

AD _____

Award Number: W81XWH-08-2-0171

TITLE: Circadian Genes and Risk for Prostate Cancer

PRINCIPAL INVESTIGATOR: Dr. Ann Hsing

CONTRACTING ORGANIZATION: The Geneva Foundation
Lakewood, WA 98499

REPORT DATE: September 2011

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for public release; distribution unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.					
1. REPORT DATE (DD-MM-YYYY) 01-09-2011		2. REPORT TYPE Annual		3. DATES COVERED (From - To) 1 SEP 2008 - 31 AUG 2011	
4. TITLE AND SUBTITLE Circadian Genes and Risk for Prostate Cancer				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-08-2-0181	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Dr. Ann Hsing E-Mail: hsinga@mail.nihg.gov				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) The Geneva Foundation Lakewood, WA 98499				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT We propose that genetic susceptibility to prostate cancer may be in part due to variations in the core circadian genes that regulate circadian rhythms and that serum sex steroid hormone levels modify the effect of circadian gene polymorphisms on prostate cancer risk. Our study is nested within the Prostate Cancer Prevention Trial (PCPT), a randomized placebo-controlled clinical trial to determine if finasteride (an inhibitor of androgen bioactivation) could prevent prostate cancer. In Year 3 of the award, we completed genotyping at the University of Texas Health Science Center at San Antonio (UTHSCSA) genotyping facility We have also worked with the PCPT Statistical Center to ensure that the genotyping assays for our study is of good quality. A subset of the data was presented at the DoD PCRP IMPaCT Meeting in Orlando, FL in March 2011. We have also been involved in analyzing and manuscript preparation on the serum androgen data, a separate study whose results will help guide analysis for Aim 2 of our study. Data analysis and manuscript preparation is underway and will be completed in the nocost extension year of the grant.					
15. SUBJECT TERMS None provided.					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT UU	18. NUMBER OF PAGES 6	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U			19b. TELEPHONE NUMBER (include area code)

Table of Contents

	<u>Page</u>
Introduction.....	1
Body.....	1
Key Research Accomplishments.....	2
Reportable Outcomes.....	2
Conclusion.....	2
References.....	3
Appendices.....	3

INTRODUCTION: Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

Prostate cancer is the most commonly diagnosed cancer and the second leading cause of cancer death in men in the United States yet the only established risk factors for prostate cancer are race, age, and family history [1]. Recent data from observational studies on sleep duration [2], light at night [3], rotating shift workers [4, 5], and male airline pilots [6-8] suggest that circadian rhythm disruptions increase prostate cancer risk; no underlying molecular mechanism has yet been identified. We propose that genetic susceptibility to prostate cancer may be in part due to variations in genes from a number of pathways including the core circadian genes that regulate circadian rhythms. The goal of this project is to test the novel hypothesis that variants in circadian genes alter the risk of prostate cancer and that serum sex steroid hormone levels modify the effect of circadian polymorphisms on prostate cancer risk. Our study is nested within the Prostate Cancer Prevention Trial (PCPT), a randomized placebo-controlled clinical trial to determine if finasteride (an inhibitor of androgen bioactivation) could prevent prostate cancer. Included in our study are approximately 1,800 case-control pairs (3,600 individuals), for which several biological measurements are available, including serum sex hormone levels, which we will also incorporate into our study to test our hypothesis.

BODY: This section of the report shall describe the research accomplishments associated with each task outlined in the approved Statement of Work. Data presentation shall be comprehensive in providing a complete record of the research findings for the period of the report. Provide data explaining the relationship of the most recent findings with that of previously reported findings. Appended publications and/or presentations may be substituted for detailed descriptions of methodology but must be referenced in the body of the report. If applicable, for each task outlined in the Statement of Work, reference appended publications and/or presentations for details of result findings and tables and/or figures. The report shall include negative as well as positive findings. Include problems in accomplishing any of the tasks. Statistical tests of significance shall be applied to all data whenever possible. Figures and graphs referenced in the text may be embedded in the text or appended. Figures and graphs can also be referenced in the text and appended to a publication. Recommended changes or future work to better address the research topic may also be included, although changes to the original Statement of Work must be approved by the Army Contracting Officer Representative. This approval must be obtained prior to initiating any change to the original Statement of Work.

Our study has three specific aims, all of which utilizes genotyping data that is to be generated as part of the grant. The following is a report as it pertains to each task in the statement of work:

Task 1 Data management

We have been in constant communications with the PCPT Statistical Center at the Fred Hutchinson Cancer Research Center (Seattle, WA) since the project's inception. Genotyping data for this project has been incorporated into the PCPT central database as are data from serum androgen assays (completed as part of a separate study but will be used for Aim 2 of this study). With the PCPT Statistical Center, we have completed the quality control analysis of the data and have found the genotyping data as high quality and usable for further analysis. Data analysis for the three aims is underway.

Task 2 Develop and perform genotyping assays on 320 SNPs (including 40 putatively functional and 270 tag SNPs as well as additional SNPs to account for control SNPs and potential SNP assay failures) of circadian genes in approximately 4,000 samples including 1,800 case-control pairs (3,600 subjects) and approximately 400 duplicate quality control samples.

During Award Year 3, we completed the QC work necessary for genotyping in the newly approved genotyping laboratory at University of Texas Health Science Center at San Antonio (UTHSCSA; DoD approved in Award Year 2) including reconfiguring and re-plating the DNA to accommodate the new genotyping platform at the NCI biorepository; shipping the plated DNAs to UTHSCSA; and working with UTHSCSA to ensure that the new genotyping platform will still allow us to genotype the SNPs included in our study. Genotyping was subsequently completed at UTHSCSA and data has been delivered to the PCPT Statistical Center. In total, genotyping was performed for 308 SNPs on 1023 cases and 1153 controls. SNPs that were not genotyped from

the original list were not able to be designed on the new genotyping platform and study subjects who were not included in the genotyping did not have sufficiently good quality for genotyping.

Task 3 Monitor quality of genotyping results on an ongoing basis

With the PCPT Statistical Center, we have completed the quality control analysis of the data and have found the genotyping data as high quality and usable for further analysis. Data analysis for the three aims is underway.

Task 4 Gather, ship, process, and archive biospecimens

The DNAs have been shipped and genotyped at UTHSCSA.

Task 5 Prepare hormone data from PCPT

In Award Year 2, we worked with the PCPT Statistical Center on analyzing data related to serum androgen levels as part of the PCPT Program Project. Dr. Ann Hsing, the PI of the current award, is leading the analysis and two manuscripts describing the results are in preparation. These data will help guide data analysis necessary to complete Aim 2 of the current study.

Tasks 6 Perform statistical analysis

Data analysis and manuscript preparation is underway and will be completed in the no-cost extension year of the grant.

Task 7 Prepare scientific presentations & manuscripts

Preliminary data on a subset of the genotyping data was presented at the DoD PCRP IMPaCT Meeting in Orlando, FL in March 2011. The complete set of genotyping data has since been delivered. Data analysis and manuscript preparation is underway and will be completed in the no-cost extension year of the grant.

KEY RESEARCH ACCOMPLISHMENTS: Bulleted list of key research accomplishments emanating from this research.

- Completed genotyping all variations in circadian genes that could be designed as an assay for the current genotyping platform for all subjects with DNA that could be used for genotyping.
- Presented preliminary results at the DoD PCRP IMPaCT Meeting in Orlando, FL in March 2011.

REPORTABLE OUTCOMES: Provide a list of reportable outcomes that have resulted from this research to include: manuscripts, abstracts, presentations; patents and licenses applied for and/or issued; degrees obtained that are supported by this award; development of cell lines, tissue or serum repositories; informatics such as databases and animal models, etc.; funding applied for based on work supported by this award; employment or research opportunities applied for and/or received based on experience/training supported by this award.

There are currently no reportable outcomes from this project as data analysis is underway.

CONCLUSION: Summarize the results to include the importance and/or implications of the completed research and when necessary, recommend changes on future work to better address the problem. A "so what section" which evaluates the knowledge as a scientific or medical product shall also be included in the conclusion of the report.

The goal of this project is to test the novel hypothesis that variants in circadian genes alter the risk of prostate cancer and that serum sex steroid hormone levels modify the effect of circadian polymorphisms on prostate cancer risk. In Year 3 of the award, we completed genotyping on 308 SNPs for 2,176 subjects at the the University of Texas Health Science Center at San Antonio (UTHSCSA) genotyping facility. We have been worked with the PCPT Statistical Center to ensure that the genotyping assays for our study using the new genotyping platform are of high quality and are in the process of conducting data analysis. A subset of the data was presented at the DoD PCRP IMPaCT Meeting in Orlando, FL in March 2011. We have also been actively involved in analyzing and manuscript preparation on the serum androgen data, which is a separate study but whose results will be used to guide analysis for Aim 2 of our study. Data analysis and manuscript preparation is underway and will be completed in the no-cost extension year of the grant.

REFERENCES: List all references pertinent to the report using a standard journal format (i.e. format used in *Science*, *Military Medicine*, etc.).

- 1 Hsing AW, Chokkalingam AP. Prostate cancer epidemiology. *Front Biosci* 2006;11:1388-413.
- 2 Kakizaki M, Inoue K, Kuriyama S, et al. Sleep duration and the risk of prostate cancer: the Ohsaki Cohort Study. *Br J Cancer* 2008;99:176-8.
- 3 Kloog I, Haim A, Stevens RG, et al. Global Co-Distribution of Light at Night (LAN) and Cancers of Prostate, Colon, and Lung in Men. *Chronobiol Int* 2009;26:108 - 25.
- 4 Kubo T, Ozasa K, Mikami K, et al. Prospective cohort study of the risk of prostate cancer among rotating-shift workers: findings from the Japan Collaborative Cohort Study. *Am J Epidemiol* 2006;164:549-55.
- 5 Conlon M, Lightfoot N, Kreiger N. Rotating shift work and risk of prostate cancer. *Epidemiology* 2007;18:182-3.
- 6 Band PR, Le ND, Fang R, et al. Cohort study of Air Canada pilots: mortality, cancer incidence, and leukemia risk. *Am J Epidemiol* 1996;143:137-43.
- 7 Irvine D, Davies DM. British Airways flightdeck mortality study, 1950-1992. *Aviat Space Environ Med* 1999;70:548-55.
- 8 Pukkala E, Aspholm R, Auvinen A, et al. Cancer incidence among 10,211 airline pilots: a Nordic study. *Aviation, space, and environmental medicine* 2003;74:699-706.

APPENDICES: Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

None

SUPPORTING DATA: All figures and/or tables shall include legends and be clearly marked with figure/table numbers.

None.