Fiscal Year:	FY 2020	**Task Last Updated:**	FY 06/22/2020
PI Name:	Luderer, Ulrike M.D., Ph.D.		
Project Title:	Ovarian Cancer and Space Radiation		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:			
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	(1) **SR**:Space Radiation		
Human Research Program Risks:	(1) **Cancer**:Risk of Radiation Carcinogenesis		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
PI Email:	uluderer@uci.edu	**Fax:**	FY
PI Organization Type:	UNIVERSITY	**Phone:**	949-824-8081
Organization Name:	University of California - Irvine		
PI Address 1:	Center for Occupational and Environmental Health		
PI Address 2:	100 Theory, Suite 100		
PI Web Page:			
City:	Irvine	**State:**	CA
Zip Code:	92617-3055	**Congressional District:**	45
Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	2018 HERO 80JSC018N0001-Crew Health and Performance (FLAGSHIP, OMNIBUS). Appendix A-Flagship, Appendix B-Omnibus
Start Date:	08/20/2019	**End Date:**	08/19/2021
No. of Post Docs:	0	**No. of PhD Degrees:**	0
No. of PhD Candidates:	0	**No. of Master' Degrees:**	0
No. of Master's Candidates:	1	**No. of Bachelor's Degrees:**	0
No. of Bachelor's Candidates:	0	**Monitoring Center:**	NASA JSC
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:			
Key Personnel Changes/Previous PI:			
COI Name (Institution):			
Grant/Contract No.:	80NSSC19K1620		
Performance Goal No.:			
Performance Goal Text:			

Thirty percent of astronauts are women, but the risks of space radiation to women’s reproductive health and risks of gynecological cancers remain poorly understood. Radiation treatment for cancer is known to cause temporary infertility and premature menopause. Premature menopause increases women’s risks for cardiovascular disease, osteoporosis, and Alzheimer’s disease. In addition, animal studies and studies of atomic bomb survivors have shown that radiation exposure increases the risk for ovarian cancer. Ovarian cancer has a high mortality rate and is the leading cause of gynecological cancer deaths in women. To best protect the health of women astronauts, it is important to understand whether space radiation has similar effects on the ovary as the types of radiation exposure that are common on Earth. Our prior pilot study showed that the ovary is highly sensitive to follicle destruction by charged particle radiation, typical of exposures in space. Exposure to charged iron and oxygen particles resulted in dose-dependent follicle depletion and

Task Description:	premature ovarian failure. Exposure to charged iron particles induced epithelial ovarian tumors later in life; ovarian tissues from oxygen charged particle irradiated mice of two strains and charged iron irradiated mice of the second mouse strain were archived for future analysis for tumor endpoints. We propose to leverage these stored tissue and blood samples, together with ovaries from gamma-irradiated mice from the NASA tissue archive to 1) compare ovarian tumor prevalence and molecular characteristics after low dose charged particle irradiation (oxygen and iron ions) with gamma irradiation in adult female mice; 2) examine the persistence and types of ovarian oxidative damage after irradiation and evaluate serum concentrations of a clinically utilized biomarker of ovarian reserve, Anti-Müllerian Hormone (AMH), as a potential early biomarker of ovarian tumorigenesis. We will quantify the effects of charged particles on numbers of ovarian follicles and ovarian tumor number and size. We will use in situ methods to assess oxidative damage and to molecularly characterize the ovarian tumors. Our analyses will provide critical insights into whether preneoplastic changes in ovarian follicle numbers, serum AMH, as well as ovarian oxidative damage caused by exposure to charged particles demonstrate similar dose-response as ovarian tumor induction. The analyses will also examine the relative biological effectiveness of gamma versus charged particle irradiation for these endpoints. These studies will help to fill important gaps in our understanding of the effects of space radiation on ovarian function and ovarian carcinogenesis and will lead to better ways to prevent ovarian cancer and protect reproductive health in women astronauts.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	The research will increase understanding of the effects of low dose gamma- and charged particle radiation on the ovary. Both gamma and charged particle radiation are used for cancer therapy. Therefore, it is important to understand side-effects of radiation therapy that may impact cancer survivors' quality of life.
Task Progress:	Introduction Women made up 50% and 45%, respectively, of the 2013 and 2017 NASA astronaut classes. Astronauts are exposed to galactic cosmic rays during travel in deep space. Galactic cosmic rays consist of protons, helium ions, and charged particles heavier than helium, such as silicon, iron,,, and oxygen. Our published work demonstrates profound sensitivity of the ovary to charged particle radiation, with destruction of the irreplaceable ovarian follicle pool and 4-fold as many ovarian tumors as in control non-irradiated mice. Comparison of our data with published studies of ovarian follicle depletion and ovarian tumorigenesis by exposure to gamma radiation suggest that charged particle radiation may be a more potent inducer of both premature ovarian follicle depletion and ovarian tumors, but this has not been directly tested. We hypothesize that ovarian follicle depletion by iron and oxygen charged particle radiation is greater than ovarian follicle depletions by gamma-radiation at comparable doses and that silicon, iron, and oxygen charged particle radiation cause ovarian tumors at lower doses than gamma-radiation. Aim 1: Utilize archived ovaries to compare ovarian tumor induction by irradiation with silicon charged particles or gamma-rays. Comparison of ovarian tumors in 3-4 month old CB6F1 mice irradiated with 0.4, 0.8, 1.2, or 1.6 Gy gamma-rays or 0.04, 0.08, 0.16, and 0.32 Gy 260 MeV/u silicon and concurrent controls at 15-16 months after irradiation. We will conduct detailed histopathology of ovaries and molecular characterization of tumors using immunostaining for tumor markers. Aim 2: Utilize archived ovaries harvested at various time points after irradiation with low doses of oxygen or iron charged particles to examine the persistence of ovarian oxidative lipid, protein, and DNA damage, archived serum to measure a biomarker of ovarian reserve, and evaluate these as potential early biomarkers of ovarian tumorigenesis. Irradiate mice with low doses of gamma-radiation and harvest ovaries at 1 week after irradiation in order to compare ovarian follicle depletion by charged iron or oxygen particles with gamma-radiation. Our published work demonstrates oxidative damage and dose-dependent apoptotic depletion of ovarian follicles after exposure to 0, 0.05, 0.3, and 0.5 Gy charged iron or oxygen particles. Serum luteinizing hormone (LH) and follicle stimulating hormone (FSH) were significantly elevated in 0.5 Gy-irradiated mice 8 wk after irradiation, consistent with loss of negative feedback due to follicle depletion, but serum LH and FSH are not optimal serum markers of ovarian reserve because they vary with estrous cycle stage and are secreted episodically, and we did not perform immunohistochemical analyses of ovaries at 8 wk after irradiation. We will examine oxidative lipid, protein, and DNA damage by immunostaining as potential biomarkers of ovarian tumor risk in archived ovaries from mice sacrificed 8 wk after irradiation with charged iron or oxygen particles. We will measure Anti-Müllerian Hormone (AMH), a serum marker of ovarian reserve that is used clinically, in archived serum from mice sacrificed 1 wk and 15 months after irradiation. 3-month old female C57BL/6J mice will be irradiated with 0, 0.05, 0.15, or 0.5 Gy gamma-rays and sacrificed one week post irradiation for ovarian follicle counts, which will be compared to our published data on charged iron or oxygen particle-irradiated mice. Materials and Methods Aim 1: Utilize archived ovaries to compare ovarian tumor induction by irradiation with silicon charged particles or gamma-rays. Fixed ovary samples from female CB6F1 mice irradiated with 0, 0.4, 0.8, 1.2 ,and 1.6 Gy gamma-rays and 0, 0.04, 0.08, 0.12, and 0.32 Gy silicon charged particles and sacrificed 16 months after irradiation will be obtained from the NASA tissue bank. The ovaries will be processed for histomorphometric analyses of ovarian follicle numbers, ovarian tumor histopathology, and immunostaining for tumor markers. Aim 2: Utilize archived ovaries harvested at various time points after irradiation with low doses of oxygen or iron charged particles to examine the persistence of ovarian oxidative lipid, protein, and DNA damage, archived serum to measure a biomarker of ovarian reserve, and evaluate these as potential early biomarkers of ovarian tumorigenesis. Irradiate mice with low doses of gamma-radiation and harvest ovaries at 1 week after irradiation in order to compare ovarian follicle depletion by charged iron or oxygen particles with gamma-radiation. 3-month old female C57BL/6J mice were irradiated with 0.05, 0.15, or 0.5 Gy gamma-rays or transported and restrained in an identical manner and not irradiated (0 Gy). All mice were sacrificed one-week post irradiation (N=8 per dose). One ovary per mouse was processed for counting ovarian follicles, and the other ovary was processed for immunostaining to measure proliferation, cell death, and oxidative damage. Blood serum was also collected from the gamma-irradiated mice, and together with archived serum from the Principal Investigator’s published studies will be analyzed for follicle stimulating hormone (FSH), luteinizing hormone (LH), and anti-Müllerian hormone (AMH), as

biomarkers of ovarian dysfunction.

Results

Aim 1: Utilize archived ovaries to compare ovarian tumor induction by irradiation with silicon charged particles or gamma-rays. We have not been able to begin work on this aim due to the COVID-19 pandemic.

Aim 2: Utilize archived ovaries harvested at various time points after irradiation with low doses of oxygen or iron charged particles to examine the persistence of ovarian oxidative lipid, protein, and DNA damage, archived serum to measure a biomarker of ovarian reserve, and evaluate these as potential early biomarkers of ovarian tumorigenesis. Irradiate mice with low doses of gamma-radiation and harvest ovaries at 1 week after irradiation in order to compare ovarian follicle depletion by charged iron or oxygen particles with gamma-radiation.

Body weights, ovarian weights, and uterine weights were measured at the time of sacrifice. The uterus was evaluated for presence of ballooning, which is an increase in uterine fluid and tissue mass characteristic of the proestrous stage of the estrous cycle. There was a statistically significant effect of gamma-radiation dose on body weight, with 0.5 to 1 g decreased body weight in all three gamma-irradiated groups compared to unirradiated controls. The mean paired ovary/oviduct weight was 1 to 1.5 mg lower in irradiated groups than in the control group. However, the effect of irradiation on paired ovary/oviduct weight was not statistically significant.

Because the mice were sacrificed at one week after irradiation without regard to estrous cycle stage, uterine weights were analyzed with adjustment for ballooning. The effect of radiation dose was statistically significant for the non-ballooned uteri, with the irradiated groups having 13 to 16 mg lower uterine weights on average than the sham-irradiated group.

Ovarian follicle counts on one ovary from each of these mice are in progress. Counts on 5 of 32 ovaries were completed before the COVID-19 pandemic research shut-down.

Conclusion

The decreased uterine weights observed one week after gamma-radiation in the present study are consistent with prior studies that showed that uterine irradiation decreases uterine size and thickness in premenopausal women and rats. Our finding of non-significantly decreased ovarian weights is consistent with our published observations that antral follicle numbers are decreased after charged iron particle-irradiation. Antral follicles are large structures, and a decrease in their number could reasonably be expected to reduce ovarian weight.

Bibliography Type: Description: (Last Updated: 08/10/2022)