SF 424 R&R and PHS-398 Specific

Table of Contents

SF 424 R&R Face Page............................................................................................................................ 2
Research & Related Other Project Information.......................................................................................... 3
Abstract..................................................................................................................................................... 4
Project Narrative........................................................................................................................................ 5
Facilities and Other Resources.................................................................................................................. 6
PHS 398 Cover Page Supplement ............................................................................................................ 7
PHS 398 Research Plan............................................................................................................................ 9
Specific Aims........................................................................................................................................... 10
Research Strategy................................................................................................................................... 11
Protection of Human Subjects................................................................................................................. 17
Inclusion of Women and Minorities .......................................................................................................... 19
Targeted/Planned Enrollment Table ........................................................................................................ 20
Inclusion of Children............................................................................................................................... 21
PI: HASHIBE, MIA

Title: Epidemiology of testicular cancer in the Utah population

FOA: PAR08-237

FOA Title: SMALL GRANTS PROGRAM FOR CANCER EPIDEMIOLOGY (R03)

1 R03 CA159357-01

Organization: UNIVERSITY OF UTAH

<table>
<thead>
<tr>
<th>Senior/Key Personnel:</th>
<th>Organization:</th>
<th>Role Category:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mia Hashibe PhD</td>
<td>University of Utah</td>
<td>PD/PI</td>
</tr>
<tr>
<td>Jim VanDerslice PhD</td>
<td>University of Utah</td>
<td>Co-Investigator</td>
</tr>
<tr>
<td>Geraldine Mineau PhD</td>
<td>University of Utah</td>
<td>Other(Specify)-Other Significant Contributor</td>
</tr>
<tr>
<td>Lorenzo Richiardi PhD</td>
<td>University of Utah</td>
<td>Other(Specify)-Other Significant Contributor</td>
</tr>
<tr>
<td>Kerry Rowe PhD</td>
<td>Intermountain Healthcare</td>
<td>Other(Specify)-Other Significant Contributor</td>
</tr>
</tbody>
</table>
RESEARCH & RELATED OTHER PROJECT INFORMATION

1. * Are Human Subjects Involved?  ☑ Yes  ☐ No
   1.a If YES to Human Subjects
      Is the Project Exempt from Federal regulations?  ☐ Yes  ☑ No
      If no, is the IRB review Pending?  ☑ Yes  ☐ No

2. * Are Vertebrate Animals Used?  ☐ Yes  ☑ No

3. * Is proprietary/privileged information included in the application?  ☐ Yes  ☑ No

4a. * Does this project have an actual or potential impact on the environment?  ☐ Yes  ☑ No

5. * Is the research performance site designated, or eligible to be designated, as a historic place?  ☐ Yes  ☑ No

6. * Does this project involve activities outside of the United States or partnerships with international collaborators?  ☐ Yes  ☑ No
ABSTRACT

The incidence rate for testicular cancer in Utah is the highest of all the cancer registries in the United States (8.3 per 100,000 in 2007). On a worldwide level, approximately 52,549 cases and 9,906 deaths occur due to testicular cancer each year. It is one of the few cancers with increasing incidence over the last few decades in the US and Europe. In Utah, the age-adjusted incidence rates for men aged 15-49 years increased from 6.4 in 1973 to 13.8 in 2007. The five year survival among testicular cancer patients in the US was 96.0% for men > 20 years old (1988-2001). The well-established testicular cancer risk factors include age, contralateral testicular cancer, cryptorchidism, race/ethnicity and family history of testicular cancer. Other factors that have been examined but have led to conflicting results across studies include lower birth order, higher maternal age, short gestational duration, and low birth weight. Thus far, an epidemiologic study on testicular cancer in Utah has never been conducted. The Utah Population Database (UPDB) is an existing data source that provides an excellent opportunity to examine testicular cancer trends, risk factors and prognosis in Utah. It has been used in various gene identifying and familial clustering studies for breast cancer, colorectal cancer, melanoma and prostate cancer, but this will be the first application of using this database for studying testicular cancer risk factors. Additionally, the UPDB has been used to study prenatal factors from birth certificate records as possible risk factors for outcomes such as preterm births and autism spectrum disorders, but prenatal factors have not been studied for any cancers thus far in the UPDB. The UPDB has over 14.5 million records with linkage across cancer registry data, birth certificate records, death records, driver's license records, and medical records. We also have access to geocoded data on proximity to specific agricultural activities (as a proxy for pesticide exposure) and exposure to contaminants in drinking water in Utah, which will be linked to the UPDB records. We propose to conduct the following studies within the UPDB: 1) a descriptive epidemiology of testicular cancers, 2) a population-based case-control study, and 3) a follow up study of testicular cancer patients. We expect to include approximately 1,826 testicular cancer patients (1973-2007) for the descriptive epidemiology and follow up studies. For the case-control study, we will include 1,826 testicular cancer patients and 5,478 controls (3 controls per case). Our specific aims are in parallel to the study designs: 1) to investigate the testicular cancer trends for the Utah population, 2) to examine prenatal and perinatal factors, history of previous disease, family history of cancer, and rural residence as possible risk factors for testicular cancer, and 3) to study survival, and incidence of second primary tumors, cardiovascular disease, depression and other diseases among testicular cancer patients in Utah. This study will be the first epidemiologic study of testicular cancer in Utah. We will take advantage of a unique existing data resource to contribute to a better understanding of testicular cancer in Utah.
PROJECT NARRATIVE

Our project on testicular cancer in Utah is important for public health because it will contribute to a better understanding of the trends over time and the risk factors are important for testicular cancer in this high risk population. We will also study the prognosis of testicular cancer patients and examine what factors affect prognosis. Our results will be relevant for public health planning of prevention efforts against testicular cancer in Utah.
FACILITIES AND OTHER RESOURCES

Laboratory
Not applicable.

Clinical
Not applicable.

Animal
Not applicable.

Computer
In the Division of Public Health, Department of Family and Preventive Medicine, University of Utah School of Medicine, the computers are managed by two computer specialists in the department. A desktop computer is available for Dr. Hashibe. Computers will be ordered for the Zachary Burningham (graduate student) who will analyze the data for this project. These computers are connected through the central server of the department and have access to the University of Utah electronic library. All faculty and staff have access to the University’s computer facilities and computer support services. The computer system is supported by Departmental personnel.

Office
The Division of Public Health is part of the Department of Family and Preventive Medicine (DFPM) in the University of Utah School Of Medicine. The Department has 12,000 square feet of space that is available to the Division of Public Health for housing study personnel. The space contains offices for faculty and cubicles for staff, office furniture, and desk top computers. Study personnel who are already employees of the Division have offices or cubicles with the necessary furniture and desk top computers and are housed within these 12,000 square feet. All personnel will have access to a photo copier, scanners, fax machine, various printers, and storage space.

Dr. Hashibe has her own office on the second floor in the Division of Public Health. For Zachary Burningham, cubicle office space is available in the shared student and fellow area of the Division of Public Health.
### 1. Project Director / Principal Investigator (PD/PI)

- **Prefix:**
- **First Name:** Mia
- **Middle Name:**
- **Last Name:** Hashibe
- **Suffix:** PhD

### 2. Human Subjects

- **Clinical Trial:** No
- **Agency-Defined Phase III Clinical Trial:** Yes

### 3. Applicant Organization Contact

- **Prefix:**
- **First Name:** Michael
- **Middle Name:**
- **Last Name:** Dickman
- **Suffix:**

- **Phone Number:** 801-585-6201
- **Fax Number:** 801-585-5749
- **Email:** michael.dickman@osp.utah.edu

- **Title:** Sponsored Projects Officer
- **Street 1:** 75 South 2000 East Room 211
- **City:** Salt Lake City
- **County/Parish:** Salt Lake
- **State:** UT: Utah
- **Country:** USA: UNITED STATES
- **Zip/Postal Code:** 84112-8930
4. Human Embryonic Stem Cells

* Does the proposed project involve human embryonic stem cells?  

[ ] No  [ ] Yes
**PHS 398 RESEARCH PLAN**

### 1. Application Type:

From SF 424 (R&R) Cover Page. The response provided on that page, regarding the type of application being submitted, is repeated for your reference, as you attach the appropriate sections of the Research Plan.

*Type of Application:*

- [X] New
- [ ] Resubmission
- [ ] Renewal
- [ ] Continuation
- [ ] Revision
SPECIFIC AIMS

(Please note: the bibliography with the references listed throughout this section in the original grant application was omitted in order to decrease the file size.)

The incidence rate for testicular cancer in Utah is the highest in the United States, compared to other cancer registries (8.3 per 100,000; SEER 2009). On a worldwide level, approximately 52,549 cases and 9,906 deaths occur due to testicular cancer each year (Ferlay 2010). The highest incidence rates in the world are observed in Scandinavian countries such as Denmark (12.2 per 100,000) and Norway (11.3 per 100,000). The overall incidence in the US is 5.1 per 100,000, but more testicular cancer cases occur in the United States (n=8,480) than in all of Northern Europe combined (3,442 cases). Furthermore, it is one of the few cancers with increasing incidence over the last few decades in the US. In Utah, the age-adjusted incidence rates for men aged 15-49 years increased from 6.4 in 1973 to 13.8 in 2007 (SEER 2009).

Various risk factors have been hypothesized for testicular cancer including prenatal, postnatal, environmental and genetic factors. The well established risk factors include age, contralateral testicular cancer, cryptorchidism, race/ethnicity and family history of testicular cancer. Other factors that have been examined but have led to conflicting results across studies include lower birth order, higher maternalage, short gestational duration, and low birth weight. The Utah Population Database (UPDB) provides an excellent opportunity to study testicular cancer trends, risk factors and survival in Utah since it links cancer registry data with birth certificate, death records, driver’s licenses, and medical records. For cancer research, it is a unique resource comparable to the excellent record linkage conducted in Scandinavian countries which have been used in various cancer research analyses. A unique characteristic about the Utah population is that family history data are available not only for first and second degree relatives, but also for third, and fourth degree relatives. An additional advantage is that the family history information is based on records rather than self reports which are commonly used in epidemiologic studies.

Our overall strategy will be to use the following records in the UPDB for epidemiologic analyses: 1) birth certificate records, 2) medical records, 3) drivers license records, 4) family history records, 5) environmental factors from geocoded data, and 6) cancer registry records. Our specific aims with corresponding hypotheses for this project are:

**Specific Aim 1:** To investigate the trends of testicular cancer in the Utah population. We will conduct a descriptive epidemiology study of testicular cancers within the UPDB, and explore possible reasons for the trends in Utah by estimating age-adjusted incidence rates by subgroups such as rural vs. urban, by race/ethnicity and histology.

**Hypothesis:** The increasing testicular cancer incidence trends are mainly due to the race/ethnicity distribution in Utah of a high proportion of northern Europeans and a low proportion of Asians and African-Americans.

**Specific Aim 2:** To study the risk factors for testicular cancer in Utah by estimating odds ratios and attributable risks in a population-based case-control study within the UPDB.

**Hypothesis:** Maternal bleeding during pregnancy, lower birth order, and greater sibship size are risk factors for testicular cancer in Utah.

**Hypothesis:** Having had cryptorchidism or hypospadia is a risk factor testicular cancer in Utah, but family history of cryptorchidism or hypospadia is not a risk factor for testicular cancer in Utah.

**Specific Aim 3:** To follow up a cohort of testicular cancer patients in the Utah population database and estimate survival, and incidence of second primary tumors, cardiovascular disease, and other diseases.

**Hypothesis:** A higher proportion of testicular cancer patients in Utah will have cardiovascular disease, depression, neurotoxicity (paresthesias), impaired renal function and respiratory disease compared to the general population in Utah.

**Expected outcome:** Our study takes advantage of a unique existing database to examine testicular cancer trends, risk factors, and survival in the high risk population of Utah. We will incorporate epidemiologic study designs including a descriptive epidemiology study, a population-based case-control study, and a follow up study of testicular cancer patients in Utah. This is the first epidemiologic study of testicular cancer in Utah. Considering that the incidence rate of testicular cancer in Utah is the highest across all cancer registries in the US and is rising steadily, this study will be very important in contributing to a better understanding of testicular cancer in Utah to design prevention efforts.
RESEARCH STRATEGY

SIGNIFICANCE: Importance of the problem
In 2010, it is estimated that 8,480 cases of testicular cancer will be diagnosed and that 350 men will die from testicular cancer in the United States (ACS 2010). Worldwide, approximately 52,549 cases and 9,906 deaths occur due to testicular cancer each year (Ferlay 2010). Of the 52,549 cases, 29,508 occur in more developed countries and 23,041 occur in less developed countries. Though it is a rare cancer overall, it is the most common cancer among men who are 15 to 35 years old in the US (SEER 2009).

The incidence rates vary across regions in the world, from nearly 12.2 per 100,000 person-years in Denmark to less than 1 in African countries such as Zimbabwe and Uganda (Ferlay 2010). For men in Asia, the testicular cancer incidence rate is around 1 per 100,000 in Japan, and close to 2 per 100,000 in Hong Kong, China. The overall incidence in the US is 5.1 per 100,000, but more testicular cancer cases occur in the United States (8,840 cases) than in all of Northern Europe combined (3,442 cases) each year. Within the US, the incidence rate for testicular cancer in Utah is the highest compared to other cancer registries at 8.3 per 100,000 (SEER 2009). Figure 1 shows the Utah cancer incidence compared to the overall US cancer incidence for specific cancer sites. The testicular cancer incidence rate in Utah is almost 40% above the US rate. Other cancer registries with relatively high testicular cancer rates within the US include Seattle-Puget Sound (6.1), Iowa (6.3) and Connecticut (6.8).

The proportions of individuals who are Caucasian are 79.8% in the United States overall and 92.9% in the state of Utah (US Census Bureau, 2008). Utah also has a higher proportion of individuals whose ancestry is in specific countries with high testicular cancer incidence (68.1% in Utah and 54.0% in the US overall; US Census Bureau, 2006-2008). The countries of ancestry with higher testicular incidence than the US overall incidence of 5.1 per 100,000 are: Italy (6.4), the United Kingdom (6.7), Sweden (6.8), France (7.1), Hungary (7.3), the Czech Republic (8.1), Netherlands (8.1), Ireland (8.1), Germany (8.5), Slovakia (8.8), Switzerland (9.0), Norway (11.3), and Denmark (12.2; Ferlay 2010). Perhaps the reason that Utah has the highest incidence in the US is because of the ancestral distribution of the population. However, the reasons for the high testicular cancer incidence rate are currently unknown and needs to be studied.

The incidence rates of testicular cancer have been increasing in the United States and most other regions of the world including Europe, Asia and South America (Purdue 2005). In Utah, the age-adjusted incidence rates for men aged 15-49 years increased from 6.4 in 1973 to 13.8 in 2007 (SEER 2009). Thus on average from 1973 to 2007, the incidence of testicular cancer in Utah increased 1.5% per year (SEER 2009).

The overall five year survival among testicular cancer patients was 96.0% for men who were more than 20 years old for 1988-2001 (Ries 2007). Men with seminoma have a slightly higher survival of 98.0% compared to men with non-seminoma (92.6%). African-American men have lower 5-year survival (89.7%) then Caucasian men (96.2). Testicular cancer survival rates for Utah have not yet been reported in the literature. A recent commentary by Travis et al highlighted research priority areas for testicular cancer on the late effects of
Various risk factors have been hypothesized for testicular cancer including prenatal, postnatal, environmental and genetic factors. The well-established risk factors include age, contralateral testicular cancer, cryptorchidism, ethnicity and family history of testicular cancer (Richiardi 2008). A recent cohort study in Denmark showed that both cryptorchidism (RR=3.71, 95%CI=3.29-4.19) and hypospadia (RR=2.19, 95%CI=1.26-3.61) are risk factors for testicular cancer, but that the family history of cryptorchidism or hypospadia was not correlated with testicular cancer risk (Schnack 2010). These findings suggest that the hypothesis that cryptorchidism, hypospadia and testicular cancer are on the same pathway, the testicular dysgenesis syndrome, is incorrect. Reports prior to the results by Schnack et al were inconsistent for the association between family history of cryptorchidism and testicular cancer risk. Though the study by Schnack et al was very large with 5,441 testicular cancer patients, more studies are needed to confirm their observations.

Probable relationships exist between testicular cancer risk and early puberty, tallness and subfertility (Richiardi 2008). Other factors that have been examined but have led to conflicting results across studies include lower birth order, higher maternal age, short gestational duration, and low birth weight. A recent meta-analysis of perinatal factors reported an increased testicular cancer risk of 1.33 (95%CI=1.02-1.73) for maternal bleeding during pregnancy, and decreased risks of 0.80 (95%CI=0.69-0.94) for being the fourth child compared to the first born child, and 0.75 (95%CI=0.62-0.90) for sibship size of 4 compared to 1 (Cook 2009). In this meta-analysis, associations were not observed with maternal age, maternal hypertension, pre-eclampsia, or breech delivery (Cook 2009). For cesarean sections, an association was not observed overall (OR=1.20, 95%CI=0.87-1.65), but an association was observed when the studies were restricted to those in the US (OR=1.67, 95%CI=1.07-2.56; Cook 2009). Dairy intake, bacterial and viral infections are also suspected but unestablished risk factors. Factors thought generally to not be associated with testicular cancer include tobacco smoking, alcohol drinking and vasectomies. The Utah Population Database provides an opportunity to examine many of the above factors as possible risk factors for testicular cancer.

Environmental risk factors such as serum organochlorine pesticide residue exposure (Biggs 2008; McGlynn, 2008) and fertilizer use (Kristensen 1996) have been associated with testicular cancer risk. Several studies have shown that rural residence is a risk factor for testicular cancer (Graham 1977; Kristensen 1996; Nori, 2006; Walschaerts 2007). It would be of interest to understand the testicular cancer risk differences by rural vs. urban residence in Utah, taking into account the role of pesticide use, and also whether rural residence affects the prognosis of testicular cancers in Utah.

Although linkage studies have been conducted in the International Testicular Cancer Consortium, susceptibility loci have not been identified (Crockford 2006), suggesting that moderate risk alleles contribute to the genetic risk of testicular cancer. Recent genome-wide association studies of testicular cancer have identified genetic variants in various genes including KITLG (12q21 region), SPRY4 (5q31), BAK1 (6p21), TERT (5p15), DMRT1 (9p24) and ATF7IP (12p13; Turnbull 2010).

**How the proposed project will improve scientific knowledge.** We will provide risk estimates for testicular cancer for the Utah population for the first time for: 1) established risk factors such as contralateral testicular cancer, cryptorchidism, race/ethnicity and family history of cancer, and 2) suspected risk factors such a maternal age, birth order, birth weight, and family history of cryptorchidism. Since these exposure data are linked with the cancer registry data, we will be able to examine potential sources of the increasing incidence of testicular cancer in Utah. We will also report on survival differences for testicular cancer by demographic factors (rural vs. urban residence), tumor characteristics and risk factors identified from the case-control analysis.

**How the concepts, methods, preventative interventions will be changed if the proposed aims are achieved.** Our results will contribute to the literature on testicular cancer epidemiology and provide further
evidence for testicular cancer risk factors. If testicular cancer risk factors specific to the Utah population are identified, our results may impact the preventative interventions against testicular cancer.

INNOVATION

How the application challenges and seeks to shift current research or clinical practice paradigms
We aim to shift current research paradigms of testicular cancer to focus on the high risk Utah population. We will also focus on research priorities as outlined by Travis et al (Travis 2010), and will examine the late effects of testicular cancer and its treatment such as risk cardiovascular disease, depression, decreased fertility, respiratory disease, which has the potential to shift clinical practice paradigms.

Advantage over existing methodologies, instrumentation or intervention(s)
Our advantage over the existing methodology of conducting a case-control study with recruitment of cancer patients and controls to study risk factors is that we will analyze existing data. We expect that our project will provide an understanding of the important testicular cancer risk factors in Utah. The Utah Population Database (UPDB) provides a unique and excellent resource for such studies that is analogous to the Scandinavian country health records that have been linked for many epidemiologic studies. The UPDB also has very detailed family history data that goes back for many generations, thus we can assess family history of cancer in third or even fourth degree relatives from records. An advantage is that the family history information will be based on records, and not self reports, as is typical in other epidemiologic studies.

Refinements, improvements or new applications of approaches or methodologies
The UPDB has been used in various gene identifying and familial clustering studies for breast cancer, colorectal cancer, melanoma and prostate cancer (Cannon Albright 2008), but this will be the first application of using this database for testicular cancer risk factors. Additionally, prenatal factors from birth certificate records have been examined as possible risk factors for outcomes such as preterm births and autism spectrum disorders (Bilder 2009; Esplin 2008), but these factors have not been examined for any cancers thus far.

APPROACH

1) Overall strategy. Our overall strategy will be to use the following records for epidemiologic analyses: 1) birth certificate records, 2) medical records, 3) drivers license records, 4) family history records, 5) environmental factors from geocoded data, and 6) cancer registry records. The objectives of this proposed study are to assess the role of the following factors on testicular cancer risk:

1. From birth certificate records, Prenatal/perinatal factors: birth weight, gestational age, weight for gestational age, maternal height, maternal smoking, maternal alcohol use, maternal and paternal race, maternal and paternal occupation, conditions during the pregnancy (ex. gestational hypertension, anemia, eclampsia, gestational diabetes, uterine bleeding), birth abnormalities or anomalies (ex. cleft palate, heart malformations), apgar score, multiple births, complications of labor and/or delivery, method of delivery, residential address

2. From medical records (Intermountain health data, University of Utah Health Science Center (UUHSC) Data Resource Center and Utah Department of Health (UDOH) Health Facility Administration Data):
   a. Postnatal factors of subject: height, weight, cryptorchidism (undescended testes), orchiopexy (including age at operation for cryptorchidism), hormonal treatment for cryptorchidism, hypospadias (urethral opening is located along the underside rather than the tip of the penis), vasectomy, testicular trauma (ex. Injury), orchitis (inflammation of the testicle), inguinal hernia, viral infections, vaccinations during childhood, history of infertility including time to pregnancy, high cholesterol, genetic disorders (cystic fibrosis, down’s syndrome, Klinefelter syndrome), xray and other medical radiation exposures, testicular microlithiasis
   b. Treatment for cancer: type of chemotherapy, type of radiotherapy
   c. Disease history after cancer diagnosis of subject: cardiovascular disease, decreased fertility, hypogonadism, paresthesias (neurotoxicity from cancer treatment), impaired renal function (nephrotoxicity from cancer treatment), respiratory disease, depression

3. From driver’s license records,
   a. Subject characteristics: height, weight, residential address
b. **Father's characteristics**: height, weight

4. **From family records, family history of cancer and family information**: sibship size, birth order of subject, number of older/younger siblings (to try to distinguish between sibship size and birth order), for twins unlike-sex vs. same-sex twins, number of children fathered, number of first/second/third/fourth degree relatives with cancer, number of first/second/third/fourth degree relatives with hypospadia or cryptorchidism

5. **From geocoded data, environmental factors** (street address, geocodes, census tract): rural vs. urban, proximity to specific agricultural activities (as proxy for pesticide exposure), exposure to contaminants in drinking water (e.g. total alpha activity).

Co-investigator Dr. Jim VanDerslice, an environmental epidemiologist has just completed a GIS layer of all public water systems and agricultural activities in the state. We will be able to identify each subject’s water system and link them to the existing water quality data. Each of these linkages is based on the subject’s residential location at some point in time. In order to identify the most relevant exposure over time, we will compile as complete of a residential history as possible using residential location from as many points in a person’s life as possible.

The outcome variables will be obtained from the Utah cancer registry data—age and year of diagnosis, ICD site code, grade, stage, histology, second primary tumors, laterality, tumor size, metastasis, lymph nodes. Cases will be individuals who have been diagnosed with a first primary testicular cancer (ICD site Codes: C62.0-C62.9).

We will stratify the case group in all analyses by histology: seminoma (90613-90663); nonseminoma (90703-91023). We will also obtain race/ethnicity, and treatment (surgery, radiotherapy, chemotherapy) information from the Utah cancer registry records.

This proposal was submitted to the Resource for Genetics and Epidemiology Research (RGE: [http://www.research.utah.edu/rge/](http://www.research.utah.edu/rge/)), the office which reviews all new proposals based on the UPDB and for ethical approval with the University of Utah IRB in April 2010. We received comments from the RGE reviewing committee and have improved our proposal accordingly. We expect to obtain approval by August 2010. The data across the records will be linked and prepared by the Pedigree and Population resource staff that manage the UPDB ([http://www.hci.utah.edu/groups/ppr/index.html](http://www.hci.utah.edu/groups/ppr/index.html)).

Dr. Geri Mineau (key personnel for this grant) is the director of the UPDB and has been providing scientific input for this project. The medical records data will be accessed through the UPDB for the University of Utah Healthcare. The Utah population is also served by Intermountain Healthcare, a nonprofit system of hospitals and clinics. Dr. Kerry Rowe (key personnel for this grant), a bioinformatist who oversees the research data at Intermountain will provide scientific support for the project in terms of extracting medical records from Intermountain. After Intermountain records are extracted, the UPDB staff will link the data with the other records. Dr. Lorenzo Richiardi, an expert in testicular cancer epidemiology who has published over 23 papers in the field, will provide scientific input for the data analysis and manuscript preparation as key personnel. Drs. Mineau, Rowe and Richiardi have all provided letters of support for this proposal.

### Table 1. Characteristics of Testicular Cancer Patients in Utah, 1973-2007

<table>
<thead>
<tr>
<th>Diagnosis Time period</th>
<th>Total N=1,826</th>
<th>Total %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1973-1978</td>
<td>172</td>
<td>9.4%</td>
</tr>
<tr>
<td>1979-1984</td>
<td>183</td>
<td>10.0%</td>
</tr>
<tr>
<td>1985-1990</td>
<td>271</td>
<td>14.8%</td>
</tr>
<tr>
<td>1991-1996</td>
<td>335</td>
<td>18.3%</td>
</tr>
<tr>
<td>1997-2002</td>
<td>407</td>
<td>22.3%</td>
</tr>
<tr>
<td>2003-2007</td>
<td>458</td>
<td>25.1%</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=14</td>
<td>32</td>
<td>1.8%</td>
</tr>
<tr>
<td>15-19</td>
<td>109</td>
<td>6.0%</td>
</tr>
<tr>
<td>20-29</td>
<td>684</td>
<td>37.5%</td>
</tr>
<tr>
<td>30-39</td>
<td>577</td>
<td>31.6%</td>
</tr>
<tr>
<td>40-49</td>
<td>289</td>
<td>15.8%</td>
</tr>
<tr>
<td>50-59</td>
<td>81</td>
<td>4.4%</td>
</tr>
<tr>
<td>60+</td>
<td>54</td>
<td>3.0%</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>1674</td>
<td>91.7%</td>
</tr>
<tr>
<td>Hispanic White</td>
<td>123</td>
<td>6.7%</td>
</tr>
<tr>
<td>African American</td>
<td>2</td>
<td>0.1%</td>
</tr>
<tr>
<td>Native American</td>
<td>19</td>
<td>1.0%</td>
</tr>
<tr>
<td>Asian/Pacific islander</td>
<td>8</td>
<td>0.4%</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seminoma</td>
<td>963</td>
<td>52.7%</td>
</tr>
<tr>
<td>Nonseminoma</td>
<td>831</td>
<td>45.5%</td>
</tr>
<tr>
<td>Embryonal</td>
<td>241</td>
<td>13.2%</td>
</tr>
<tr>
<td>Yolk sac</td>
<td>32</td>
<td>1.8%</td>
</tr>
<tr>
<td>Teratoma</td>
<td>50</td>
<td>2.7%</td>
</tr>
<tr>
<td>Mixed germ cell</td>
<td>491</td>
<td>26.9%</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td>17</td>
<td>0.9%</td>
</tr>
<tr>
<td>Non-germ cell &amp; unspecified</td>
<td>32</td>
<td>1.8%</td>
</tr>
</tbody>
</table>

Based on SEER 2009
2) Preliminary studies. A query of the SEER data from 1973-2007 showed that there are 1,826 patients who were diagnosed with testicular cancer in Utah (Table 1). A larger proportion of patients have been diagnosed in more recent years (25.1% in 2003-2007). The 20-39 year age groups accounted for the majority of testicular cancer cases (69.1%). Most patients were non-hispanic White (91.7%) and had seminoma (52.7%).

In preliminary trend analysis with the Joinpoint Regression program (Kim 2000), we observed that the incidence rate of testicular cancer has increased annually in the US, around 2.45% per year from 1973 to 1989 (Figure 2). This trend has since slowed to an annual increase of 0.72% a year, from 1989 to 2007. In Utah, from 1973 to 2007, the incidence of testicular cancer increased roughly 1.5% per year (Figure 3). There has been no sign of this trend slowing, unlike the overall results for the United States.

![Figure 2](image2.png)  
**Figure 2.** Annual percentage change of testicular cancer incidence rates in the *United States*. SEER 1973-2007 (Joinpoint software; Kim 2000)

![Figure 3](image3.png)  
**Figure 3.** Annual percentage change of testicular cancer incidence rates in the *Utah*. SEER 1973-2007 (Joinpoint software; Kim 2000)

Testicular cancer survival rates for Utah have not yet been reported in the literature. We conducted preliminary analysis based on the SEER data (SEER 2009). Survival of testicular cancer has generally improved over the decades. The 5-year survival in the United States was 73.9% in 1973 and increased to 95.4% in 2002 (Figure 4). In Utah, the 5-year survival was 83.5% in 1973 and 93.1% in 2002. Survival appears to have remained more stable in the United States compared to Utah (Figure 4). This may largely be due to the combined effects of a smaller number of cases being analyzed in Utah versus the United States and the rarity of the disease in general.

![Figure 4](image4.png)  
**Figure 4.** Testicular Cancer 5-Year Survival, Utah vs. U.S. (1973-2002)

3) Detailed approach by specific aim. Methodology and analyses for Aim 1: Descriptive epidemiology study. To investigate the trends of testicular cancer specifically in the Utah population, we will use the Utah cancer registry data (1973-2007) and the US population data available from SEER for 1973-2007, to calculate ageadjusted testicular cancer incidence rates. Incidence rates over the years will be calculated for subgroups such as rural vs. urban, by five year age groups, race/ethnicity, and histology in order to understand which of these factors plays a larger role in the increasing trend. We will also use the JoinPoint Regression Program (Kim 2000) to analyze the trends in the subgroups with the average annual percent change.

Methodology and analyses for Aim 2: Case-control study. For the case-control study to identify risk factors, controls will be randomly sampled from a group of eligible testicular cancer-free men, and individually matched on age at the time of the case’s identification (density sampling). The ratio of controls to cases will be 3:1, to increase statistical power. The exposure-disease associations will be assessed by calculating odds ratios (OR) and 95% confidence intervals from conditional logistic regression. ORs adjusted for age and
potential confounders where appropriate (race/ethnicity, cryptorchidism, family history of cancer) will be estimated. When associations are observed, we will adjust for those factors when examining other potential risk factors. Stratified analysis will be conducted by age groups, race/ethnicity, socioeconomic status, and histologic type of testicular cancer (seminoma vs. non-seminoma). For the risk factors identified, we will test possible interactions among the factors. Population attributable risk will be estimated for the risk factors with the equation \( p(ec) \times \frac{(OR-1)}{OR} \), where \( p(ec) \) is the proportion exposed among the cases (Rothman 2008).

Methodology and analyses for Aim 3: Follow up study. For the follow up study of testicular cancer patients in Utah, five year survival rates will be assessed with the Kaplan Meier survival curves. Differences in survival by tumor characteristics, demographic variables and risk factors identified from the case-control analysis will be assessed by the log-rank test. The proportional hazards model will be used to estimate the hazard ratio (HR) and 95% confidence intervals for prognostic factors. We will estimate standardized incidence ratios for second primary tumors. We will also determine the incidence of cardiovascular disease, depression, paresthesias, impaired renal function and respiratory disease among testicular cancer patients in Utah and compare the incidence to the general Utah population.

Statistical power. The sample size required to detect ORs ranging from 1.2 to 2.0 are presented in Figure 5. Our study including 1,800 cases and 5,400 controls will be able to detect an OR of 1.2 with a power of 0.8 and \( \alpha \) of 0.05 for exposure ranges of 22% to 74%. For ORs of 1.5 and 2.0, our study has sufficient power for exposure ranges of 5% to 95%. For the survival analysis, assuming 95% overall survival, our study of 1,800 cases will be able to detect an HR of 2.0 with a power of 0.8 and \( \alpha \) of 0.05 for exposure ranges of 15% to 83%.

4) Potential limitations. Some potential limitations are that the statistical power may be low for examining trends, especially by subgroups such as race/ethnicity. Though some of our analyses might be limited, we believe it is still worthwhile to explore patterns in the trend. Another limitation is that each analysis is limited to the records available. Birth certificates are available for all subjects in the study population, but the detailed information on pregnancy complications are only available from 1992 and on. However, there are 1150 cases from 1992-2007, thus the sample size is still sufficient. For driver’s license records, a small proportion of our study population will be too young (1.8% <= 14 years) to have driver’s licenses, and not all individuals obtain driver’s licenses. However, the majority of individuals do obtain driver’s licenses and the information we need will also be available from medical records (height, weight). Thus we do not expect these issues to be major limitations.

5) Benchmarks for success
Benchmarks for success include: 1) identifying possible sources for the increasing testicular cancer incidence in Utah, 2) identifying specific risk factors for testicular cancer in Utah and proposing priorities for primary intervention, 3) determining the incidence of second primary tumors, cardiovascular disease, depression and other diseases, and survival in testicular cancer patients in Utah.

6) Conclusion
Our proposed project will be the first epidemiologic study of testicular cancer in Utah. We expect to contribute further knowledge to the scientific community on the testicular cancer trends, risk factors and prognosis. Some future directions for this project will include new hypothesis generation for a future epidemiologic study in Utah with recruitment of testicular cancer patients. We would also be interested in developing a cohort of testicular cancer survivors in Utah to further study late effects of the cancer and its treatment, including quality of life and psychosocial aspects as recommended recently in the literature (Travis 2010).
PROTECTION OF HUMAN SUBJECTS

A) Risks to subjects

Human Subjects Involvement
The human subjects included in our study will consist of male testicular cancer patients who are residents of Utah, in the Utah Cancer registry for 1973-2007. Controls will be population-based males, matched on age and county of residence from the UPDB existing database. Three controls will be matched for every testicular cancer case.

Human Subjects Characteristics: Based on an initial query of the SEER cancer registry data, we expect to have approximately 1826 testicular cancer cases and 5478 matched controls without disease.

Sampling plan and Design: Within the existing database (UPDB), we propose to conduct three study designs: 1) descriptive epidemiology of testicular cancers, 2) a population-based case-control study with retrospective and ecological assessment of exposures, 3) outcome study of testicular cancer (examining survival and second primary tumor development). The first study design will include the testicular cancer patients (n=1826) and US census population data from SEER to calculate incidence rates. The second study design involves the 1826 testicular cancer cases and 5478 matched controls from the Utah population. The third study design will involve only the 1826 testicular cancer patients. Our project is based on existing data and will not involve contacting any individuals as study subjects.

Rationale for involvement of vulnerable populations
Our study does not involve fetuses, neonates, pregnant women, prisoners, or institutionalized individuals. This study will include children since testicular cancer is the most common cancer among men who are 15 to 35 years old. Our aim for the project is to understand the risk factors for testicular patients overall in Utah, including all ages. For the case-control study within this project, we will include three controls per testicular cancer case, matched on age and county of residence. Thus the controls matched to the testicular cancer patients <21 years of age will also be <21 years of age.

Collaborating sites and roles of sites/investigators
University of Utah. Dr. Hashibe will act as PI for the project and will oversee the project scientifically, prepare the manuscripts and progress reports.

Dr. James VanDerslice will contribute scientifically to the overall project and specifically for the environmental exposure assessment with the geocoded data for the Utah population on water systems, radon potential and pesticide exposure.

B) Sources of materials:
This project involves accessing existing data on living individuals. The data sources are birth certificate records, driver’s license records, cancer registry records, family history records, geocoded environmental data and death records. We will not collect any new data from human subjects for this project.

We will not have any access to names, but we will access information on street addresses and geocodes, census tracts/block numbers, which is considered identifying data. Dr. Hashibe, Dr. VanDerslice and the data analyst will have access to the identifying data. The data concerning the participation in the study will be kept confidential to the full extent permitted by law and used only for scientific purposes. Data with information that could allow identification of subjects are maintained in separate databases with security systems to limit access to authorized personnel only. All data are kept on a secure computer system to which only study personnel have access.

C. Potential risks:
We do not foresee any psychological, financial, legal or other risks to subjects.
ADEQUACY OF PROTECTION AGAINST RISKS

A. Recruitment and informed consent:
This study does not involve recruitment of subjects and is based on existing data. In the IRB application with the University of Utah for this project, we have requested a waiver of consent because we will not have any contact with participants.

B. Protection against risk:
Each study participant will be provided a study subject ID. The participant will be identified only based on this random ID so they remain completely anonymous. We will minimize potential risks including risks to privacy of individuals or confidentiality of data by maintaining the data with identifiers on password protected computers to which only study personnel have access. The data without identifiers will be kept in folders on the department server, which is backed up daily. The data with identifiers will be kept in regular folders on the computer (not on the department server) and will NOT be backed up to minimize risks to confidentiality.

POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS
We do not expect that there will be any immediate benefits from the results of the study, to the participants. The goal of this study is to identify important risk and prognostic factors of testicular cancer in Utah; thus, the benefit will be directed more towards the general population (and future generations) of Utah.

IMPORTANCE OF THE KNOWLEDGE TO BE GAINED
Since the incidence rate for testicular cancer in Utah is the highest in the US compared to other cancer registries (8.3 per 100,000; SEER 2007), this is a very important cancer to study in the Utah population. We will provide risk estimates for testicular cancer for the Utah population for the first time for: 1) established risk factors such as contralateral testicular cancer, cryptorchidism, ethnicity and family history of cancer, and 2) suspected risk factors such as prenatal factors (including maternal age, birth order, birth weight), occupations, and viral infections. Since these exposure data are linked with the cancer registry data, we will be able to examine potential sources of the increasing incidence of testicular cancer in Utah. We will also report on survival differences for testicular cancer by demographic factors (rural vs. urban residence), tumor characteristics and risk factors identified from the case-control analysis.
INCLUSION OF WOMEN AND MINORITIES

Women are not included in this study because we are studying testicular cancer which only occurs in men.

All minorities will be included. We will include data on all testicular cancer patients from the Utah cancer registry for the years 1973-2007. We estimate that there are approximately 1,826 testicular cancer patients that meet our eligibility criteria for inclusion in our study. Of the 1,826 patients, 123 are Hispanic White, 2 are African-American, 19 are Native American and 8 are Asian/Pacific Islanders. Though the number of testicular cancer patients who are minorities are small, we will attempt to examine differences in trends and risk factors by race/ethnicity.

Since our project is based on existing data, we will not be contacting any individuals who are minorities for this study.
**Study Title:** Epidemiology of testicular cancer in the Utah population

**Total Planned Enrollment:** 1826 cases and 5478 controls = 7304 subjects

<table>
<thead>
<tr>
<th>TARGETED/PLANNED ENROLLMENT: Number of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ethnic Category</strong></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td><strong>Ethnic Category: Total of All Subjects</strong> *</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Racial Categories</th>
<th><strong>Females</strong></th>
<th><strong>Males</strong></th>
<th><strong>Total</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>American Indian/Alaska Native</td>
<td>0</td>
<td>76</td>
<td>76</td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>Native Hawaiian or Other Pacific Islander</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Black or African American</td>
<td>0</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>White</td>
<td>0</td>
<td>7,188</td>
<td>7,188</td>
</tr>
<tr>
<td><strong>Racial Categories: Total of All Subjects</strong></td>
<td>0</td>
<td>7,304</td>
<td>7,304</td>
</tr>
</tbody>
</table>

* The "Ethnic Category: Total of All Subjects" must be equal to the "Racial Categories: Total of All Subjects."
INCLUSION OF CHILDREN

This study will include children since testicular cancer is the most common cancer among men who are 15 to 35 years old. Our aim for the project is to understand the risk factors for testicular patients overall in Utah, including all ages. For the case-control study within this project, we will include three controls per testicular cancer case, matched on age and county of residence. Thus the controls matched to the testicular cancer patients <21 years of age will also be <21 years of age.

We also plan to investigate testicular cancer risk factors by age subgroups, including the subgroup of individuals <21 years old. The overall incidence rate for testicular cancer in the United States is 5.1 per 100,000 (SEER 2007). The age specific testicular cancer incidence rates are approximately 3.5 per 100,000 in men 15-19 years old and <1 per 100,000 for males <15 years of age. It is a rare cancer that is difficult to study, but in our project we have the unique opportunity to have enough testicular cancer patients who are children for a meaningful analysis. We expect to include approximately 200 testicular cancer patients <20 years old from Utah, based on cancer registry data from 1973-2007.

Since our project is based on existing data, we will not be contacting children for this study.