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13. ABSTRACT (Maximum 200 Words)

This proposal evaluates interindividual differences in the response to genotoxic stress as prostate cancer risk factors. To this end we use measurements of mutagen sensitivity, apoptosis, comet assay, and single nucleotide polymorphisms in DNA repair genes OGG1 and XRCC1. These biomarkers are evaluated in 100 prostate cancer cases and 100 controls matched on age and race in order to measure response to bleomycin exposure is short-term cultured lymphocytes to define prostate cancer risk. During the second year of funding, a study coordinator recruited 21 prostate cancer cases and 20 matched controls at the Georgetown University Hospital. A research assistant created a sample repository consisting of serum, plasma, buffy coat, urine, toenail clipping and saliva for every participant. We also created a computerized database of the samples in Microsoft Access. The research assistant measured mutagen sensitivity in all the subjects and determined the mean breaks in lymphocytes exposed to bleomycin in cases (mean 0.88 SD 0.32) and controls (mean 0.74 SD 0.34). We continue to optimize the apoptosis and comet assay protocols to measure DNA repair kinetic and cell death in exposed cells. We expect to proceed rapidly with the case-control study in the third year with the recruitment protocol in place.

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Introduction: Despite the fact that prostate cancer is the most common tumor among US males, relatively little is known about the causative mechanisms. The known risk factors include age, ethnicity or race, high-fat diet and family history of prostate cancer, but these factors are not sufficient for identification of men with increased susceptibility. Establishing new biomarkers of cancer risk would greatly benefit the field of prostate cancer prevention and surveillance.

Molecular epidemiology can elucidate prostate cancer risk factors by applying biomarker measures to population based methodologies. This is a case-control study testing variation in the response to genotoxic stress as a biomarker of prostate cancer risk. The study evaluates mutagen sensitivity, apoptosis, and polymorphism in *OGG1* and *XRCC1* as biomarkers of prostate cancer risk; the study also provides preliminary data on comet as an alternative biomonitoring tool.

Mutagen sensitivity is an established biomarker of risk (1). Comet assay is an increasingly popular tool for human biomonitoring (2) with the potential to identify cancer-prone individuals in the general population (1). Both comet assay and mutagen sensitivity measure DNA damage in short-term cultured human lymphocytes exposed to bleomycin (or other mutagens) as either tail moment (comet assay) or number of chromatid breaks (mutagen sensitivity). While mutagen sensitivity is an established tool in population-based studies of cancer risk and was associated with increased risk of glioma, lung, colon, hepatocellular, and HN carcinoma, comet assay was used only recently in three pilot studies of breast, cervical, and lung cancer (1). Surprisingly, neither assay was used to study prostate cancer risk. Even though the exact mechanism underlying these phenotype is unknown, variability in DNA-repair capacity is consistent with the available experimental results (3). Moreover, it was shown in twin studies that mutagen sensitivity is heritable in non-cancer subjects. The correlation coefficient was 0.79 (95% confidence interval = 0.65-0.88) in monozygotic twins while for dizygotic twins the coefficient was 0.42 (95% confidence interval = 0.00-0.71) (4). Mutagen sensitivity phenotype therefore reflects multiple genetic traits related to DNA repair capacities, which predispose an individual to cancer risk. Comet assay has several advantages compared to mutagen sensitivity: 1. An independent measure of DNA repair; 2. Higher throughput, better reproducibility and quantification, and lower cost per assay; and 4. Smaller sample size (also called SCGE, single cell gel electrophoresis assay) (2). We propose to compare the use of comet assay and mutagen sensitivity for screening of prostate cancer susceptibility.

Apoptosis is a molecular pathway eliminating, besides other functions, cells unable to cope efficiently with genotoxic stress. Deficient apoptosis is a likely candidate for a cancer-prone phenotype. Apoptosis was implicated in regulation of response to radiation therapy in prostate cancer (5), malignancy of prostatic tumor (6), and recurrence of prostate carcinoma following surgery (7). For example, in 54 prostate cancer patients treated with radiotherapy the response was negative in 84% cases with positive bcl-2 immunohistochemistry and bcl-2 was an independent prognostic variable for treatment with odds ratio of 7.3 (5). Apoptotic index was associated with disease recurrence in a study of 47 men following radical prostatectomy (7). But apoptosis was not yet examined as a phenotypic predictor of prostate cancer risk. Since the apoptotic phenotype is a composite measure of a number of converging mechanistic pathways, it is advantageous to the measurement of each individual genotype in the pathway.

DNA repair consists of two major categories, excision repair (base excision repair and nucleotide excision repair) and recombination repair (homologous and non-homologous) (8). Numerous polymorphisms in the DNA repair genes have been identified (9) and are likely to contribute to cancer risk through decreased efficiency of response to genotoxic stress. But two functional polymorphisms in DNA repair genes, *OGG1* and *XRCC1*, are particularly relevant to this study. Both genes are involved in the repair of 8-hydroxy-guanine (8-OHdG) and other oxidative lesions (10); and our study examines mainly how variability in the response to oxidative DNA damage modifies risk for prostate cancer (bleomycin is a radiomimetic which induces oxidative DNA damage and mutagen sensitivity is mainly a model of this pathway). OGG1 is a DNA glycosylase/AP lyase involved in base excision repair of 8-OHdG and XRCC1 is a DNA ligase III terminating the base excision repair cascade (10). The OGG1 Ser(321)Cys polymorphism codes for a protein with a lower 8-OHdG repair capacity and leads to several splicing variants of unknown functional significance (11). This variant occurs at a frequency of 0.4 in Japanese and was associated with an increased risk of lung cancer in a study of 241 cases and 197 controls with an OR=3.01 (95% CI 1.33-6.83) (12). This variant was found in a Caucasian population at a frequency of 0.22 and was not associated with lung cancer in this study (13). Examination of this polymorphism in prostate cancer is therefore highly relevant. The XRCC1 Arg(399)Gln polymorphism was associated with increased sensitivity of human lymphocytes to DNA damage (14), increased risk of squamous cell carcinoma of the head and neck (15), increased risk of early onset colorectal carcinoma (16), and increased risk of adenocarcinoma of the lung (17). The polymorphism occurs in 37% of Caucasians and 17% of African-Americans (19). An examination of the XRCC1 'at risk' polymorphism as a risk factor for prostate cancer was not reported.

The proposal is innovative because the proposed biomarkers were to our knowledge not examined in connection with prostate cancer risk. If mutagen sensitivity, comet assay, apoptosis, or DNA repair-variants correlate with prostate cancer risk, they could serve as readily obtainable biomarkers to identify men with increased risk of prostate cancer. The phenotypic biomarkers could be used to better identify the currently poorly understood genotoxic insults leading to cancer risk (improved risk models in case-control studies). Elucidating mechanisms of the early stages of prostate carcinogenesis would have an immediate impact for prevention and surveillance. Better prevention strategies (including chemoprevention) could be designed and tested based on the identified targets. And new hypotheses focusing on the genetic and environmental factors associated with prostate cancer risk could be formulated and evaluated.

Body: This is a case-control study of prostate cancer risk. The population of 100 cases and 100 controls under study continues to be recruited at the Georgetown University Hospital. Our recruitment will be also expanded to the Washington Hospital Center and to Veterans Administration Hospital, Washington DC in the near future. This will allow us to recruit a large number of African American participants for a comparison of DNA repair differences as a possible cause of the health disparity observed in prostate cancer. The recruitment was originally to be carried out by Dr. Trock. We did organize the recruitment at Georgetown University after Dr. Trock relocated to Johns Hopkins

University, Baltimore. We take advantage of additional funding of Dr. Goldman from the American Cancer Society to accomplish the recruitment for this prostate cancer study.

The recruitment of prostate cancer cases and matched controls was approved by the joint Medstar Research Institute-Georgetown University IRB (see appendix). We developed the alternative case-control recruitment strategy in collaboration with our colleagues from the Department of Urology (Dr. Lynch), Radiation Oncology (Dr. Dritschilo), and Medical Oncology (Dr. Amin). Our preliminary research indicates that Georgetown University, Department of Urology, sees about 150 new prostate cancer cases per year which is more then enough to cover recruitment for the proposed study. We can also complement this by recruitment at the Washington Hospital Center and Veterans administration Hospital if needed.

We have designed a recruitment strategy and established the entire infrastructure for patient/control recruitment including sample collection together with the GCRC laboratory and Biomarker Core at Georgetown University. The patients for this study are adult residents of the Washington, DC area, ages 18 and older. We enroll all eligible patients that cover the full spectrum of tumor stage and grades. All subjects are briefly informed about the study by the attending physician and referred to a study coordinator. Most patients are seen at the clinic several times prior to treatment and can be enrolled prior to radiation, surgery, or chemotherapy. The coordinator explains the study to the patients, screens for eligibility using a one-page form, obtains informed consent from eligible participants, administers a questionnaire, and assists with collection of specimen (blood, saliva, toenail clipping, and urine) in collaboration with the general clinical research center (GCRC). The personnel of the Histopathology and Tissue Shared Resource collects the tissue not needed for diagnosis at surgery. Flash frozen, OCT embedded, and paraffin embedded tissue is collected in this order as available. Paraffin embedded tissue is also collected for diagnostic purposes by the department of pathology.

Controls are obtained among healthy visitors accompanying other patients to the hospital. We exclude spouses and blood relatives to avoid overmatching on genetic factors. The interviewer identifies potential candidates, investigates their willingness to participate, and screens for eligibility using a one-page form. The interviewer works from a table of enrolled cases and frequency-matches the eligible controls (see below). The candidates are either enrolled immediately or registered in a list of willing eligible controls and join the study at a later time convenient for them or when a match is identified. The interviewer obtains informed consent, questionnaire data, and collects 45cc blood sample, saliva, urine, and toenail clipping in collaboration with the GCRC.

The slow growth of prostate cancer and presence of a large percentage of asymptomatic cancer cases in the population presents a challenge to studying prostate cancer. Although the use of PSA and what cut point to use in the clinic is debated, we plan to determine total serum PSA for all recruited controls. We consider serum PSA>2.5 ng/ml as uncertain, in agreement with the latest research. It was shown in population screening of 22,500 participants that total serum PSA is > 4.0 ng/ml in 9% Caucasian and 13% African American males; additional 9% males are positive in the PSA range <2.5-4.0> ng/ml. In our study of 100 controls, PSA screen will therefore detect about 10 controls with PSA>2.5 ng/ml. About 20-40% of the 10 with PSA>2.5 ng/ml, are expected to have cancer at biopsy within next few years. Sufficient controls (approximately 110) will be recruited in order to recruit the 100 controls with PSA<2.5ng/ml as proposed. All

assays will be conducted on the larger sample of controls so that they can be included in some analyses. The most restrictive analyses will exclude all controls with PSA > 2.5 ng/ml, with subsequent analyses excluding controls with PSA > 4.0 and PSA > 10.0 ng/ml. Inclusion of the PSA screening as part of the control selection protocol further provides us with the opportunity to explain PSA testing and promote awareness of cancer screening. This is of greatest need in the African American community as the positive predictive value is higher in African American males (45%) compared to Caucasians (25%). All controls with PSA > 2.5 ng/ml will be given referrals to a urologist.

We considered several methods of accruing controls according to the described control selection guidelines. Random-digit phone dialing is likely to have low participation rates because we obtain blood sample for each participant; sibling controls could lead to overmatching on genetic factors; nominated peer controls were not an efficient group - most patients refuse to have their neighbors contacted because they do not want to disclose their disease state. We chose therefore the visitors accompanying other patients. These controls are unbiased with respect to geography and socioeconomic status as they came to the hospital from the same referral area as the cancer cases. The subjects usually accompany a person to the hospital repeatedly, are motivated to participate, are easily contacted as they wait in the clinic, and typically do not make a special trip to the clinic for the study. It is a nonrandom subset, but was shown to be an excellent comparison group in several large studies.

Controls are matched to HNSCC cases on age (5 years), and race. It is important to match on these factors so that hypothesis testing is not compromised by severe imbalances in subject characteristics. We use frequency-matching whereby the proportions of cases and controls in each 5-year age group within each race category are held as closely similar as possible. In practice, this is accomplished by tabulating patient frequencies (updated monthly). This table shows the categories of race and age that were underrepresented among previously recruited controls, which helps the interviewer to choose an appropriate control. We have found that monthly adjustment of the recruitment tables allows us to control emerging characteristics of the case and control groups and to adjust recruitment where needed.

Subjects are interviewed face-to-face by a trained interviewer. In special cases the interview can be conducted over-the-phone or mailed in (for patients with speech problems). The questionnaire asks about demographic information, reproductive history, tobacco use, alcohol consumption, general medical history and family history, occupational exposures, residential history, exercise, and education. Every newly completed questionnaire is checked by a supervisor; together they identify and correct any errors or inconsistencies prior to data entry. Double data entry is performed with automated range and consistency checks (in Microsoft Access). The files are protected by passwords and encryption.

An experienced phlebotomist collects the blood samples at each recruitment site. Each subject provides a single 45 cc blood sample drawn into pre-labeled vacutainer glass tubes. Urine, toenail, and saliva are collected according to standard procedures and frozen for future studies as needed. The surgical tissue not needed for diagnosis is collected at surgery by the personnel of the Histopathology and Tissue Shared Resource. Flash frozen, OCT embedded and paraffin embedded tissue is collected in this order as available. The blood tubes are immediately refrigerated and delivered on ice within 6

hours to the GCRC core facility at Georgetown University for processing. Case-control status is masked to the lab personnel since the blood collection tubes show only a numeric study ID and sample collection date. We collect two red top tubes (no preservative), two green top tubes (sodium heparin), and one purple top tube (EDTA). Each sample is centrifuged and the blood components are separated into serum, clot, buffy coat, and plasma within 2 hours of reception. The blood components are divided into aliquots of 0.5-to-1 ml each, frozen at -80°C and stored in a centrally monitored freezer facility.

We have recruited 21 cases and 20 controls **(Table 1)** and obtained samples of serum, plasma, buffy coat, mouth wash, urine, and toenail clipping for each participant.

Table 1.

Characteristic	Cases	Controls
	n=21	n=20
Age		
less than 50	1	1
50-60	7	7
60-70	9	9
more than 70	4	3
Race		
white	17	16
black	4	4

These samples constitute a repository of samples for prostate cancer biomarker research and serve for the testing of mutagen sensitivity and other endpoints in this study as described below. Dr. Goldman's laboratory at Georgetown University relocated two times in 2003 as part of the expansion of the Lombardi Comprehensive Cancer Center. In the first stage, our laboratory relocated to a temporary location, and in December 2003 we moved to a newly renovated space in the Cancer Center. The laboratory has 750sq feet and contains all the equipment necessary for the proposed research including refrigerated centrifuges, incubators and tissue culture hoods, and microscopes including a fluorescent microscope with a comet imaging system. We also benefit from a nearby high throughput genotyping facility equipped with five 96-well PCR machines, 2 tetrad PCR machines (4 blocks X 384 wells), a Perkin-Elmer 377 sequencer, ABI 7900HT, Amersham Megabase 96 capillary sequencer, Transgenomic Wave dHPLC, Quiagen M48 Biorobot, Multimek robotics, Affymetrix microarray scanner with 2 hypbridization sytems, 96 well format automated sequencer, a Perkin-Elmer 770 flourescent DNA analyzer, and a Biorepository system with a server. The laboratory is CLIA certified. There is a centrally monitored storage facility with –80°C freezers. The established recruitment and optimized sample processing in the new laboratory allows rapid expansion of the study.

Aim 1. Determine whether high mutagen sensitivity is associated with high prostate cancer risk.

Mutagen sensitivity is a well validated phenotypic assay in our laboratory (20). This work is carried out by Michelle Xia Ma, who was trained in the mutagen sensitivity procedure and demonstrated her competence in tests of reproducibility of the

measurement. This was futher shown by duplicate slide preparation of samples obtained from three participants **(Table 2)**.

Table 2		
Case	Breaks/cell 1	Breaks/cell 2
1	0.88	0.9
2	0.7	0.74
3	0.44	0.68

We have analyzed mutagen sensitivity in 21 cases and 20 matched controls. For each person, a 62 hour culture of fresh whole blood collected in a green top (sodium heparin) vacutainer tube is established and the lymphocytes are stimulated with phytohemagglutinine. The cells are exposed for 5 hours to bleomycin, fixed, and microscopic slides with chromosomal spreads are stained with Giemsa stain as described previously (20). The results show that mean breaks in cases (mean 0.88 SD 0.32) are higher than in controls (mean 0.74 SD 0.34), but the result is not statistically significant **(Table 3)**.

ID	Status	Breaks/cell	ID	Status	Breaks/cell
11591	case	0.5			
11592	case	0.88	**11742**	control	0.4
11662	case	0.36	**11906**	control	0.74
11852	case	0.78	**13699**	control	0.92
11910	case	0.56	**13701**	control	1.76
11940	case	0.66	**13715**	control	1.16
11943	case	0.96	**13717**	control	0.9
11996	case	0.92	**13721**	control	0.78
12085	case	1.1	**13725**	control	0.58
12248	case	0.56	**13727**	control	0.42
12350	case	1.04	**13728**	control	0.6
12369	case	0.76	**13730**	control	0.58
13471	case	1.1	**13731**	control	0.7
13654	case	1.76	**13732**	control	0.44
13734	case	1	**13733**	control	0.9
13742	case	1.1	**13739**	control	0.66
13748	case	0.52	**13741**	control	1.12
13755	case	1.32	**13759**	control	0.88
13756	case	0.68	**13770**	control	0.42
13761	case	0.88	**13772**	control	0.38
13782	case	1.02	**13741**	control	0.42
Mean		**0.88**	**Mean**		**0.74**
St Dev		**0.32**	**St Dev**		**0.34**

The sample size is not large enough yet to expect significant differences. The completed recruitment of 100 cases and controls in the 3rd year of the study will provide sufficient number of subjects for the hypothesis testing.

In addition to the mutagen sensitivity, we began evaluating comet assay as an alternative protocol for DNA damage/repair. This assay is an increasingly popular tool for human biomonitoring (1) with the potential to identify cancer-prone individuals in the general population (2). Both comet assay and mutagen sensitivity measure DNA damage in short-term cultured human lymphocytes exposed to bleomycin (or other mutagens). While mutagen sensitivity is an established tool in population-based studies of cancer risk and was associated with increased risk of glioma, lung, colon, hepatocellular, and HN carcinoma (1), comet assay was used only recently in three pilot studies of breast, cervical, and lung cancer (1). The largest of the studies examined 100 lung cancer patients and 110 controls using comet assay and found correlation of cancer risk with increased DNA damage (OR 4.2; CI 2.2-7.4) (21). In addition, DNA repair (measured as rate of damage disappearance) was an independent predictor of risk (OR 2.1; CI 1.1-4.0). Comet assay has several advantages compared to mutagen sensitivity: 1. Comet assay provides independent measures of DNA damage and repair; 2. Comet assay is reported to have higher throughput, better reproducibility and quantification, and lower cost per assay; and 4. Comet assay uses small sample size (also called SCGE, single cell gel electrophoresis assay) (2). Our preliminary results are encouraging.
Our first experiments follow published experimental settings with minor modifications (21). Agarose slides for this procedure were prepared as follows:

1) Coat microscope slide with normal melting point agarose (NMPA), solidify on ice for 5 min
2) Add cell suspension to low melting point agarose (LMPA) and form a layer of cell suspension on the NMPA coated slide
3) Dip the preparation in cold alkaline (pH>13) lysing solution (4°C) for 3 hours
4) Transfer the preparations from lysing solution to alkaline electrophoresis buffer for 40 minutes to unwind DNA
5) Separate DNA for 25 minutes at 4°C by alkaline electrophoresis using 0.92 V/cm and 300 mA current
6) Fix preparations with methanol, wash with distilled water
7) Stain with 0.01% ethidium bromide
8) Acquire 50 cell images per experiment (2 slides per experiment) using a fluorescent microscope with CDD camera (Olympus) and evaluate average fluorescent intensity in the head (intact nuclear DNA) and tail (damaged DNA) using comet imaging software (Loats Inc., Gaithersburg, MD). This imaging system was purchased by Lombardi Cancer Center and installed in our laboratory.

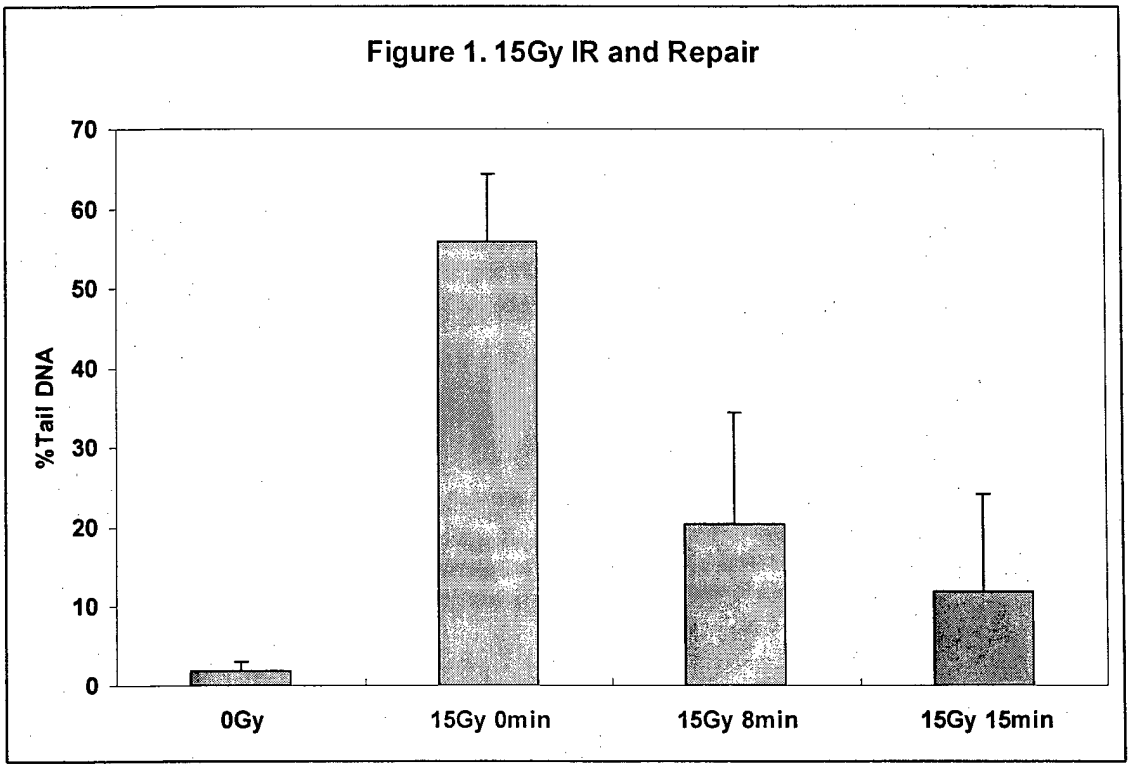
Lymphocytes from short term culture in the presence of PHA (62 hours) and IL2 (24 hours) were treated with 60 μg/ml bleomycin solution. Control samples were treated with the same volume of medium. After 30 min the samples were washed with fresh medium and subjected immediately to alkaline lysis (analysis of DNA damage) or incubated in fresh medium for 8 and 15 min at 37°C before alkaline lysis (analysis of DNA damage repair). The experiment was done on three independent cultures from the same blood sample and each performed in duplicate for a total of 6 measurements at each dose/time **(Table 4)**.

Table 4. Reproducibility of Bleomycin Induced Comets				
Experiment	0 ug/ml	60ug/ml 0min	60ug/ml 8min	60ug/ml 15min
1	0.964	90.023	77.01101124	31.513
2	0.163	92.257	57.45676768	35.2921
3	2.53	82.6808	31.4653	22.4742
4	5.58	76.0992	46.7498	18.5163
5	1.2675	38.998	13.1558427	1.355384615
6	1.3635	33.717	24.8144	3.1712
Mean	1.98	68.96	41.78	18.72
SD	1.92	25.94	23.35	14.11

This experiments (and several subsequent repeats with modifications) revealed that the measurement is not sufficiently reproducible between cultures to allow screening of samples in a population study. This prompted us to test ionizing radiation, which is known to yield the best results in terms of dosing and reproducibility. This experiment was done initially using 0-2 Gy of radiation, but even the highest dose resulted in only minor increase in % tail DNA. As we are interested in the quantification of DNA repair, this dose was not sufficient and we increased the dose to 5-15 Gy subsequently. We did also modify the electrophoretic conditions by increasing electrophoresis time to 40 minutes. With these conditions, we achieved better reproducibility of the experiments as exemplified by the presented exposure to 15 Gy **(Table 5)**.

Table 5. Reproducibility of IR induced Comets				
Experiment	0Gy	15Gy 0min	15Gy 8min	15Gy 15min
1	2.78	54.35	12.51	8.89
2	3.33	46.28	18.41	8.38
3	0.90	67.21	48.77	36.74
4	0.36	55.61	14.82	5.16
5	1.75	47.32	13.37	6.42
6	1.93	64.47	14.64	5.64
Mean	1.84	55.87	20.42	11.87
SD	1.11	8.60	14.03	12.27

The mean and standard deviation are summarized in the in **Figure 1**.



We are investigating currently what percentage of cells undergoes apoptosis following the exposure to ionizing radiation, what is the kinetic of DNA repair at longer time points, and the reasons for the higher variability of the assays using bleomycin as the damaging agent. It was suggested in the literature that the repair of DNA damage following radiation is biphasic with a relatively fast repair of single strand breaks (within 15 minutes) and a slower repair of the residual damage, presumably double strand breaks, with a kinetic of hours. We hope to incorporate the optimized protocol into the population study and compare the repair phenotypes measured by mutagen sensitivity and comet assay.

Aim 2. Determine whether low apoptotic response is associated with increased prostate cancer risk.

We did perform Anexin V assay for phosphatidylserine flipping based on flow cytometry on 10 cases and 10 control samples of short term cultured lymphocytes **(Table 6)**.

Table 7. Apoptosis following exposure to bleomycin

	0ug/ml	20ug/ml	60ug/ml		0ug/ml	20ug/ml	60ug/ml
Control	12.92	31.38	38.74	case	10.13	26.32	39.76
Control	11.55	25.05	33.18	case	29.06	12.50	36.25
Control	9.04	19.90	30.20	case	35.01	44.96	47.22
Control	25.07	34.85	40.37	case	82.99	87.09	85.07
Control	11.58	29.77	40.29	case	20.82	37.72	39.32
Control	7.00	19.84	36.44	case	19.10	28.09	37.68
Control	11.96	25.04	37.54	case	18.50	25.67	41.42
Control	64.43	63.37	63.49	case	35.68	53.52	61.69

Control	33.96	44.19	49.92	case	36.39	50.83	53.98
Control	20.13	38.42	51.23	case	17.90	33.06	36.71
Mean	20.76	33.18	42.14	Mean	30.56	39.98	47.91
SD	17.43	13.18	9.96	SD	20.50	20.78	15.48

We did previously modify the tissue culture procedure by addition of IL2 following the culture in the presence of PHA in order to decrease variability of the assay. This worked reasonably well when performed on volunteer blood, but less well in the study as can be seen in Table 6. There are a number of samples with high background of Anexin V staining, especially in cancer cases. This can be due to the unhealthy lifestyle, treatment with antibiotics, or other unknown reasons. It is also possible that the treatment with bleomycin is not sufficiently reproducible in this experimental setting even though we take care to use the same lot of reagent and aliquot the reagent as carefully as possible. We are currently evaluating the option to perform the apoptosis measurements on cells exposed to ionizing radiation and we are further optimizing the tissue culture protocol to eliminate the observed variability.

Aim 3. Determine whether the 'at risk' genetic variants of *OGG1* and *XRCC1* are risk factors for prostate cancer.

The testing of single nucleotide polymorphisms is a straightforward application of established procedures. Both the OGG1 and XRCC1 genotyping protocols were tested on pedigree DNA and are fully prepared for the population testing. In addition, we have access to a newly established High Throughput Genotyping Facility at the Lombardi Cancer Center which will allow us to screen a number of relevant polymorphisms in a very short time.

Key Research Accomplishments

1. The infrastructure for recruitment of cases and controls at Georgetown University Hospital was fully established. We have obtained questionnaire data and biological specimen form 21 cases and 20 matched controls. Tumor tissue was obtained for 2 cases so far.
2. The measurement of mutagen sensitivity was performed for all the participants and shows that men breaks are higher in cases (mean 0.88 SD 0.32) than in controls (mean 0.74 SD 0.34).
3. We did develop a complementary procedure for quantification of DNA repair capacity based on comet assay. This measurement is currently in final stages of optimization/validation and we plan to incorporate the measure in this study if the funds permit.
4. Lombardi Cancer Center created a high throughput genotyping facility directed by Dr. Shields. This center will facilitate rapid analysis of any number of polymorphisms that we will study as the recruitment reaches the established goal of 100 cases and matched controls.

Reportable Outcomes

None. The study will provide reportable results as the recruitment reaches a critical mass. We hope to report also a paper describing the comet assay and apoptosis in cultured peripheral blood lymphocytes.

Conclusions

The study progresses slower than expected due to the development of a new recruitment strategy for cases and controls. We have established the recruitment procedures, sample collection, processing, repository, and data management. This is a substantial effort that is made possible by generous support from the Lombardi Cancer Center through the GCRC, Biomarker Core, Histopathology and Tissue Core, and additional funding of Dr. Goldman form the American Cancer Society. We carried out mutagen sensitivity experiments on all received blood samples and also continue to optimize comet assay as an additional measure of DNA repair and response to genotoxic stress. Genotyping assays can be easily accomplished when the recruitment reaches the proposed goal of 100 cases and control. We have optimized all the genotyping assays and have access to a newly established High Throughput Genotyping Facility at the Lombardi Cancer Center which will allow us to screen a number of relevant polymorphisms in a very short time.

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How to Become Involved

You may become involved in this study if you:

- are living in the greater Washington DC area including Maryland and Virginia
- have no prior cancer history

OR

- are a prostate cancer patient
- are between the ages of 18-90

Upon contact, we will inform you about the study and verify your eligibility to participate. We will collect information about your alcohol and tobacco history, occupational history, family history, diet and exercise. You will be asked to donate a small sample of blood, urine, saliva, nail clipping and the left over tumor tissue that may have been removed if you are a cancer patient. Contact us at any time if you need more information or decide to participate. You can enter the study right now as you are waiting in the clinic by calling the number below or by notifying clinic staff.

Principal Investigator: Radoslav Goldman, Ph.D.
Interviewer/Recruiter: Melissa Kalil
Prostate Cancer Biomarker Resource
Lombardi Cancer Center
3800 Reservoir Road, NW
S-Level, Rm. 180
Washington, DC 20007
Ph: (202) 687-0343
email: mik5@georgetown.edu

MedStar Research Institute

Washington Hospital Center

Lombardi Cancer Center

Prostate Cancer Biomarker Resource Study

Study number:_ Principal Investigator (s): Radoslav Goldman
Title Molecular Epidemiology of Prostate Cancer

Informed Consent for Clinical Research (controls)

MedStar Research Institute/Georgetown Medical Center

INSTITUTION: GUMC + WHC

INTRODUCTION

We invite you to take part in a research study. The study is called 'Molecular Epidemiology of Prostate Cancer'. Please take your time to make your decision. Discuss it with your family and friends. It is important that you read and understand several general principles that apply to all who take part in our studies:

(a) Taking part in the study is entirely voluntary;

(b) Personal benefit to you may or may not result from taking part in the study, but knowledge may be gained from your participation that will benefit others;

(c) You may withdraw from the study at any time without any of the benefits you would have received normally being limited or taken away.

The nature of the study, the benefits, risks, discomforts and other information about the study is discussed below. Any new information discovered, at any place during the research, which might affect your decision to participate or remain in the study will be provided to you. You are urged to ask the staff members any questions you have about this study and the staff members will explain the questions to you. The investigator (person in charge of this research study) is Dr. Radoslav Goldman. The research is being sponsored by the Department of Defense. The Department of Defense is called the sponsor and the Georgetown University is being paid by the Department of Defense to conduct this study with Dr. Radoslav Goldman as the primary investigator.

WHY IS THE STUDY BEING DONE?

You are being asked to participate in this study because a comparison group free of prostate cancer is needed to evaluate the results. Your blood and other samples may show us how cancer develops and what the factors are that help increase cancer risk.

The purpose of this study is to learn about the natural history of prostate cancer and its causes and treatments. This research is being done because the causes of prostate cancer are not well understood at present. The purpose of this research is to see how someone's ability to respond to genetic damage

modifies risk of prostate cancer. We will test how your ability to repair damaged DNA and eliminate cells that did not repair the damage modifies prostate cancer risk.

We will examine your blood, cheek swabs, saliva, nail clippings and urine to see if tests for your response to chemical exposure can help us predict who might be at greater risk of prostate cancer. The specimens will not be used for diagnostic purposes or for purposes related to your medical care. That is, the experiments done on these samples will not be used for decisions about your personal risk of prostate cancer. These specimens will be available to qualified medical researchers for scientific studies that have been approved by the Principal Investigator, listed above, and an oversight committee. Researchers who receive these samples will not have access to your name or other identification information. We hope that this research can lead to the discovery of new tests for cancer risk, including genetic tests.

Men older than 18 years of age free of prostate cancer are eligible to participate in this study. To minimize the possibility that you have undetected prostate cancer, we will use the result of a test for prostate specific antigen (PSA) obtained within the last six months. If you did not have a PSA test within the last six months, we will perform the test on a portion of your blood sample free of charge to you. If your test shows a PSA value greater than 2.5ng/ml, a follow up examination by a doctor will be recommended.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 600 people (300 patients and 300 controls) will take part in this study and will be recruited at Washington Hospital Center and Georgetown University Medical Center. Participants in the study are referred to as "subjects".

WHAT IS INVOLVED IN THE STUDY?

Upon reviewing and signing this informed consent, you will begin the study. We will ask you questions using a form that will take about an hour to finish. If you do not want to do the whole questionnaire at the time you give blood, we can do only one part lasting about 15 minutes and then we will contact you later to finish the study. Your blood, cheek cells, saliva, nail tissue, and urine will be tested for their response to chemical exposure, in order to identify tests that may predict cancer risk. This research will be conducted on an experimental basis only, and you will not be provided with any information about your test results.

Study number:_ Principal Investigator (s): Radoslav Goldman
Title Molecular Epidemiology of Prostate Cancer

If you take part in this study, you will have the following tests and procedures:

1. Upon reviewing and signing this informed consent, you will begin the study.
2. Undergo an in person interview lasting about one hour administered by a trained interviewer.
3. Provide a blood sample that is about 3 tablespoons.
4. Provide a urine specimen.
5. Provide two cheek swab samples.
6. Provide saliva.
7. Provide nail clippings.

HOW LONG WILL I BE IN THE STUDY?

We expect that your participation in the study will take about an hour. The study is completed after you complete your questionnaire and donate your blood, urine, nail clippings, saliva and a cheek sample. However, if you agree below, we may call you in the future for additional information and/or sample collection. We will use your sample for different tests as described above and as new hypotheses develop for as long as it lasts and is useful for our testing. If the sample is no longer useful, it will be destroyed. However, you can request that your blood, cheek cells, saliva, nail tissue, and urine be destroyed at any time. To have your samples destroyed, you can contact Dr. Goldman at 202-687-9868.

The investigators, physicians or sponsors may stop the study or take you out of the study at any time should they judge that it is in your best interest to do so, if you experience a study-related injury, or if you do not comply with the study plan. They may remove you from the study for various other administrative and medical reasons. They can do this without your consent.

In the future, it might be necessary to contact you for further information or an additional blood sample (or other type of biological sample). If this is okay, please indicate below. You can refuse to do so now or later. Please check and initial below:

I ____may ____may not be contacted in the future for further information or biological samples.

_____ Sign your initials here.

WHAT ARE THE RISKS OF THE STUDY?

There is a very slight chance of a bruise or an infection from the blood draw, but we use only trained medical technicians to draw your blood and they will use the best available precautions. Another possible risk is that your genetic information might be obtained by persons outside the study. We will minimize this chance by maintaining the confidentiality of your test results and study records at all times (see below). For more information about risks and side effects, ask the research staff or contact Radoslav Goldman at 202-687 9868.

ARE THERE ANY BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there is no direct medical benefit to you. We hope the information learned from this study will benefit others in the future.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to protect your personal information to the extent allowed by law. Medical records of research study participants are stored and kept according to legal requirements. You will not be identified in any reports or publications resulting from this study. Organizations that may request, inspect and/or copy your research and medical records for quality assurance and data analysis include groups such as: Department of Defense, Food and Drug Administration, MedStar Research Institute, Georgetown University, and Institutional Review Board (IRB).

We will store your blood, cheek, saliva, nail and urine samples, or genetic material prepared from your blood, urine, cheek, saliva and nail in a secure room with restricted access. Only people working on this research project can work on your samples. Because we want to protect your confidentiality, your samples will have only a number on the tube and will not have your name or other identifier information.

We will protect your genetic and other testing results. We will control access to the computer files that hold this information. Access to the computer files can only be obtained through multiple passwords. Only authorized study personnel can link your sample to you. This information will not be released to anyone. "Anyone" includes you, your family, your doctor, your insurance company, or your employer. This is because the research is at a very early stage and we would not be able to tell you what your results mean. This information will not be included in any medical records.

Study number: Principal Investigator (s): Radoslav Goldman
Title Molecular Epidemiology of Prostate Cancer

CERTIFICATE OF CONFIDENTIALITY

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of Federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You should understand that the Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

WHAT ARE THE COSTS?

You should not expect any one to pay you for pain, worry, lost income, or non-medical care costs that occur from taking part in this research study.

You or your insurance company will be charged for continuing medical care and/or hospitalization that are not a part of the study.

RESEARCH RELATED INJURY

The Department of Defense is partially funding this research. Should you be injured as a direct result of participating in this research, you will be provided medical care at no cost to you. You will not receive any injury compensation, only medical care. Your insurance company will be billed, but you will not be liable for any costs not covered by your insurance. Additional information on this subject

may be obtained from the Office of the Medical Director, Georgetown University Hospital at (202) 784-3011.

You *will not* be paid for participating in this study.

COMMERCIAL INTEREST

On rare occasions, laboratory research on human specimens results in discoveries that are the basis for new research products or diagnostic and therapeutic methods. It is the policy of Georgetown University Medical Center, MedStar, Inc., and their affiliates not to compensate you for any future financial claim to your tissues for research and development for commercial and noncommercial purposes. No funds are available or will be paid by the MedStar Research Institute, MedStar Health or Georgetown University to repay you in case of injury.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part in or leave the study at any time. If you choose to not take part in or to leave the study, your regular care will not be affected and you will not lose any of the benefits you would have received normally.

We will tell you about new information that may affect your health, welfare, or participation in this study.

WHO DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study, problems, unexpected physical or psychological discomforts or injuries related to the study, contact day or night the research doctor, Radoslav Goldman at 202-687-9868. If you would like to write to him, please send mail to: Radoslav Goldman, Georgetown University, 3970 Reservoir Road NW, Research Building W309A, Washington DC 20057.

Study number:_ Principal Investigator (s): Radoslav Goldman
Title Molecular Epidemiology of Prostate Cancer

If you are a participant at Washington Hospital Center and have questions about your rights as a research participant, contact the MedStar Research Institute. Direct your questions to Dr. Barbara Howard at Medstar Research Institute:

MedStar Research Institute
6495 New Hampshire Ave., Suite 201
Hyattsville, MD 20783
Tel: (301) 853-7532
Pager: 1-888-663-6842

Or

If you are a participant at Georgetown University Medical Center and have questions about your rights as a research participant, contact the Georgetown University IRB Office. Direct your questions to:

Ms. Laura Miller, Executive Officer, Institutional Review Board at:
Address: Georgetown University Medical Center Telephone: (202) 687-1506
3900 Reservoir Road, N.W.
NE 105 Med-Dent
Washington, D.C. 20007

Study number:_ Principal Investigator (s): Radoslav Goldman
Title Molecular Epidemiology of Prostate Cancer

SIGNATURES

As a representative of this study, I have explained the purpose, the procedures, the benefits and risks that are involved in this research study. Any questions that have been raised have been answered to the individual's satisfaction.

_____ _____

Signature of person obtaining the consent Date

I, the undersigned have been informed about this study's purpose, procedures, possible benefits and risks, and I have received a copy of this consent. I have been given the opportunity to ask questions before I sign, and I have been told that I can ask other questions at any time. I voluntarily agree to participate in this study. I am free to withdraw from the study at any time without need to justify my decision. This withdrawal will not in any way effect my future treatment or medical management. I agree to cooperate with Dr. Radoslav Goldman and the research staff and to inform them immediately if I experience any unexpected or unusual symptoms.

_____ _____

Signature of Subject Date

_____ _____

Signature of Witness Date

_____ _____

Principal Investigator (if not person obtaining consent) Date

Study number:_ Principal Investigator (s): Radoslav Goldman
Title Molecular Epidemiology of Prostate Cancer

Informed Consent for Clinical Research (cases)

MedStar Research Institute/Georgetown Medical Center

INSTITUTION: GUMC + WHC

INTRODUCTION

We invite you to take part in a research study. The study is called 'Molecular Epidemiology of Prostate Cancer'. Please take your time to make your decision. Discuss it with your family and friends. It is important that you read and understand several general principles that apply to all who take part in our studies:

(a) Taking part in the study is entirely voluntary;

(b) Personal benefit to you may or may not result from taking part in the study, but knowledge may be gained from your participation that will benefit others;

(c) You may withdraw from the study at any time without any of the benefits you would have received normally being limited or taken away.

The nature of the study, the benefits, risks, discomforts and other information about the study is discussed below. Any new information discovered, at any place during the research, which might affect your decision to participate or remain in the study will be provided to you. You are urged to ask the staff members any questions you have about this study and the staff members will explain the questions to you. The investigator (person in charge of this research study) is Dr. Radoslav Goldman. The research is being sponsored by the Department of Defense. The Department of Defense is called the sponsor and the Georgetown University is being paid by the Department of Defense to conduct this study with Dr. Radoslav Goldman as the primary investigator.

WHY IS THE STUDY BEING DONE?

You are being asked to participate in this study because you are suspected of having prostate cancer or have prostate cancer. Your prostate tumor, blood and other samples may show us how cancer develops and what are the factors that helped increase the cancer risk.

The purpose of this study is to learn about the natural history of prostate cancer and its causes and treatments. This research is being done because the causes of prostate cancer are not well understood at present. The purpose of this research is to see how someone's ability to respond to genetic damage

modifies risk of prostate cancer. We will test how your ability to repair damaged DNA and eliminate cells that did not repair the damage modifies prostate cancer risk.

We will examine your blood, cheek samples, saliva, nail clippings and urine to see if tests for your response to chemical exposure can help us predict who might be at greater risk of prostate cancer. If you are going to have surgery, or had surgery, or if you are going to have a biopsy or had a biopsy, we will use samples of tumor tissue, as well as adjacent normal tissue, to determine whether markers in the tissue suggest how the cancer developed. The specimen will not be used for diagnostic purposes or for purposes related to your medical care. That is, the experiments done on these samples will not be used for decisions about your personal risk of prostate cancer, your treatment or your prognosis. These specimens will be available to qualified medical researchers for scientific studies that have been approved by the Principal Investigator, listed above, and an oversight committee. Researchers who receive these samples will not have access to your name or other identification information.

If you wish, you will be given the opportunity to identify friends living in your geographical area to be controls in the study. This would help us to identify a group of controls subjects without prostate cancer. We hope that this research can lead to the discovery of new tests for cancer risk, including genetic tests.

All men older than 18 years of age at all stages of presentation are eligible to participate in this study.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 600 people (300 patients and 300 controls) will take part in this study and will be recruited at Washington Hospital Center and Georgetown University Medical Center. Participants in the study are referred to as "subjects".

WHAT IS INVOLVED IN THE STUDY?

Upon reviewing and signing this informed consent, you will begin the study. We will ask you questions using a form that will take about an hour to finish. If you do not want to do the whole questionnaire at the time you give blood, we can do only one part lasting about 15 minutes and then we will contact you later to finish the study. This research will be conducted on an experimental basis only, and you will not be provided with any information about your test results.

Study number:_ Principal Investigator (s): Radoslav Goldman
Title Molecular Epidemiology of Prostate Cancer

If you take part in this study, you will have the following tests and procedures

1. Upon reviewing and signing this informed consent, you will begin the study.
2. Undergo an in person interview lasting about one hour administered by a trained interviewer.
3. Provide a blood sample that is about 3 tablespoons.
4. Provide a urine specimen.
5. Provide two cheek swab samples.
6. Provide saliva
7. Provide nail clipping.
8. Allow us to use the unneeded portion of your prostate tissue, as well as a small sample of adjacent normal tissue for research purposes.

HOW LONG WILL I BE IN THE STUDY?

We expect that your participation in the study will take an extra hour in addition to your scheduled examination. The study is completed after you finish your questionnaire and donate your blood, urine, nail, cheek sample, saliva and tissue from surgery/biopsy not needed for diagnostic purposes. However, if you agree below, we may call you in the future for additional information and/or sample collection. We will use your sample for different tests as described above and as new hypotheses develop for as long as it lasts and is useful for our testing. If the sample is no longer useful, it will be destroyed. However, you can request that your blood, cheek, saliva, nail, urine and prostate tissues be destroyed at any time. To have your samples destroyed, you can contact Dr. Goldman at 202-687 9868.

The investigators, physicians or sponsors may stop the study or take you out of the study at any time should they judge that it is in your best interest to do so, if you experience a study-related injury, or if you do not comply with the study plan. They may remove you from the study for various other administrative and medical reasons. They can do this without your consent.

In the future, it might be necessary to contact you for further information or an additional blood sample (or other type of biological sample). If this is okay, please indicate below. You can refuse to do so now or later. Please check and initial below:

I ____may ____may not be contacted in the future for further information or biological samples.

_____ Sign your initials here.

Study number:_ Principal Investigator (s): Radoslav Goldman
Title Molecular Epidemiology of Prostate Cancer

WHAT ARE THE RISKS OF THE STUDY?

There is a very slight chance of a bruise or an infection from the blood draw, but we use only trained medical technicians to draw your blood and they will use the best available precautions. Another possible risk is that your genetic information might be obtained by persons from outside the study. We will minimize this chance by maintaining the confidentiality of your test results and study records at all times (see below). For more information about risks and side effects, ask the research staff or contact Radoslav Goldman at 202-687- 9868.

ARE THERE ANY BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there is no direct medical benefit to you. We hope the information learned from this study will benefit others in the future.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to protect your personal information to the extent allowed by law. Medical records of research study participants are stored and kept according to legal requirements. You will not be identified in any reports or publications resulting from this study. Organizations that may request, inspect and/or copy your research and medical records for quality assurance and data analysis include groups such as: Department of Defense, Food and Drug Administration, MedStar Research Institute, Georgetown University, and Institutional Review Board (IRB).

We will store your tissue, blood, cheek, saliva, nail and urine samples, or genetic material prepared from your blood, urine, cheek, nail or prostate tissue, in a secure room with restricted access. Only people working on this research project can work on your sample. Because we want to protect your confidentiality, your samples will have only a number on the tube and will not have your name or other identifier information.

We will protect your genetic and other testing results. We will control access to the computer files that hold this information. Access to the computer files can only be obtained through multiple passwords. Only authorized study personnel can link your sample to you. This information will not be released to anyone. "Anyone" includes you, your family, your doctor, your insurance company, or your employer. This is because the research is at a very early stage and we would not be able to tell you what your results mean. This information will not be included in any medical records.

Study number:_ Principal Investigator (s): Radoslav Goldman
Title Molecular Epidemiology of Prostate Cancer

CERTIFICATE OF CONFIDENTIALITY

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of Federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You should understand that the Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

WHAT ARE THE COSTS?

You should not expect any one to pay you for pain, worry, lost income, or non-medical care costs that occur from taking part in this research study.

You or your insurance company will be charged for continuing medical care and/or hospitalization that are not a part of the study.

RESEARCH RELATED INJURY

The Department of Defense is partially funding this research. Should you be injured as a direct result of participating in this research, you will be provided medical care at no cost to you. You will not receive any injury compensation, only medical care. Your insurance company will be billed, but you will not be liable for any costs not covered by your insurance. Additional information on this subject may be obtained from the Office of the Medical Director, Georgetown University Hospital at (202) 784-3011.

You *will not* be paid for participating in this study.

COMMERCIAL INTEREST

On rare occasions, laboratory research on human specimens results in discoveries that are the basis for new research products or diagnostic and therapeutic methods. It is the policy of Georgetown University Medical Center, MedStar, Inc., and their affiliates not to compensate you for any future financial claim to your tissues for research and development for commercial and noncommercial purposes. No funds are available or will be paid by the MedStar Research Institute, MedStar Health or Georgetown University to repay you in case of injury.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part in or leave the study at any time. If you choose to not take part in or to leave the study, your regular care will not be affected and you will not lose any of the benefits you would have received normally.

We will tell you about new information that may affect your health, welfare, or participation in this study.

Study number:_ Principal Investigator (s): Radoslav Goldman
Title Molecular Epidemiology of Prostate Cancer

WHO DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study, problems, unexpected physical or psychological discomforts or injuries related to the study, contact day or night the research doctor, Radoslav Goldman at 202-687 9868. If you would like to write to him, please send mail to: Radoslav Goldman, Georgetown University, 3970 Reservoir Road NW, Research Building W309A, Washington DC 20057.

If you are a participant at Washington Hospital Center and have questions about your rights as a research participant, contact the MedStar Research Institute. Direct your questions to Dr. Barbara Howard at Medstar Research Institute:

MedStar Research Institute
6495 New Hampshire Ave., Suite 201
Hyattsville, MD 20783
Tel: (301) 853-7532
Pager: 1-888-663-6842

If you are a participant at Georgetown University Medical Center and have questions about your rights as a research participant, contact the Georgetown University IRB Office. Direct your questions to:

Ms. Laura Miller, Executive Officer, Institutional Review Board at:
Address: Georgetown University Medical Center
3900 Reservoir Road, N.W.
NE 105 Med-Dent
Washington, D.C. 20007
Telephone: (202) 687-1506

Study number:_ Principal Investigator (s): Radoslav Goldman
Title Molecular Epidemiology of Prostate Cancer

SIGNATURES

As a representative of this study, I have explained the purpose, the procedures, the benefits and risks that are involved in this research study. Any questions that have been raised have been answered to the individuals satisfaction.

_____ _____

Signature of person obtaining the consent Date

I, the undersigned have been informed about this study's purpose, procedures, possible benefits and risks, and I have received a copy of this consent. I have been given the opportunity to ask questions before I sign, and I have been told that I can ask other questions at any time. I voluntarily agree to participate in this study. I am free to withdraw from the study at any time without need to justify my decision. This withdrawal will not in any way effect my future treatment or medical management. I agree to cooperate with Dr. Radoslav Goldman and the research staff and to inform them immediately if I experience any unexpected or unusual symptoms.

_____ _____

Signature of Subject Date

_____ _____

Signature of Witness Date

_____ _____

Principal Investigator (if not person obtaining consent) Date