medical illnesses, allergies, medications, smoking, drinking and exercise habits and family history. It will take 20-30 minutes to complete. If you have been seen in the digestive diseases clinic before, this questionnaire will be updated by the study doctor seeing you.
 - b) GI symptom checklist: This questionnaire asks about whether you have any digestive symptoms or problems such as diarrhea, constipation, change in your bowel habits, etc. It will take about 10 minutes to complete.
 - c) Food frequency questionnaire: This questionnaire asks about your diet and the foods that you eat. This will take about 45 minutes to complete.
 - d) Breast cancer risk factor questionnaire: This questionnaire asks about potential breast cancer risk factors such as previous use of female hormones, problems with infertility if any, number of children you have, the age at which you got your first period etc. This will take about 20 minutes to complete.
4. You will have blood drawn from your arm (the amount is about 6 teaspoonfuls). If you have recently had a recent blood draw (specifically a complete blood count; complete metabolic profile examining your kidney and liver related blood values; and blood for research purposes) within the last 3 months as part of your clinical care, we will obtain these bloodwork results from your oncology or GI clinician or from the clinician who has performed these. If you have not had blood drawn, you will get both of these blood tests free of charge.
5. You will be asked to bring a stool sample to your next visit and will be given a stool collection kit.

The screening visit will take approximately 2-3 hours in total.

Limited flexible sigmoidoscopy visit (Groups 1, 2 and 3): This visit is only done for research purposes and will be free of charge. This visit may occur on the same day as your screening visit or within 1 month of the screening visit, as per your choice. This visit is only done for research purposes. You will have a limited flexible sigmoidoscopy with biopsy, which will be performed by one of the study doctors (Drs. Mutlu, Quander or Keshavarzian). This means that unlike a flexible sigmoidoscopy done for colon cancer check up which examines the last 2 feet of the colon on the left side, this flexible sigmoidoscopy will only look at the last 2/3 of a foot of your left colon. The flexible sigmoidoscopy will also not require any colon cleansing or sedation; and will be very limited to the most distal (closest to the anus) 20 cm (which is about 8 inches). The procedure is usually less than 5 minutes in duration. Since this is a limited procedure, it is not totally adequate for a colon cancer check- up. During the procedure, the doctor will get seven biopsies of your colon. Biopsies are small tissue pieces that are 1-2 mm (which is about 1/16 to 1/32 inches) in size. This is about 1/2 to 1/3 of the size of a rice kernel. The doctor will also get some stool out from your colon. This visit will take approximately 20 minutes.

Follow up: You will be contacted via phone for within 10-14 days after your limited flexible sigmoidoscopy visit to make sure you have not had any problems after the procedure. This phone call should take about 5-7 minutes. We will also look at your medical records for one year to determine what has happened to you clinically in terms of your breast cancer. We will also ask that we look at your medical records to obtain the results of any colon cancer screening tests that you have had within the last year after study and we will call to determine if whether you have developed any digestive problems.

How long will you be in the study?

Even though you only need 1-2 visits for this study, you can expect to be in the study for one-year because we will be looking at your medical records and charts. We may need to call you to obtain any missing information at the end of 1 year.

You may be removed from this study without your consent for any of the following reasons: the study doctor decides that continued participation in the study will be harmful to you or the study is canceled.

What are the possible risks of the study?

You will have blood drawn from your arm on 1 occasion. Drawing blood involves placing a tight wrap on your upper arm and inserting a needle into a vein in your arm and withdrawing blood. You may experience discomfort at the time of blood draw and/or bleeding, and bruising at the site where the needle enters the body. In rare cases, fainting or infection occurs. To minimize discomfort and local bruising, an experienced staff member will complete the blood draw.

If you decide to have a limited flexible sigmoidoscopy, (group 1, 2, 3), the limited flexible sigmoidoscopy involves the doctor looking at the lower part of your colon in order to obtain tissue from the colon. This procedure may be uncomfortable however, most patients either experience no discomfort or little discomfort similar to having a rectal exam or minimal bloating due to the air being puffed into their colon. With any procedure, there is a risk of bleeding when tissue samples or biopsies are taken. This risk is estimated to be less than 1 in 1000. If bleeding occurs, it will usually stop by itself and does not usually require hospitalization, transfusion, or other interventions. If the bleeding does not stop, you may need another sigmoidoscopy during which the doctor may apply heat to cauterize the bleeding area or place a clip over the area to stop it from bleeding. There is also a risk of a tear (in other words perforation) in your colon. This is extremely rare (1/10000), but a possible complication. If a tear occurs, you may experience severe abdominal pain and fever. If you think you are experiencing bleeding or a tear, you should contact the Principal Investigator of the study, Ece Mutlu, M.D., immediately, by calling 312 942 5861. Please do not leave any voice mail messages but ask to be connected to Dr. Mutlu (or one of the study doctors in her absence) immediately. The researchers of this study have also done other studies using limited flexible sigmoidoscopy and have not had any episodes of bleeding or perforation from the limited flexible sigmoidoscopy procedure in the past.

You will be asked to collect a stool sample and bring it from home. Although you will be provided with gloves and containers, collecting stool may be emotionally upsetting.

Your medical records will be examined. This may put you at risk for breach of confidentiality. However, we will follow all federal rules such as the Health Insurance Portability and Accountability Act (also known as HIPAA) to minimize this risk as we normally do for your clinical care.

Even though blood draws and flexible sigmoidoscopy are routine procedures in medical care of patients, there may be currently unforeseeable risks of these procedures that may be discovered at a later time.

Are there any anticipated pregnancy risks?

If you are pregnant or breastfeeding or still having periods, you cannot take part in this study. This study is open to patients who are in menopause. If you become pregnant, you must notify the study doctor immediately.

Are there benefits to taking part in the study?

There may be no direct benefit to you for participating in this study. If you choose to participate in this study, you will be increasing scientific knowledge about the effect of bacteria on breast cancer. Such knowledge may lead to completely new treatments or tools for early detection of breast cancer for a high risk individual. If you are a breast cancer patient and have not had a check up for colon cancer screening, you will also be provided with information about colon cancer by the study doctors. You will also receive a free blood count at the time of your screening visit, unless you have had these blood tests by your regular medical doctor within the last 3 months. Specifically, you will get a complete blood count (known also as a CBC) and a complete metabolic profile (also known as a CMP), both of which will be free of charge. There is a chance that your doctor may see a suspicious lesion for colon cancer at the time of your limited flexible sigmoidoscopy, which may lead to early detection of colon cancer. However, you should note that this limited exam by itself is not adequate for detection of colon cancer or its early findings such as polyps.

What other options are there?

The only alternative to participating in this study is not to participate. You do not have to participate in this research project in order to receive care and treatment. You may choose to simply not participate in this study. This will not affect your medical care or treatment at Rush University Medical Center. If you decide to participate, you are free to withdraw your consent and discontinue participation at any time without prejudice.

What happens when you or the doctor decides that you should withdraw from this study?

If you decide to withdraw from this study after you complete your colon test and biopsies, we will not use any of your information or samples. You can withdraw your biopsies up to 1 year after you start this study. If you decide to withdraw from the study, you will need to send a letter addressed to Dr. Mutlu at 1725 W. Harrison, Suite 206, Chicago, Illinois 60612. We will also still call you for follow up to make sure that you are safe and have not had any complications after your endoscopy.

The investigator may withdraw you from participating in this research if circumstances arise which warrant doing so. If you experience any of the following side effects such as excessive bleeding or if you become ill during the research, you may have to drop out, even if you would like to continue. The investigator will make the decision and let you know if it is not possible for you to continue. The decision may be made either to protect your health and safety, or because it is part of the research plan that people who develop certain conditions may not continue to participate.

What about confidentiality of your information?

Records of participation in this research study will be maintained and kept confidential as required by law. Any records identifying you will also be kept confidential to the extent

permitted by applicable laws and/or regulations. The researchers are HIPAA trained and will abide by HIPAA rules.

We will assign a unique study number for identifying your written information. Your study information will be kept under lock at the Section of Digestive Diseases Offices at Rush University in Suites 337 or 206. Your study questionnaires will only contain your unique study subject number. The study information will also be stored in an electronic database. This will not contain your name or other personal information but only your assigned study number. This database is within the Rush computer system and has the same protection as your medical files at Rush. This database will be password protected by research personnel and will not have specific information that can identify you.

When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity. If photographs, or videos, or audio-tape recordings of your colon test will be used for educational purposes, your identity will be protected or disguised.

In order to conduct the study, the study doctor, Ece Mutlu, M.D., will use and share personal health information about you. This includes information already in your medical record, as well as information created or collected during the study. Examples of the information that may be shared include your medical history, physical exam and laboratory test results. The study doctor will use this information about you to complete this research.

Confidentiality and disclosure of your personal information is further described in the attachment to this form. The attachment is entitled HIPAA Authorization to Share Personal Health Information in Research (2 pages).

Your identity will not be revealed on any report, publication, or at scientific meetings.

The Rush Institutional Review Board (IRB) will have access to your files as they pertain to this research study. The IRB is a special committee that reviews human research to check that the rules and regulations are followed.

The Department of Defense who funds this study will also have access to your files. Authorized representatives of the U.S. Army Medical Research and Materiel Command (USAMRMC), FDA, and IRB at George Mason University may need to review your records. As a result, they may see your name; but they are bound by rules of confidentiality not to reveal your identity to others. Since this is completely new field of research, we will not destroy any of your clinical data or the answers you gave as part of questionnaires that you have filled out.

What are the costs of your participation in this study?

There is no cost to you for getting examined by the doctor, advice on colon cancer check ups, blood tests, stool collection, or limited flexible sigmoidoscopy nor will you have to pay for parking.

Your study doctor is being paid by Department of Defense to conduct this research. A portion of this money will go to Rush University Medical Center to compensate for other institutional research related costs.

All costs that are part of your usual medical care, such as the costs of your colon cancer

check up tests done as part of your colon cancer screening will be considered outside of this study and will be charged to you or your insurance company. You will be responsible for all costs that are not paid by your insurance company. You should check with your insurance company before you enroll in this research study.

Will you be paid?

You will be compensated \$250 for your time and effort if you elect to under go the research procedure, Groups 1, 2 and 3. If you do not elect to under go the procedure, Group 4 you will be compensated \$100. This will be provided to you after completion of the study requirements which are completion of your questionnaires, obtaining your medical records for the study and sample collection with the limited flexible sigmoidoscopy procedure. All participants will also be given a parking sticker or \$8 (same as the cost of a parking sticker) for bus fare, etc for study participation.

What happens if you experience a research related injury?

If you experience any injury or illness as a direct result of your participation in this research study, immediate treatment will be provided. However, the cost of that treatment will be billed to you or your insurance company. Your insurance company may not pay. Rush University Medical Center has no program for financial compensation or other forms of compensation for injuries which you may incur as a result of participation in this study.

If you are hurt or get sick because of this research study, you can receive medical care at an Army hospital or clinic free of charge. You will only be treated for injuries directly caused by the research study. The Army will not pay for your transportation to and from the hospital or clinic. If you have questions about this medical care talk to the principal investigator for this study, Dr. Ece Mutlu at 312 942 5861. If you pay out of pocket for medical care elsewhere for injuries caused by this research study, contact the principal investigator. If the issue cannot be resolved, contact the U.S. Army Medical Research and Materiel Command (USAMRMC) Office of the Staff Judge Advocate (legal office) at 301 619-7663/2221.

What happens if you need emergency care?

If you need emergency care while you are participating in this study, it is important that you inform emergency personnel of your participation in this study.

What about new findings from this study?

During the course of the study, you will be informed of any significant new findings (either good or bad), such as changes in the risks or benefits resulting from participation in the research or new alternatives to participation, that might cause you to change your mind about continuing in the study. If new information is provided to you, your consent to continue participating in this study will be re-obtained.

What will happen to your samples?

During this study you will be asked to provide blood, stool and colon tissue. These samples will be used for study of bacteria in the colon and their role in breast cancer and may also be used for research purposes that are currently unknown. There is a chance that the samples that you are donating under this study may be used in other research studies and may have some commercial value. There are no currently anticipated products to be developed from

your samples. However, should your donated sample(s) lead to the development of a commercial product, Dr. Mutlu and Rush University will own it and may take action to patent and license the product. They do not intend to provide you with any compensation for your participation in this study nor for any future value that the samples you have given may be found to have. You will not receive any notice of future uses of your sample(s).

_____ Samples can be stored for future use.

_____ Samples to be used in the current study only. Samples cannot be stored for future use.

If you decide to withdraw the future use of your samples after you sign this form, you may withdraw them by writing a letter to Dr. E. Mutlu stating your wishes and mail the letter to 1725 W. Harrison, Suite 206, Chicago, Illinois 60612 within the first 1 year after you start this study. In this case, your samples will be destroyed.

Whom do you call if you have questions or problems?

Questions are strongly encouraged. If there are any questions about this research study or if you experience a research related injury, please contact: Ece Mutlu, M.D. at 312 942 5861.

Questions about the rights of research subjects may be addressed to the Rush Research & Clinical Trials Administration Office at 312-942-5498.

By signing below, you are consenting to participate in this research study. You have read the information given or someone has read it to you. You have had the opportunity to ask questions, which have been answered satisfactorily to you by the study personnel. You do not waive any of your legal rights by signing this consent document. You will be given a copy of the signed and dated consent document for your records.

SIGNATURE BY THE SUBJECT

Name of Subject

Signature of Subject

Date of Signature

SIGNATURE BY THE WITNESS

I observed the signing of this consent document.

Signature of Witness

Date of Signature

SIGNATURE BY THE INVESTIGATOR/INDIVIDUAL OBTAINING CONSENT:

I attest that all the elements of informed consent described in this document have been discussed fully in non-technical terms with the subject. I further attest that all questions asked by the subject were answered to the best of my knowledge.

Signature of Individual Obtaining Consent

Date of Signature

Signature of the Principal Investigator

Date of Signature