DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute

Report to Congress:

Use of Funds Received for Semipostal Stamp for Breast Cancer Research

Fiscal Year 2014

March 2015

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Introduction

In December 2011, Congress reauthorized the Stamp Out Breast Cancer Act, which extended the authority of the U.S. Postal Service to issue a semipostal stamp to raise funds for breast cancer research. A provision of this law requires that the National Institutes of Health (NIH) and the Department of Defense each submit an annual report concerning the use of any amounts received from the sale of the stamps, including a description of any significant advances or accomplishments, to Congress and the Government Accountability Office (GAO) (39 U.S.C. 414). To fulfill this requirement, the following report has been prepared by the National Cancer Institute (NCI), NIH, Department of Health and Human Services.

This report highlights the research currently funded by proceeds from the semipostal stamp for breast cancer research. Additional information related to the Breast Cancer Research Stamp is available electronically on the NCI web page at
http://www.cancer.gov/aboutnci/overview/contributing

Background

In the United States, breast cancer is the most common non-skin cancer and the second leading cause of cancer death, after lung cancer, among women. It is estimated that 232,670 women in the United States were diagnosed with breast cancer in 2014, and 40,000 women died from the disease that year.

Since 1998, added support for breast cancer research has come from funding through the highly successful Stamp Out Breast Cancer Act. The breast cancer research stamp is offered through the United States Postal Service as an alternative to a first class postage stamp. The Stamp Out Breast Cancer Act (The Stamp Act), which Congress initially enacted in 1997, stipulates that 70 percent of the proceeds from the stamp surcharge be directed to the NIH for breast cancer research and 30 percent to the Department of Defense for the same purpose. Congress reauthorized the Stamp Act in 2011, extending the sales period through 2015.

In November 1998, the NCI began receiving Breast Cancer Research Stamp proceeds from the United States Postal Service. Since then, the NCI has allocated the proceeds – totaling $55.1 million – to eligible research. Of this amount, NCI obligated $40.6 million by the close of fiscal year 2014 through four different extramural grant programs, as well as some NCI intramural research programs. NCI senior leadership select programs for funding based on their potential to make significant progress against breast cancer.

The sections of this report that follow discuss the NCI research programs in detail. The currently funded programs include only female study subjects. Of the remaining $14.5 million in

proceeds, NCI plans to obligate $4.4 million in the near future. The balance of $10.1 million is available to NCI to fund existing research programs or initiate new programs.

The NCI receives the Breast Cancer Stamp funds in May and November of each fiscal year. The table below lists the annual amounts received during each fiscal year since the inception of the program.

Breast Cancer Research Stamp Act Collections	
FY	**Total**
1999	$ 4,150,210.00
2000	$ 3,101,033.00
2001	$ 5,556,224.67
2002	$ 3,594,619.80
2003	$ 5,175,938.00
2004	$ 4,813,994.00
2005	$ 4,372,191.62
2006	$ 4,467,540.23
2007	$ 3,006,105.81
2008	$ 4,855,539.01
2009	$ 3,403,204.50
2010	$ 2,344,610.59
2011	$ 2,048,555.12
2012	$ 1,622,774.59
2013	$ 1,403,656.50
2014	$ 1,160,055.41
Total	**$55,076,252.85**

A summary below lists all of the programs that NCI has supported with Breast Cancer Stamp collections:

Fiscal Year(s)	NCI Program Title	Total
2000-2002	Insight Awards	$9,507,950
2003-2008	Exceptional Opportunities in Breast Cancer Research	$12,505,650
2006	TAILORx Trial	$4,500,000
2006-present	Breast Pre-Malignancy Program funding both intramural and extramural research projects	$13,230,773
2014-2015	Molecular and Cellular Characterization of Screen-Detected Lesions	Up to $10.3M

Ongoing NCI Breast Cancer Research Programs

During fiscal year 2014, the Breast Cancer Stamp Fund continued to provide funding for research within the Trans-NCI Breast Pre-Malignancy Program. Since 2006, this Trans-NCI program has supported a suite of research projects that address a broad spectrum of questions in breast cancer pre-malignancy research. These questions relate to:

- the characterization and imaging of breast cancer stem cells;
- the biology of breast pre-malignancy;
- the molecular epidemiology of mammographic density;
- strategies to improve accuracy of mammography interpretation;
- the evaluation of decision-making approaches used by women recruited for chemoprevention trials; and
- molecular target identification (biomarkers), imaging, and translational research.

Funding these areas of research will lead to a better understanding of how cancers originate and evolve, which is essential to advancing prevention, screening, diagnosis, and treatment. In addition to research supported with Breast Cancer Stamp funds, NCI has also established a collaborative and integrated scientific community across NCI divisions and centers to support research in breast pre-malignancy.

Breast Cancer Stamp funding supports projects within the NCI's intramural and extramural research programs. During fiscal year 2014, the NCI allocated Breast Cancer Stamp funds to four projects within the Trans-NCI Breast Pre-Malignancy Program:

1) *The Biology of Estrogen Receptor-Negative Breast Cancer in Various Racial and Ethnic Groups*
2) *The Breast Cancer Metabolomics Project*
3) *Linked Registry Study of Maternal Pregnancy Factors and Maternal Breast Cancer Risk*
4) *Maternal Pregnancy Factors and Breast Cancer Risk Study*

Progress reports for ongoing projects in the Trans-NCI Breast Pre-Malignancy Program:

1) The Biology of Estrogen Receptor-Negative Breast Cancer in Various Racial and Ethnic Groups" (RFA CA09-026) *(an extramural component.)* The objectives and goals of this component of the Trans-NCI program are to:

- identify the differences between estrogen receptor positive (ER +) and estrogen receptor negative (ER -) human breast cancers
- identify the subtypes or heterogeneity within ER - breast cancers using human samples (normal and malignant)
- determine possible differences in the biology of ER - breast cancers among various racial and ethnic groups.

Through this Request For Applications (RFA), NCI awarded three grants in September 2010 – each for a five-year duration.

Stanford University – (CA154209): One of the aims of the grant is to use single cell genomics technology to understand the cellular hierarchy of triple negative breast cancer (TNBC) in different racial groups. The researchers have found a single marker, ELF5, that appears to predict outcome when patients are treated with adjuvant chemotherapy. If this finding is further validated, this will be the first predictive marker for TNBC. The PI is in discussions with Eastern Cooperative Oncology Group (ECOG) to access their clinical trial database and confirm this marker as predictive. They have also identified another gene, BCL11b, as a prognostic marker in TNBC. Patients whose tumors expressed the BCL11b marker were found to have significantly reduced survival.

Ohio State University – (CA154200): Researchers funded by this grant have completed sub-typing TNBC tumor samples to improve treatment strategies and clinical outcomes for patients. These samples were categorized into two sub-groups based on the immunohistochemistry (IHC) markers that they expressed: 1) Core Basal (CB) and 2) five negative (5NP). In addition, the expression of a four non-coding RNA (4-miR) signature was used to further classify the two tumor subtypes. The diagnostic and prognostic values of both the IHC subtyping as well as the 4-miR signature were tested using survival data from patients treated with two commonly used chemotherapy regimens – anthracycline or anthracycline plus taxanes. They found that both have prognostic value, which is important to consider when developing drugs targeted to the different TNBC subtypes in order to maximize patient outcome.

University of Michigan – (CA154224): The goal of this project is to understand the function of the protein EZH2 in ER-negative breast cancer in women of various ethnicities. During the past year, the researchers have made enormous advances by identifying a non-canonical function of EZH2 in TNBC and demonstrating that EZH2 is a novel regulator of NOTCH signaling, which has therapeutic implications. They have also developed a novel mouse model overexpressing EZH2 in the mammary gland to determine the biological significance of high EZH2 levels in TNBC in various ethnic groups.

2) The Breast Cancer Metabolomics Project *(an intramural component)*

The primary aim of NCI's Breast Cancer Metabolomics Project is to identify metabolic profiles that precede the development of breast cancer. The research team is using the most advanced metabolic profiling technology to simultaneously characterize levels of more than 500 circulating metabolites, including lipids, proteins, and sex hormones in prediagnostic blood samples through two different studies. The first study will include 360 breast cancer cases and 360 women without breast cancer from a large, well-characterized cohort of women residing in Shanghai, China. The second study will include 500 breast cancer cases and 500 women without breast cancer from a large, well-characterized cohort of women residing in the United States.

The project was designed to proceed in three stages. In 2010-2011, the research team completed the first stage, which involved evaluating four leading metabolic profiling labs using six different metabolic profiling technologies, and selecting a lab to perform the work for future stages. In 2011-2012, the team completed the second stage of the study, which entailed identifying

metabolic profiles for two breast cancer-related exposures, excess body weight and physical activity. By analyzing samples from nearly 1,000 study participants from the U.S. and Shanghai, the research team identified 40 body weight–related metabolites, many with no previously known link to body weight. They also identified three novel metabolites correlated with physical activity levels, as measured by wearable physical activity monitors. Two manuscripts have been published describing results from this second stage. The third stage of the study – metabolomics analysis of the breast cancer cases and controls – was initiated in August 2012. The analysis has been completed for the first study (Shanghai, China). The second study (United States) has had all laboratory assays completed and the statistical analysis is underway. We anticipate that the manuscript related to this research will be submitted in June 2015.

The preliminary data from this project have been highly informative and formed the basis for two recent successful grant applications by the research team to expand their analyses into a breast cancer replication study and a pancreatic cancer study.

3) Linked Registry Study of Maternal Pregnancy Factors and Maternal Breast Cancer Risk *(an intramural component)*

The NCI is pursuing a research program on the maternal and prenatal factors that contribute to the causes of cancer in mothers and their offspring. Pregnancy conditions and exposures have important consequences for subsequent breast cancer risk of the mother, but the reasons for this are not understood. Often, research studies try to obtain information by interviewing women about their previous pregnancy complications. However, women frequently do not know or remember features of their past pregnancies, especially if the pregnancies occurred many years or even decades earlier. For this reason, it has been difficult to study pregnancy exposures. Relying on birth records data to measure possible risk factors can help assess these exposures, thereby avoiding problems with inaccurate recall. Researchers hope this method may lead to developing cancer risk profiles that could potentially aid in identifying women at increased or decreased risk of breast cancer.

4) Maternal Pregnancy Factors and Breast Cancer Risk Study *(an intramural component)*

The goal of this study is to identify possible links between pregnancy factors and breast cancer risk. Investigators at the NCI, in collaboration with researchers at the Fred Hutchinson Cancer Research Center in Seattle, Washington, compared pregnancy-related information from women who delivered babies prior to a breast cancer diagnosis to the information from women without breast cancer who had deliveries during the same period. The study results suggest that delivery of a large (4,000 grams or more) infant and bleeding in the first trimester and later in the pregnancy may be associated with an increased risk of breast cancer. In addition, having a pregnancy complicated by preeclampsia, or carrying a twin/multiple gestation may be associated with a decreased risk of breast cancer. These results were presented at the International Federation of Placenta Associations annual meeting, and a manuscript describing the findings was published in *Cancer Epidemiology, Biomarkers and Prevention* (2013;22:835-47).

In addition, the principal investigators are exploring the feasibility of conducting a large-scale study using combined linked data. They surveyed the capability and interest of all 50 U.S. states to contribute a linkage of their state birth and cancer registries' data. The goal is to provide a resource that includes information on the pregnancy as well as breast cancer diagnoses to more easily study the influence of maternal and prenatal factors on breast cancer in the mother and daughter. The research team is preparing a draft manuscript describing the results of this research.

New NCI Breast Cancer Research Initiative

During fiscal year 2015, NCI also intends to support meritorious applications in breast premalignancy that respond to the RFA entitled "*Molecular and Cellular Characterization of Screen-Detected Lesions" (*RFA-CA-14-010 and RFA-CA-14-011*)*

Molecular and Cellular Characterization of Screen-Detected Lesions *(a new extramural component for FY 2015 funding)*

A new NCI initiative has been approved to address one of the most challenging problems in oncology: predicting more precisely whether lesions that are detected by sensitive screening tests are indolent (hence, not requiring extensive treatment) or progressive and potentially life-threatening. The overarching goal of this initiative is to identify cellular and molecular characteristics that distinguish progressive from non-progressive lesions. NCI published two Funding Opportunity Announcements (RFA-CA14010 and RFA-CA14011) soliciting applications from multi-disciplinary teams to undertake a comprehensive molecular characterization of tumor tissue, cell, and microenvironment components of screen-detected early lesions, interval, and symptom-detected cancers in one or more of these specified tumor sites (breast, prostate, lung, melanoma, and pancreas). Use of enabling approaches and technologies will be encouraged to determine both the cellular and molecular phenotypes of early lesions, to assess the degree to which the behavior of these lesions is predictable or not, and to allow better predictions of the fate of such lesions. The NCI plans to use the Breast Cancer Stamp Fund to support meritorious applications received in response to these solicitations that are specifically focused on breast cancer.

Conclusion

Breast cancer research has benefited from the innovative funding source that Congress established in the Stamp Out Breast Cancer Act. The additional funding has allowed cancer researchers to increase our knowledge of genetics and molecular biology in ways that may support the development of more effective and less toxic treatments for breast cancer. Moreover, through the trans-NCI breast pre-malignancy program funded by Stamp Act proceeds, the NCI is able to support investigations to recognize and define the attributes of pre-malignant stages of breast cancer, which in turn may contribute to detecting and preventing breast cancer malignancies.