



THE ASSISTANT SECRETARY OF DEFENSE

1200 DEFENSE PENTAGON
WASHINGTON, DC 20301-1200

HEALTH AFFAIRS

The Honorable Carl Levin
Chairman
Committee on Armed Services
United States Senate
Washington, DC 20510

JUL 14 2014

Dear Mr. Chairman:

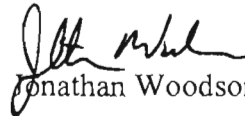
The enclosed report responds to House Report 113-113, page 277, accompanying H.R. 2397, the Department of Defense (DoD) Appropriations Bill, 2014, and to Senate Report 113-85, page 191, accompanying S. 1429, the DoD Appropriations Bill, 2014. Both the House and Senate requested the Assistant Secretary of Defense for Health Affairs provide a report on the status of the Peer-Reviewed Cancer Research Program (PRCRP). Appendix A details the Fiscal Year (FY) 2009–2012 PRCRP research area investment; Appendix B provides the full PRCRP research list and military relevance of FY 2009–2012 projects.

For FY 2013, Public Law 113-6 appropriated \$15 million (M) for the PRCRP. Vision setting for the FY 2013 PRCRP was held in January 2013, with program announcements released in May 2013. In FY 2013, a military focus targeted program announcement, “Idea Award with Special Focus,” was released to solicit applications in areas of relevance to military exposures and cancer risks. In addition, the Career Development Award program announcement encouraged applications in military-relevant focus areas including as military deployments, environmental exposures, and risk. Application receipt occurred in October 2013, peer-review completed in December 2013, and programmatic review concluded in February 2014. Award obligation is anticipated no later than September 30, 2014.

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Thank you for your interest in the health and well-being of our Service members, veterans, and their families. A similar letter is being sent to the Chairmen of the other congressional defense committees.

Sincerely,


Jonathan Woodson, M.D.

Enclosure:
As stated

cc:
The Honorable James M. Inhofe
Ranking Member



THE ASSISTANT SECRETARY OF DEFENSE

1200 DEFENSE PENTAGON
WASHINGTON, DC 20301-1200

HEALTH AFFAIRS

The Honorable Richard J. Durbin
Chairman
Subcommittee on Defense
Committee on Appropriations
United States Senate
Washington, DC 20510

JUL 14 2014

Dear Mr. Chairman:

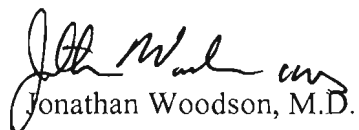
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Jonathan Woodson, M.D.

Enclosure:
As stated

cc:
The Honorable Thad Cochran
Vice Chairman



THE ASSISTANT SECRETARY OF DEFENSE

1200 DEFENSE PENTAGON
WASHINGTON, DC 20301-1200

HEALTH AFFAIRS

The Honorable Howard P. "Buck" McKeon
Chairman
Committee on Armed Services
U.S. House of Representatives
Washington, DC 20515

JUL 14 2014

Dear Mr. Chairman:

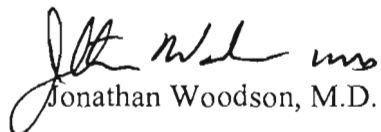
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Sincerely,



Jonathan Woodson, M.D.

Enclosure:
As stated

cc:
The Honorable Adam Smith
Ranking Member



THE ASSISTANT SECRETARY OF DEFENSE

1200 DEFENSE PENTAGON
WASHINGTON, DC 20301-1200

HEALTH AFFAIRS

The Honorable Rodney Frelinghuysen
Chairman
Subcommittee on Defense
Committee on Appropriations
U.S. House of Representatives
Washington, DC 20515

JUL 14 2014

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Sincerely,


Jonathan Woodson, M.D.

Enclosure:
As stated

cc:
The Honorable Peter J. Visclosky
Ranking Member

REPORT TO THE CONGRESSIONAL DEFENSE COMMITTEES

“PEER REVIEWED CANCER RESEARCH PROGRAM”

**SUBMITTED BY THE OFFICE OF THE ASSISTANT SECRETARY OF
DEFENSE (HEALTH AFFAIRS)**

**SUPPORTED BY THE U.S. ARMY MEDICAL RESEARCH AND
MATERIEL COMMAND, CONGRESSIONALLY DIRECTED MEDICAL
RESEARCH PROGRAMS**



July 2014

The estimated cost of this report for the Department of Defense in expenses and labor is approximately \$7,470 in Fiscal Year 2014. This includes \$5,410 in expenses and \$2,060 in DoD labor.

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**Peer Reviewed Cancer Research Program
Report to Congress**

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BACKGROUND AND PURPOSE OF REPORT

The Assistant Secretary of Defense (Health Affairs) is requested by House Report 113-113, page 277, and Senate Report 113-85, page 191, to provide a report to the congressional defense committees on the status of the Peer Reviewed Cancer Research Program (PRCRP), and, for each research area, include the funding amount awarded, the progress of research, and the relevance to Service members and their families. This report provides an update on the detailed status of the Fiscal Year (FY) 2009 to FY 2013 PRCRP cycle, research accomplishments, and the relevance of this type of research for U.S. military Service members and their families.

The Office of the Assistant Secretary of Defense for Health Affairs is supported by the U.S. Army Medical Research and Materiel Command (USAMRMC) for the purpose of executing medical research activities, to include the PRCRP, by the office of the Congressionally Directed Medical Research Programs (CDMRP), a subordinate organization within the USAMRMC. Tasked with program execution and management, the CDMRP is responsible for planning, coordinating, integrating, programming, budgeting, and executing assigned research programs. The CDMRP's flexible execution and management cycle includes the receipt of annual congressional appropriations, inaugural stakeholders meeting for new programs, vision setting, release of request for pre-applications or full applications, pre-application screening and invitation to submit full applications, full application receipt and review, recommendation of grants for funding, and oversight of research grants.

Each program's advisory board (Integration Panel, Steering Committee) of leading scientists, clinicians, military members, and/or disease survivors (consumers), recommends an investment strategy for the upcoming year that meets the unique needs of the research field, consumer community, and the military. The investment strategy is unique to each program and to each fiscal year cycle. By revisiting the investment strategy yearly, the program is able to explore innovative scientific ideas and research gaps spanning from basic laboratory science to clinical trials. Program announcements requesting research applications through specific award mechanisms are subsequently prepared and released.

The basic programmatic cycle for award recommendation is a two-tiered system. To ensure that each program's research portfolio reflects not only the most meritorious science, but also the most programmatically-relevant research, the CDMRP developed this two-tiered model based upon recommendations from an Institute of Medicine (IOM) 1993 report.¹ The IOM recommended a two-step review procedure for research applications composed of a scientific peer review and a separate programmatic review. The scientific peer review is conducted by an external panel recruited specifically for each peer review session and is therefore not a standing panel. Peer review involves the expertise of scientists, clinicians, military members, and consumers. The peer review process includes evaluation of the applications based on a criterion process as delineated in the program announcements. Each application is judged on its own scientific and technical merit with respect to the described criteria. The second tier of review, programmatic review, is conducted by the program's designated advisory panel, such as the Integration Panel for the Peer Reviewed Cancer Research Program (PRCRP). The advisory panel for each program is charged with reviewing the applications based on the scientific peer review ratings and summaries, a balanced portfolio, programmatic intent, and relevance to the

Peer Reviewed Cancer Research Program Fiscal Year 2014 Report to Congress

congressional language. Scientifically sound applications that best meet the program's interests and goals are recommended for funding. Once funding recommendations are approved, awards are made in the form of one- to five-year grants, contracts, or cooperative agreements, and assigned to science officers (SOs) for full-cycle support of research and outcomes. During the management of the lifecycle of an award, the SO continues to monitor the research project for progress and outcomes as well as possible issues or pitfalls. In addition, the Program Office reviews all awards at negotiation and throughout their period of performance for any possible overlap or duplication with other funding agencies, both federal and non-federal. A detailed explanation of this process can be found at the CDMRP website (<http://cdmrp.army.mil/funding/researchDup.shtml>). The programs that comprise the CDMRP are scientifically sound, innovative, and responsive to congressional intent and the needs of Service members, their families, and the American public. The USAMRMC and the CDMRP have been praised by the IOM, which issued a report in 1997 stating it was favorably impressed with the processes implemented by the CDMRP and supported its continuation.²

PEER REVIEWED CANCER RESEARCH PROGRAM FOR FY 2009-FY 2013

Public Law 110-329 from the Consolidated Security, Disaster Assistance, and Continuing Appropriations Act, 2009, appropriated \$16 million (M) for the FY 2009 PRCRP. The funds and directed research topic areas included \$4M for melanoma and other skin cancers as related to deployments of Service members to areas of high exposure, \$2M for pediatric brain tumors within the field of childhood cancer research, \$8M for genetic cancer and its relation to exposure to the various environments that are unique to a military lifestyle, and \$2M for noninvasive cancer ablation treatment including selective targeting with nanoparticles. An inaugural stakeholders meeting was held on February 23-24, 2009, which included leading scientists, clinicians, military members, and consumers. The PRCRP Integration Panel was established in April 2009 to conduct vision setting to review the recommendations made at the stakeholders meeting, to craft a vision and mission of the program, and to develop an investment strategy. Several program announcements were released in June 2009. Following the two levels of review, 38 awards were approved across the four different topic areas.

In FY 2010, Public Law 111-118 from the 2010 Defense Appropriations Act appropriated \$15M in funding for a "peer reviewed cancer research program" that would research cancers not addressed in the breast, prostate, lung, and ovarian cancer research programs currently executed by the DoD and, specifically, the USAMRMC. Specific topics included melanoma and other skin cancers, pediatric brain tumors within the field of childhood cancer research, genetic cancer research and genomic medicine, kidney cancer, blood cancer, colorectal cancer, *Listeria* vaccine for cancer, and radiation protection utilizing nanotechnology. An Integration Panel consisting of members of the FY 2009 PRCRP Integration Panel and new members to represent the congressional target areas was convened in March 2010. Program announcements were released in May and June 2010. Following the two levels of review, 32 awards were approved across the different topic areas.

For FY 2011, Public Law 112-10 from the Department of Defense and Full Year Continuing Appropriations Act appropriated \$16M for the PRCRP. The Congressional Record of the Senate

Peer Reviewed Cancer Research Program Fiscal Year 2014 Report to Congress

dated December 14, 2010, specified topics areas of melanoma and other skin cancers, pediatric cancer research, genetic cancer research, kidney cancer, blood cancer, colorectal cancer, pancreatic cancer, mesothelioma, *Listeria* vaccine for infectious disease and cancer, and radiation protection utilizing nanotechnology. This was later revised to remove *Listeria* vaccine for infectious disease. Further clarification acknowledged the requirement for relevance to Service members and their families and that the funding would be directed toward research on cancers not addressed in the breast, prostate, lung, and ovarian cancer research programs currently executed by the DoD and, specifically, the USAMRMC. Vision setting was held on April 19, 2011. The FY 2011 Integration Panel consisting of members of the FY 2010 PRCRP Integration Panel and new members to represent the congressional target areas was convened to discuss research gaps, community needs, focus areas, and an investment strategy. Program announcements were released in June and September 2011. Full application receipt was in October and November 2011. Following the CDMRP process of review, 43 awards were approved across the different topic areas.

For FY 2012, Public Law 112-74 appropriated \$12.8M for the PRCRP. The committee provided funds to conduct research in melanoma and other skin cancers, pediatric brain tumors, genetic cancer, pancreatic cancer, kidney cancer, blood cancer, colorectal cancer, mesothelioma, and *Listeria* vaccine for infectious disease and cancer. This was later revised to remove *Listeria* vaccine for infectious disease. Vision setting for FY 2012 PRCRP was held in March 2012 with program announcements released in April 2012. Pre-application receipt was in June 2012 with screening completed in July 2012. Following full application receipt in September 2012 and a two-tiered review, 31 awards were approved across the different topic areas. Prior to completion of FY 2012 award negotiations, sequestration affected the total sum available for funding awards. Several awards were withdrawn due to scientific or funding overlap and/or duplication issues, which allowed for all of the remaining awards without decreases in budgets due to sequestration.

For FY 2013, Public Law 113-6 appropriated \$15M for the PRCRP. The committee provided funds to conduct research in melanoma and other skin cancers, pediatric brain tumors, genetic cancer, pancreatic cancer, kidney cancer, blood cancer, colorectal cancer, mesothelioma, and neuroblastoma. Vision setting for FY 2013 PRCRP was held in January 2013. Program announcements were released in May 2013. In FY 2013, a military focus targeted program announcement, "Idea Award with Special Focus," was released to solicit applications in areas of relevance to military exposures and cancer risks. Additionally, the Career Development Award program announcement encouraged applications in military-relevant focus areas including as military deployments, environmental exposures, and risk. Pre-application receipt was in July with screening occurring in September 2013. Full application receipt was in October 2013, with peer review in December 2013. Programmatic review was in February 2014, with final award obligation no later than September 30, 2014.

FY 2014 PEER REVIEWED CANCER RESEARCH PROGRAM

In FY 2014, the Public Law 113-76, Consolidated Appropriations Act, appropriated \$25M for the PRCRP. As stated in the H.R. 3547 Joint Explanatory Statement for Defense, dated January 14, 2014, the Secretary of the Navy was directed to take all necessary steps to ensure that any health effects resulting from the humanitarian mission efforts during Operation Tomodachi, in response to the earthquake and tsunami that hit Japan in March 2011, are fully addressed. It directed that a portion of the \$25M PRCRP funds should be utilized, if necessary, to carry out additional research on the health effects of radiation exposure as it relates to cancer. The committee directed these funds to conduct research in blood cancer, colorectal cancer, genetic cancer research, kidney cancer, *Listeria* vaccine for cancer, melanoma and other skin cancers, mesothelioma, myeloproliferative disorders, neuroblastoma, pancreatic cancer, pediatric brain tumors, and cancers related to radiation exposure. Vision setting for FY 2014 PRCRP was held in February 2014, and program announcements were released in April 2014. Pre-application receipt and screening will take place approximately 90 days after release of the program announcements. Full application receipt would be scheduled approximately eight weeks, or about 60 days, following the invitation to submit. Peer review would be scheduled about eight weeks later, followed by programmatic review at approximately 60 days later. Award obligation would be no later than September 30, 2015.

RESEARCH AREA INVESTMENT AND PROGRESS

Research area investment is detailed in Appendix A. Research areas include blood cancer, colorectal cancer, genetic cancer (and genomic medicine), kidney cancer, *Listeria* vaccine for cancer, melanoma and other skin cancers, non-invasive cancer ablation, and pediatric brain tumor. In FY 2010, no applications in the research areas of radiation protection utilizing nanotechnology were recommended or selected for funding. Award information for FY 2013 is pending completion of programmatic cycle for award selection and management.

A tabular summary of the proposed work and progress for each of the awards for FY 2009 through FY 2012 is contained in Appendix B (awards for FY 2013 are not complete). The log number, topic area, last name of principal investigator, award amount, institution, title, research progress, and military relevance are noted for each award. Both FY 2012 and FY 2013 were affected by sequestration where 7-8% of funds were cut and, therefore, not available for the program.

RELEVANCE TO SERVICE MEMBERS AND THEIR FAMILIES

Members of the military are exposed to hazardous environments and dangerous deployments due to the nature of their service.³ Hazardous exposures can lead to the development of cancer, many of which present a potential risk for Service members and their families. The Department of Veterans Affairs, Veterans Health Administration (VHA), identified malignancies that may be associated with military service (VHA-Directive 2003-34, Attachment B). Exposure to chemical weapons, or storage, ionizing radiation, herbicides, electromagnetic fields, jet fuel, organic materials, etc., have been linked to different malignancies (see Table 1).

TABLE 1: Malignancies Associated with Military Service^a

Exposure Type	Cancer Type
Full-body to Nitrogen, Sulfur Mustard or Nitrogen Mustard ^b	Nasopharynx, larynx, lung (except mesothelioma), squamous cell carcinoma of the skin, and acute nonlymphocytic leukemia
Ionizing Radiation ^{b,c}	Leukemia (except chronic lymphocytic leukemia), thyroid, bone, brain, breast, colon, lung, ovary, pharynx, esophagus, stomach, small intestine, pancreas, bile ducts, gall bladder, salivary gland, urinary tract (kidneys, renal pelvis, ureter, urinary bladder and urethra), lymphomas (except Hodgkin's disease), multiple myeloma, primary liver cancer, and bronchioloalveolar carcinoma (a rare lung cancer)
Certain Herbicide Agents ^{b-d}	Non-Hodgkin's lymphoma, soft-tissue sarcoma (other than osteosarcoma, chondrosarcoma, Kaposi's sarcoma, or mesothelioma), Hodgkin's disease, multiple myeloma, respiratory cancers (lung, larynx, trachea and bronchus), prostate cancer, chronic lymphocytic leukemia
Specific physical, chemical, or biological factors (electromagnetic fields, jet fuel, volatile organic materials, etc) ^{b-f}	Melanoma, testicular, thyroid, cervical, vulvar, oral squamous cell, pancreatic, and uterine

^aVHA-Directive 2003-34.; ^b Crawford RS, Wu J, Park D, and Barbour GL. 2007. A study of cancer in the military beneficiary population. *Military Medicine* 172:1084-1088.; ^cThe Selected Cancers Cooperative Study Group. 1990. The association of selected cancers with service in the US military in Vietnam. I. non-Hodgkin's lymphoma. *Arch Intern Med* 150:2473-2483.; ^d Department of Defense Automated Central Tumor Registry; ^e D'Este C, Attia JR, Brown AM, Gibberd R, Tavener M, Guest M, Horsley K, Harrex W, and Ross J. 2008. SHOAMP Study Team. 2008 Cancer incidence and mortality in aircraft maintenance workers. *Am J Ind Med* 51:16-23.; ^f Dalanger NA, Kang HK, and Thomas TL. 1995. Cancer mortality patterns among women who served in the military: The Vietnam Experience. *J Occup Environ Med* 37:298-305.

The possibility of direct or indirect links to cancer development in Service members and their families as a result of military service or deployment is still undergoing investigation.

Detailed analysis by The Automated Central Tumor Registry of the DoD published data demonstrated that the incidence of melanoma was higher in the U.S. military population in comparison to the U.S. general population.⁴ The Senate Appropriations Committee on Defense for FY14 acknowledged that melanoma diagnoses are increasing in Service members and that it is the fifth most common cancer among veterans due to the exposures to areas of high ultraviolet radiation. The Committee has encouraged investments in melanoma research to combat this cancer risk (DoD Senate Appropriations Bill, 2014, S. 1429, page 194). Current studies by the PRCRP include examination of risk factors as well as susceptibility and progression of the disease. Dr. Mohammed Kashani-Sabet and Dr. Sancy Leachman were funded by a FY 2009 Collaborative Translational Science Award to identify and validate novel determinants of

melanoma risk in a U.S. military population (DoD contract number W81XWH-10-2-0185). Studies are still ongoing.

The investigation into multiple cancer risks and military service include the study of specific chemical exposures. A meta-analysis using published epidemiological data on cancer risk in male military pilots, civilian pilots, and flight attendants revealed a higher standardized incidence ratio for melanoma and other skin cancers in those with exposure to specific physical, chemical, or biological factors (electromagnetic fields, jet fuel, volatile organic materials, etc.).⁵ In addition, studies of common military exposures, such as aircraft maintenance, have been associated with an increased risk of cancer.⁶ A recent study by Fastje et al.⁷ and funded by the PRCRP, showed that *in utero* exposure to tungsten and other environmental agents primed the immune system for aberrant responses to infectious agents and could lead to increased carcinogenic risk.

Yamane reported that the most frequent cancers diagnosed in Air Force Service members between 1989 and 2002 were different from the general U.S. population, with a higher^{8,9} incidence of melanoma, testicular, thyroid, cervical, and vulvar cancers in the Air Force population,⁸ particularly cervical and vulvar cancer. Another review demonstrated a higher rate of prostate cancer in the military beneficiary population compared to the general population.¹⁰ Occupational exposures is a frequent risk of military service. Asbestos-related lung diseases such as mesothelioma are a known risk to Naval shipyard work.¹¹ It is generally accepted that nearly 95% of all mesothelioma cases are due to asbestos exposure.

Hodgkin's disease, a blood cancer, was the most common cancer diagnosis in men who served in the U.S. Navy.¹² The Selected Cancers Cooperative Study Group showed that veterans of the Vietnam War had a 50% increase in risk of Hodgkin's disease as compared to subjects who had not served in Vietnam.¹³ Evidence links an increased risk for soft tissue sarcomas, non-Hodgkin's lymphoma, Hodgkin's disease, and chronic lymphocytic leukemia to Vietnam War service and exposure to herbicides such as Agent Orange.¹⁴ Cancer patterns of Vietnam War military women nurses in comparison to non-Vietnam War military women nurses and the general population showed that site-specific cancer patterns were different, with excess deaths from pancreatic and uterine corpus cancers in the Vietnam War military women nurses.¹⁵ As the configuration of the military population changes to include more women, consideration into research on their risks and exposures is critical.

Chemical agents are not the only hazards Service members might encounter during deployments. Many deployments are to developing countries where there may be a higher incidence of infectious vectors. It is estimated that over 18% of cancers may be a result of infections such as gastric adenocarcinoma, cervical carcinoma, and hepatocarcinoma.¹⁶ Service members are increasingly presenting with sero-positive scores for infectious agents such as *Helicobacter pylori*.¹⁷ These Service members may be more at risk for chronic inflammation and the development of cancers of the gastrointestinal track.

Indirect causative agents for cancer risk are also under investigation. Two studies funded by the PRCRP recently published results that linked higher stress to increased cancer risk.^{18, 19} Chronic stress murine models revealed an important link to attenuation of p53 (a tumor suppressor) and

tumorigenesis.¹⁸ Another study demonstrated the potent effect of neuropeptides and other stress mediators on tumor development and progression.¹⁹ Stress and related issues are a concern of the military and the ultimate health and well-being of Service members both during and after deployment.

Military families may be at risk for developing cancers due to environmental exposures as shown by investigations into leukemia clusters near military aviation facilities.²⁰ Additionally, transgenerational occupational exposures may lead to increased risk of cancer development in progeny. Children of Vietnam War veterans have an increased risk of developing acute myeloid leukemia.¹⁴ As shown by Hicks et al.,²¹ children of men in the Air Force had a higher incidence of tumors of the central nervous system (brain and spinal cord) and lymphatic system. The VHA acknowledged the toll of cancer on service members and their families when releasing its National Cancer Strategy in 2003 (VHA-Directive 2003-34). A serious illness in a family member, such as cancer, may have consequences on the warfighter's ability to complete the mission. A healthy family unit, free of serious illnesses, allows the service member to focus on his or her role as a warfighter and facilitates the overarching military mission. There are a total of 355,442 military beneficiaries with a cancer diagnosis, for a prevalence of 4.1%, comprised of over 60 different cancer types.²² The cost of cancer care within the Military Health System in FY 2002 was over \$1 billion.²² Funding studies on the detection, diagnosis, treatment, and prevention of these diseases benefits both the warfighter and the American public, ultimately leading to increased survival rates and decreased costs of medical care.

In summary, the FY 2009-FY 2013 PRCRP is managed using an established and highly-recognized management process. The FY 2014 PRCRP directly improves military welfare by providing research into cancers that may develop due to exposure in various uniquely military environments. The CDMRP will plan, execute, and manage the FY 2009-FY 2014 PRCRP with the same rigor and integrity it has demonstrated for other research programs.

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