

Cancer in Iowa 2016

In 2016, an estimated 6,400 lowans

Will die from cancer, 16 times the number caused by auto fatalities. Cancer and heart disease are the leading causes of death in Iowa. These projections are based upon mortality data the State Health Registry of Iowa receives from the Iowa Department of Public Health. The Registry has been recording the occurrence of cancer in Iowa since 1973, and is one of fourteen population-based registries and three supplementary registries nationwide providing data to the National Cancer Institute. With *2016 Cancer in Iowa* the Registry makes a general report to the public on the status of cancer. This report will focus on:

- a description of the Registry and its goals,
- cancer estimates for 2016,
- a special section on adolescent and young adult cancer,
- brief summaries of recent/ongoing research projects, and
- a selected list of publications from 2015.

The State Health Registry of Iowa

The State Health Registry of Iowa is the best statewide resource for determining the burden of cancer on the Iowa population and assessing trends in the occurrence of cancer over time. Cancer is a reportable disease as stated in the Iowa Administrative Code. Cancer data are collected by the State Health Registry of Iowa, located at The University of Iowa in the College of Public Health's Department of Epidemiology. The staff includes 50 people. Half of them, situated throughout the state, regularly visit hospitals, clinics, and medical laboratories in Iowa and neighboring states to collect cancer data. A follow-up program tracks more than 99 percent of the cancer survivors diagnosed since 1973. This program provides regular updates for follow-up and survival. The Registry maintains the confidentiality of the patients, physicians, and hospitals providing data.

In 2016 data will be collected on an estimated 16,600 new cancers among Iowa residents. In situ cases of bladder cancer are included in the estimates for bladder cancer, to be in agreement with the definition of reportable cases of the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI).

Since 1973 the Iowa Registry has been funded by the SEER Program of the NCI. Iowa represents rural and Midwestern populations and provides data included in many NCI publications. Beginning in 1990 about 5-10 percent of the Registry's annual operating budget has been provided by the state of Iowa. Beginning in 2003, the University of Iowa has also been providing cost-sharing funds. The Registry also receives funding through grants and contracts with university, state, and national researchers investigating cancer-related topics.

The goals of the Registry are to:

- assemble and report measurements of cancer incidence, survival, and mortality among Iowans,
- provide information on changes over time in the extent of disease at diagnosis, therapy, and patient survival,
- promote and conduct studies designed to identify factors relating to cancer etiology, prevention, and control,
- respond to requests from individuals and organizations in the state of Iowa for cancer data and analyses, and
- provide data and expertise for cancer research activities and educational opportunities.

Estimated Number of New Cancers in Iowa for 2016 5

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Estimated Number of Cancer Deaths in Iowa for 2016

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NEW CANCERS IN FEMALES

ТҮРЕ	# OF CANCERS	% OF TOTAL
Breast	2200	26.8
Lung	1040	12.7
Colon & Rectum	780	9.5
Uterus	600	7.3
Skin Melanoma	420	5.1
Non-Hodgkin Lymphoma	330	4.0
Thyroid	300	3.7
Leukemia	270	3.3
Pancreas	240	2.9
Kidney & Renal Pelvis	230	2.8
All Others	1790	21.9
TOTAL	8200	

CANCER DEATHS IN FEMALES

ТҮРЕ	# OF CANCERS	% OF TOTAL
Lung	740	24.7
Breast	390	13.0
Colon & Rectum	290	9.7
Pancreas	210	7.0
Ovary	150	5.0
Leukemia	120	4.0
Uterus	120	4.0
Non-Hodgkin Lymphoma	110	3.7
Brain	70	2.3
Kidney & Renal Pelvis	70	2.3
All Others	730	24.3
TOTAL	3000	

NEW CANCERS IN MALES

ТҮРЕ	# OF CANCERS	% OF TOTAL
Prostate	1550	18.4
Lung	1270	15.1
Colon & Rectum	830	9.9
Bladder (invasive and noninvasive)	630	7.5
Skin Melanoma	520	6.2
Kidney & Renal Pelvis	420	5.0
Non-Hodgkin Lymphoma	400	4.8
Leukemia	360	4.3
Oral Cavity	320	3.8
Pancreas	250	3.0
All Others	1850	22.0
TOTAL	8400	

CANCER DEATHS IN MALES

ТҮРЕ	# OF CANCERS	% OF TOTAL
Lung	930	27.4
Prostate	330	9.7
Colon & Rectum	300	8.8
Pancreas	210	6.2
Leukemia	160	4.7
Non-Hodgkin Lymphoma	140	4.1
Esophagus	140	4.1
Bladder	120	3.5
Kidney & Renal Pelvis	120	3.5
Liver	110	3.2
All Others	840	24.8
TOTAL	3400	

Fortunately for Iowans, the chances of being diagnosed with many types of cancer can be reduced through positive health practices such as smoking cessation, physical exercise, healthful dietary habits, and alcohol consumption in moderation. Early detection through self-examination and regular health checkups can improve cancer survival.

Adolescent and Young Adult Cancers in Iowa

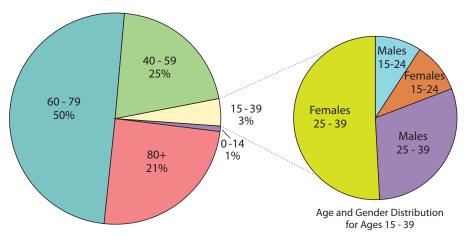
Among adolescents and young adults, most frequent cancer types/sites include thyroid, skin melanoma, lymphoma, and testicular cancers. Cancer is the leading cause of diseaserelated death in the adolescent and young adult (AYA) U.S. population, defined as people between 15 and 39 years of age. Only accidents, suicide, and homicide claim more lives than cancer in this population. About 70,000 AYAs are diagnosed with cancer each year in the U.S. In Iowa from 2004-2013, 7,115 cancers were diagnosed among AYAs compared to 1,000 cancers among children ages 0-14. AYA cancers accounted for approximately 3% of cancers diagnosed in Iowa males and 5% diagnosed in Iowa females from 2004-2013. As shown in Figure 1, the majority of AYA cancers (50%) are diagnosed in females ages 25-39, followed by males 25-39 (30%), and males and females 15-24 (10% each).

Overall AYA cancer incidence trends vary by gender and race. White females have experienced the greatest increase, with a rate change from 70 cases per 100,000 population in the 1974-1983 time period, to 95 per 100,000 population in the 2004-2013 time period. In contrast, AYA females who are black or other races have experienced a decline in cancer rates over time. Since the 1974-1983 time period, cancer cases have increased among males ages 15-39, with white males experiencing a greater increase than black males or males of other races (Figure 2).

Among AYAs, most frequent cancer types/sites include thyroid, skin melanoma, lymphoma, and testicular cancers. Among younger AYAs (ages 15-24), other common cancers include leukemias and brain cancers (Figure 3a), while breast and cervical cancers become more common in older AYA females adults (ages 25-39) (Figure 3b).

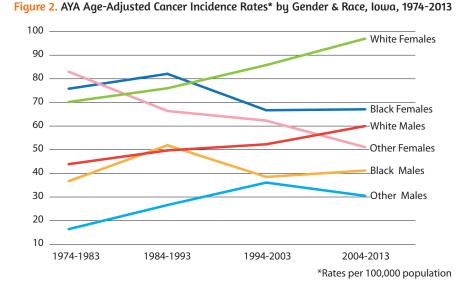
The number of melanoma and thyroid cancers has increased over time, especially among females, while testicular cancer has been increasing in males (Figures 3a & 3b). The ageadjusted rate of melanoma in those less than 40 years of age has more than doubled since 1974. As much as 90% of melanomas are estimated to be caused by UV exposure. Young adult females are particularly at risk because of the outdoor and indoor

Figure 1. Distribution of Cancer Incidence by Age, Iowa, 2004-2013

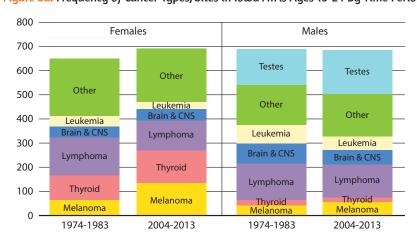


tanning behaviors in this population. Using tanning booths prior to age 35 increases the risk of melanoma by 60%. According to the 2013 National Health Interview Survey, nearly 15% of women ages 18-29 reported having used a sunlamp, sunbed, or tanning booth at least once in the 12 months preceding the survey, with non-Hispanic white women and Midwesterners reporting the greatest use in the U.S. Melanoma has been increasing in Iowa at a rate slightly higher than in other areas of the U.S. It is not known if this is due to more outdoor risk in the farming population, generally greater sun exposure and/or artificial ultraviolet light (UV) exposure in Iowa, or greater efforts to identify these cancers. Melanoma case identification can be difficult because many patients are exclusively treated in the outpatient setting, which is not a traditional source of information for cancer registries. Consequently, the State Health Registry of Iowa has been working directly with dermatology offices to identify new cases.

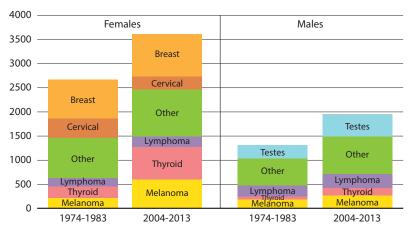
According to the National Cancer Institute (NCI), the rate of thyroid cancer has been increasing 5% per year over the past 10 years, and the median age of diagnosis is 50; however, approximately 25% of thyroid cases occur in AYAs. It is not clear why thyroid cancer rates are increasing. Some researchers have suggested that smaller thyroid cancers are being 'accidentally' detected more often due to x-rays, computed tomography scans, and other types of imaging used so commonly in medical practice. However, other researchers point out that rates are











The numbers and rates of melanoma and thyroid cancers have increased over time, especially among females, while testicular cancer has been increasing in males.

also increasing in other countries where imaging is used much less frequently. Furthermore, death rates from thyroid cancer have also been increasing, meaning the increase is not likely to be due solely to overdiagnosis of harmless lesions. About one in ten cases of thyroid cancer may be associated with an inherited gene. Those who received radiation therapy for childhood cancers are also at increased risk of developing thyroid cancer. Other theories that are being explored include increased exposure to diagnostic imaging, and exposure to environmental compounds such as polybrominated diphenyl ethers (PBDEs) used in flame retardants, building materials, electronics, plastics, and other common products. Some initial research has suggested they are endocrine disrupters, which could potentially lead to the development of cancers.

The incidence of testicular cancer has been increasing in the U.S. and many other countries for decades, but researchers have not been able determine why. The average age at the time of diagnosis of testicular cancer is 33. This is largely a disease of young and middle-aged men, but about 7% of cases occur in children and teens.

Fortunately, cancer survival rates are relatively high in the AYA population (87% in Iowans). While 5-year relative survival rates for 15-39 year olds were slightly lower in Iowa males and females compared to other SEER cancer registries during the 1974-1983 period, the survival rates ever since have been greater in Iowa than in the other registries and continue to climb, particularly among males (Figure 4).

Despite concerns that improvements in mortality seen in childhood cancers were not being seen in AYA cancers, recent analyses by NCI suggest that mortality rates among adolescents with cancer decreased in a manner similar to that observed among children aged <15 years since 2000. Likewise, Iowa analyses since

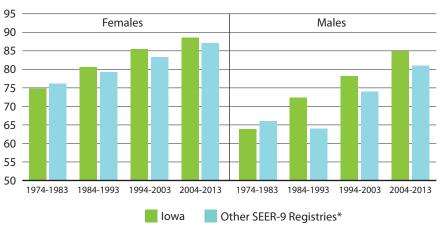


Figure 4. 5-Year Relative Survival Percent among Ages 15-39 by Gender, Time Period and Iowa vs. Other SEER-9 Registries, 1974-2013

*Other SEER-9 Registries include: Atlanta, Connecticut, Detroit, Hawaii, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah.

Fortunately, cancer survival rates are relatively high in the AYA population (87% 5-year survival in Iowans). 1974 show that survival has been improving comparably in children, AYAs overall, and in individual cancer types.

There are many challenges associated with cancer in the AYA population. They fall into four main categories: navigating the health care system, coping with diagnosis and treatment, fertility preservation, and participation in research.

Navigating the Health Care System

AYA cancer patients frequently fall between pediatric and adult oncology providers. Pediatric oncologists are generally recommended to treat cancers more common in children, whereas medical oncologists are recommended to treat cancers more common in adults. Getting consistent follow-up care when transitioning from a pediatrician to an adult oncologist can also be difficult. Lack of health insurance and other financial struggles are also major challenges among AYAs. While the passage of the Affordable Care Act provides more access to insurance coverage, especially to those under the age of 26, significant financial hurdles may remain.

Coping with Diagnosis & Treatment

Because cancer is relatively rare in young adults, these patients may encounter few patients their own age, leading to feelings of isolation. Desire for normalcy may keep them from sharing their cancer experiences with their friends, adding to their sense of isolation. Many are just starting college, a career, or a family. Losing their independence at a time they were just starting to gain it can lead to feelings of frustration, anxiety, or depression. Furthermore, treatment for their cancer may require hospitalization far from home. These factors may exacerbate the already high levels of stress associated with undergoing treatment for cancer.

Many AYAs experience late effects of treatment that can show up months to years after treatment. Depending on age at treatment, some organs and body systems may still be developing, which can make them more sensitive to cancer therapies including radiation and chemotherapy. Late effects vary by cancer site and treatment type, and can include increased risk of developing another cancer later in life, heart or lung problems, thyroid, kidney or bone issues, pain or swelling in parts of the body, learning problems, slowed growth, hormone deficiencies, and infertility. In addition, studies show that survivors of AYA cancers have more unhealthy behaviors than people without a history of cancer, including increased smoking and decreased exercising. AYA cancer survivors also experience more frequent chronic medical conditions, obesity, and poorer mental and physical health. The Children's Oncology Group (COG) has developed long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers: www.survivorshipguidelines.org.

Fertility Preservation

Although cancer treatments have evolved to cause fewer harmful side effects, radiation therapy and chemotherapy agents can still damage fertility. In 2006, the American Society of Clinical Oncology issued recommendations that oncologists discuss with all patients, both female and male, of reproductive or pre-reproductive/pre-pubertal age: 1) the possibility of treatmentrelated infertility, 2) options for preserving fertility, and 3) referrals to reproductive specialists. Several surveys, however, have found that less than half of oncologists in the U.S. are following these guidelines, and that even oncologists who regularly discuss the risk of infertility with patients rarely refer them to reproductive specialists. Options for preserving cancer patients' ability to have biological children depend on many factors, and most are costly, unlikely to be covered by health insurance, and must be undertaken before or during cancer treatment. Patients who have just received a cancer diagnosis usually have a very brief window of time in which to decide.

Participation in Research

Evidence suggests that some cancers in AYAs may have unique genetic and biological features. Researchers are working to learn more about the biology of cancers in young adults so that they can identity molecularly targeted therapies that may be effective in these cancers. Unfortunately, research on AYAs has been constrained by their exceedingly low participation in the relatively few clinical trials available to them. In addition, data on psychosocial factors specific to this population (e.g., impact of cancer on education, employment, social and family issues, fertility preservation) are lacking.

Resources for AYA cancers can be found at: http://www.cancer.gov/ types/aya.

Research Projects During 2016

The State Health Registry of Iowa (SHRI) is participating in over 60 open studies approved by the University of Iowa Human Subjects Office during 2016. Brief descriptions of a few of these studies are provided.

AGRICULTURAL HEALTH STUDY

The Agricultural Health Study (AHS) is a long-term study of agricultural exposures (including pesticides) and chronic disease (especially cancer) among commercial or private pesticide applicators (and their spouses, if married) in Iowa and North Carolina. The study is funded through the National Cancer Institute (NCI) and involves several federal agencies. We are in the 23rd year of the study.

In the first five years, 89,658 subjects (58,564 in Iowa and 31,094 in North Carolina) were enrolled in the study. The total for Iowa included 31,877 private applicators, 21,771 spouses of private applicators, and 4,916 commercial applicators. Enrollment consisted of completing questionnaires about past exposures and health. The second phase of the study for private applicators and their spouses was completed at the end of 2003. It involved a telephone interview, a mailed dietary questionnaire, and collection of a cheek cell sample from all consenting cohort members. The telephone interview asked about pesticide use since enrollment, current farming and work practices, and health changes. The dietary health questionnaire asked about cooking practices and types of foods eaten, since cooking practices and diet may play a role in cancer and other health conditions. The cheek cells are being used to understand possible links between genetics, exposures, and disease. For commercial applicators, the second phase of the study was completed at the end of 2005. The study's third phase began in 2005 and ended in 2010. It involved updating information about exposures and health. The fourth phase of the study began in the fall of 2011 and for the

University of Iowa research team primarily involves collection of blood and urine samples from a select subgroup of AHS male participants and collection of cheek cells from AHS participants diagnosed with cancer.

Since 1997, cohort members have been linked annually or biennially to mortality and cancer registry incidence databases in both states. In addition, mortality data on the cohort are being obtained from the National Death Index. More information about results from this study, the study background, frequently asked questions, other resources (internet & telephone) for agricultural health information, references for publications to date, and information for scientific collaborators can be found at the website, http://aghealth.nci.nih.gov/. This study's data have also been pooled with data from other cohort studies and analyzed as collaborative activities. The titles for over 200 publications from this study linked to PubMed are available at the website. The cancer-related references for 2015 publications are provided in the last section of this report.

AYA HOPE STUDY

The Adolescent and Young Adult (AYA) Health Outcomes and Patient Experience (HOPE) Study is another ongoing example of a cancer survivor study. This study is an initial step in addressing potential factors related to gaps in research, care, and outcomes. From 7 SEER Registries across the U.S., 525 patients (40 in Iowa), 15-39 years old at diagnosis between July 1, 2007 and October 31, 2008 have been enrolled with any of the following cancers: ovarian or testicular cancer, Hodgkin lymphoma, non-Hodgkin lymphoma, acute lymphoblastic leukemia, or selected types of sarcoma. Those who responded were representative

of all AYA cancer survivors during this time period. 91% of the 525 have completed a subsequent survey 8 to 17 months after the initial survey to obtain additional follow-up information regarding their cancer survivorship experience. Publications that have reported findings from this study in 2015 are provided in the last section of this report.

CANCER CARE OUTCOMES RESEARCH & SURVEILLANCE CONSORTIUM

This study involves a statistical coordinating center, the SHRI, and five other primary data collection and research sites around the U.S. Across these sites, we conducted population-based research in the areas of access to care and patterns of care for lung and colorectal cancer. We are evaluating the reasons for particular care decisions by patients and their physicians, including variation in disseminations of modern care protocols and practices in different geographic areas. We are also evaluating the effects of these decisions and practices on patient outcomes, including quality of life. In Iowa, this study was limited to lung cancer patients. Over 1,000 newly diagnosed lung cancer patients were enrolled between June 2003 and March 2005. Thereafter, these patients provided consent for medical record abstraction and participated in follow-up interviews. Several publications have resulted from the findings and those that occurred in 2015 are provided in the last section of this report.

PATTERNS OF CARE STUDIES

SEER Patterns of Care Studies are conducted to satisfy a U.S. Congressional directive to the NCI to "assess the incorporation of state-of-the-art cancer treatment into clinical practice and the extent to which cancer patients receive such treatments." This year's Patterns of Care Study will involve stage IV colon cancer, chronic lymphocytic leukemia, and multiple myeloma in adults diagnosed between January 1, 2014 and December 31, 2014. The objectives of the SEER Patterns of Care Study are to: 1) describe the use of adjuvant therapy, which has been verified with the treating physician, in a community setting, 2) characterize the practice patterns in different communities, 3) describe more completely the use of surgery in the treatment of specific cancers, 4) compare the patterns of treatment for cancer over time, 5) compare patterns of care by age and race/ ethnicity, 6) describe effect of comorbid conditions on treatment, and 7) describe treatment by hospital characteristics: i.e. for profit vs. not for profit, teaching vs. non-teaching, disproportionate share status, etc. The SHRI has been involved with these types of studies over the past 25 years. Publications during 2015 are provided in the last section of this report.

SECOND CANCER STUDIES INCLUDING THE WECARE STUDY

Over the past three decades, the SHRI has participated in several second cancer studies. These have consisted of cohorts with a first cancer of the cervix, ovary, testis, uterus, female breast, non-Hodgkin lymphoma, or Hodgkin lymphoma. They have been conducted primarily in collaboration with Radiation Epidemiology Branch at the NCI and other registries in North America and Europe. Generally these studies evaluate the treatment received for the first cancer and the risk it places on the patient for development of a second cancer. They typically involve medical record review and pathology material retrieval. We are evaluating esophagus, pancreas, and stomach as second cancer sites in several of these cohorts with a first cancer as mentioned above.

The WECARE (Women's Environmental Cancer and Radiation Epidemiology) Study is an example of a second cancer study. This study is designed to examine gene carrier status, demographic and lifestyle factors, as well as environmental and treatment factors reported to be associated with an initial breast cancer as they relate to the development of a second breast cancer in the opposite breast. Eligible cases were diagnosed with a first breast cancer between 1985 and 2009 that did not spread beyond the regional lymph nodes at diagnosis and a second primary contralateral breast cancer diagnosed at least one year after the first breast cancer diagnosis. Eligible controls were women with unilateral breast cancer who were individually matched to cases on year of birth, year of diagnosis, registry region, and race. The controls must have survived without any subsequent diagnosis of cancer and with an intact contralateral breast during the interval that elapsed between their matched case's first and second breast cancer diagnoses. Data collection not only involved medical record review, but also participant interviews and biosample collection, either cheek cells, saliva, or blood. More recently, the WECARE staff collected mammographic film data for its research subjects to evaluate breast density as another risk factor for a subsequent diagnosis of invasive breast cancer in the contralateral breast. A listing of publications during 2015 from second cancer studies, including the WECARE Study, is provided in the last section of this report.

SEER-MEDICARE

In the early 1990s, the cancer incidence and survival data from the SHRI was combined with other SEER Registry data and linked to Medicare data. This linked data set has been updated on several occasions since and has become an important data resource for cancer research involving epidemiologic and health services research related to the diagnosis and treatment procedures, costs, and survival of cancer patients. Over the years many publications have resulted from this linked data set including several dozen during 2015, which are listed at http://healthservices. cancer.gov/seermedicare/overview/ publications.html.

STUDIES INVOLVING TISSUE

Today, researchers are increasingly looking to obtain tissue to study molecular characteristics of cancers. Several studies that involve the SHRI have included tissue. For example, last year we began a two-year study to determine the capability of the SHRI to obtain formalinfixed, paraffin-embedded tissue to accompany data that already exists in the registry's surveillance database for breast and pancreatic cancers meeting eligibility criteria for this study. The objectives of this SEER-linked virtual tissue repository project are to: 1) assess the ability of the SHRI to serve as a resource for biospecimen research, 2) locate cases with biospecimens in pathology labs and determine the requirements to retrieve those biospecimens for research purposes, 3) provide custom annotation of specified data items for located cases, and 4) capture costs for objectives 2 and 3. This project is involving other NCI SEER cancer registries and when completed will

provide for an assessment of NCI SEER's capabilities to perform this type of study. During 2015, several articles involving tissue from Iowans were published, the references for which are provided in the last section of this report.

TRANSPLANT CANCER MATCH STUDY

Solid organ transplantation provides life-saving treatment for end-stage organ disease but is associated with substantially elevated cancer risk, largely due to the need to maintain long-term immunosuppression. Important questions remain concerning the role of immunosuppression and other factors in causing cancer in this setting. Staff at two federal agencies, the NCI and the Health Resources and Services Administration (HRSA), are creating a database through linkage of information during 1987-2009 or beyond on over 200,000 U.S. transplant recipients, wait list candidates (over 120,000 in addition to those who were subsequently transplanted), and donors (over 60,000 deceased donors, over 50,000 living donors) with information on cancer from 15 U.S. cancer registries, including the SHRI. These data are being used to conduct research concerning the spectrum of cancer risk in transplant recipients. The data will also be used by HRSA in its public health role overseeing the U.S. solid organ transplant network to maintain and improve safety of organ transplantation, and will allow NCI to better characterize the burden of cancer in this population and discover additional factors associated with cancer among this population. Several publications have resulted from the findings and those that occurred in 2015 are provided in the last section of this report.

COOPERATIVE AGREEMENTS AND OTHER REGISTRIES

In the Midwest, the SHRI maintains cooperative agreements with several hospital cancer registries and other agencies/entities. Some of the latter include:

- Iowa Department of Public Health
- Iowa Cancer Consortium
- The University of Iowa
 - Center for Health Effects of Environmental Contamination
 - Center for Health Policy and Research
 - Center for Public Health Statistics
 - Environmental Health Sciences Research Center
 - Health Effectiveness Research Center
 - Holden Comprehensive Cancer Center
 - Iowa Center for Agricultural Safety and Health
 - Iowa Center for Education and Research on Therapeutics (Iowa CERT)
 - Injury Prevention Research Center
 - Nutrition Center
 - Prevention Research Center for Rural Health
 - Preventive Intervention Center
 - Reproductive Molecular Epidemiology Research & Education Program

Selected 2015 Publications

AGRICULTURAL HEALTH STUDY

Andreotti G, Hoppin JA, Hou L, Koutros S, Gadalla SM, Savage SA, et al. Pesticide Use and Relative Leukocyte Telomere Length in the Agricultural Health Study. PLoS One. 2015;10(7):e0133382.

Blair A, Hines CJ, Thomas KW, Alavanja MC, Freeman LE, Hoppin JA, et al. Investing in prospective cohorts for etiologic study of occupational exposures. Am J Ind Med. 2015;58(2):113-22.

Hofmann JN, Hoppin JA, Lynch CF, Poole JA, Purdue MP, Blair A, et al. Farm Characteristics, Allergy Symptoms, and Risk of Non-Hodgkin Lymphoid Neoplasms in the Agricultural Health Study. Cancer Epidemiol Biomarkers Prev. 2015 Mar;24(3):587-94.

Hofmann JN, Beane Freeman LE, Lynch CF, Andreotti G, Thomas KW, Sandler DP, Savage SA, Alavanja MC. The Biomarkers of Exposure and Effect in Agriculture (BEEA) Study: Rationale, design, methods, and participant characteristics. J Toxicol Environ Health *A*. 2015;78 (21-22):1338-47.

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