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Cancer Risk in Human Spaceflight and Directions for Space Nursing: A Rapid Scoping Review

by

Brighton Blaze Krejci

An Honors Capstone

submitted in partial fulfillment of the requirements

for the Honors Diploma

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of

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Dedication

I dedicate this thesis firstly to my wonderful mother and father for always being there for me and giving me the love and support I needed throughout the entirety of my life. They have always pushed me to strive to be the very best version of myself and glorify God in all things I do. I could not have come this far without the lessons and guidance they have provided to me and their contributions to my life continue to be more and more profound with every passing day.

I would also like to dedicate this thesis to my younger brother Lundin who has been a massive inspiration for me and has been my very best friend since the day he was born. He has influenced me a lot in my life and to this day, he continues to help me understand what it means to be a leader.

Finally, I dedicate this thesis to Mrs. Bailey, Dr. Barnby, Mrs. Best, Dr. Chamness, Mrs. Hannah, Ms. Haws, Mr. Lakey, and Mr. Salamone. These educators have truly made a profound difference in my life by teaching me good character, encouraging a spirit of inquiry, guiding me through my academic journey, and providing me with support when I needed it most during some of the more challenging times of my life. The world needs more educators like them who pour their heart and soul into preparing the next generation of scientists, engineers, doctors, and nurses by going beyond their obligations as teachers.

To all of those whom I have not mentioned, you know who you are. Thank you all for being there for me and for giving me the tools to build my life. No words could ever convey how much you mean to me and how much you have impacted my life. I owe everything I am to you all and I hope I can make you all proud.

Abstract

Background: It is essential to possess an adequate understanding of the unique challenges and cancer risks associated with its exploration. One of the risks facing space crews is carcinogenesis. While utilizing engineering solutions such as radiation shielding to mitigate cancer risk is important, an over-reliance on these countermeasures would add excess mass and cost to the spacecraft. Therefore, we must have a better understanding of the cancer risks of being in a spacecraft to guide the study of health-based countermeasures while also ensuring optimal spacecraft performance.

Methods: Using PRISMA-ScR guidelines, we conducted a scoping review across PubMed, CINAHL, and ScienceDirect to explore published peer-reviewed literature about cancer risks in space. We included original research articles utilizing human subjects or cells that found or evaluated risk factors or carcinogens that can lead to oncogenesis from spaceflight as well as the references from 4 relevant reviews uncovered by our search.

Results: Our methods recovered a total of 600 unique results, of which 12 were deemed eligible for data extraction after screening. Factors contributing to alterations that could increase the incidence of cancer in space include carcinogens such as radiation, environmental toxins, and microgravity itself. Our search also discovered that spaceflight can cause other various changes in the human condition that can potentially lead to carcinogenesis such as impaired immune function, individual genetic variation, and genetic or DNA disruptions.

Discussion: Genetic disruption is the most widely researched potential facilitator of carcinogenesis in space. There is a demand for more research to be conducted in true spaceflight settings due to the lack of human settlements beyond Earth orbit. Nursing practice is underrepresented in space health and future directions for nursing research are discussed.

Introduction

Since cosmonaut Yuri Gagarin became the first man to cross the Karman line and enter space on April 12, 1961, space agencies around the world have been closely documenting and studying the effects of spaceflight on the human condition. But despite decades of research, the study of space medicine and how to effectively manage the many complications that can occur during deep space endeavors remains in its infancy, mandating much more required research as spaceflight focus shifts to deep-space missions (Pandian et al., 2022).

During spaceflight, humans are exposed to a multitude of different hazards and factors that adversely affect human health and experience extensive changes in their bodies (Garrett-Bakelman et al., 2019; Krittanawong et al., 2022). As such, the well-being of astronauts is of great importance from the time that pre-launch screening occurs and throughout the months following their safe return to Earth. However, as humans venture further into space, the ways in which spaceflight affects health are becoming vitally important topics of discussion. Of particularly noteworthy concern regarding health in deep space is that of cancer.

There are many factors that can lead to cancer in space. Radiation is a particularly well-known carcinogen that is capable of damaging chromosomes and altering the gene expression of cells. While a study by Reynolds et al. (2021) concluded that astronauts from 1959 to 2017 have had an overall cancer rate that is lower than the national average, Stanford and Jones (1999) found that most astronauts during much of that general time period never came close to reaching their maximum predetermined career radiation dose limits, which is an important consideration since future explorers will be traveling beyond the Earth's radioprotective magnetosphere, exposing them to higher levels of cosmic radiation for extended lengths of time (Stepanek et al., 2019).

Astronauts are exposed to roughly 72 mSv of radiation during a 6-month stay on the International Space Station (ISS) in low Earth orbit (LEO) (Cucinotta et al., 2008) and a 6-month mission to the Moon would result in a dose of about 170 mSv (Cucinotta & Durante, 2006). A full mission to Mars, meanwhile, could result in a total dose that may exceed 1,000 mSv for a flight lasting 180 days and a stay on the Martian surface for 500 days (Guo et al., 2022; Zeitlin et al., 2013). Therefore, a single mission to Mars would likely result in a minimum exposure amount that still exceeds the 600 mSv career limit currently enforced by NASA even when using the most ideal aluminum shielding thickness (Ramos et al., 2023).

Microgravity poses another carcinogenic risk to astronauts during space travel, as it affects human health and causes pathophysiological adaptations across the whole body (Demontis et al., 2017). Simulated microgravity, for instance, has been shown to facilitate the development of multicellular spheroids and upregulation of inflammatory cytokines such as IL-6, IL-7, and IL-8 in thyroid cells (Warnke et al., 2017). Microgravity is a constant condition when not standing on a planet's surface and, thus, could assist carcinogenic mechanisms in spaceflight.

Astronauts may also be exposed to various toxins within the environment. In space, astronauts live within an enclosed environment for extended durations of time, and many chemicals may pose carcinogenic hazards to astronaut health with repeated exposures. While metabolic wastes such as carbon dioxide pose the most significant toxicological risks to astronauts, other harmful chemicals could come from sources such as lubricants, cleaning agents, hygiene products, and payload leaks of volatile compounds (Khan-Mayberry et al., 2011). Altogether, the various environmental conditions present aboard spacecraft lead to physiological changes within the body, which can then further interact to produce cancer cells.

For the present review, a rapid scoping review was deemed to be the most appropriate method because despite its importance for human health, our understanding of cancer from space travel remains poorly understood and more research is necessary to maximize the safety of future crews (Krittanawong et al., 2022). Munn et al. (2018) described scoping reviews as reviews that “determine the scope or coverage of a body of literature on a given topic... as well as an overview (broad or detailed) of its focus.” Given the limited resources for the present study, the study was also declared a rapid review, which is performed when a systematic review process is expedited due to limited time or resources needed to conduct a full review (Ganann et al., 2010).

The purpose of this review was to gather a general overview of what oncologic risks space travelers face, what factors facilitate oncogenesis in space travelers, where research on the topic is concentrated, and to help bridge the gap that exists between spaceflight and nursing practice in preparation for future human endeavors in space. As such, the following research question was formulated: What is the general scope of and what is known from existing literature about cancer risk in human spaceflight related to radiation, microgravity, environmental toxins, and physiological changes, and how can nursing contribute to the study of cancer risk in space in the future?

Methodology

For this scoping review, we derived our protocol according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis extension for Scoping Reviews (PRISMA-ScR) and followed the checklist available on their website (<http://www.prisma-statement.org/>).

Information Sources & Search

A database search was conducted in June 2023 across ScienceDirect, CINAHL, and PubMed for relevant literature. Search terms were devised and agreed upon by both researchers

with the help of a librarian and utilized common terms for cancer (cancer, cancer risk, tumorigenesis, and oncogenesis) and spaceflight (astronaut, cosmonaut, space travel, space flight, and space exploration). The comprehensive search strategy for each database utilized for this review can be found in Appendix A.

Study Eligibility

To be included in this review, selected articles needed to be peer-reviewed papers written in English and published in academic journals that discussed risks that facilitate or factors that may lead to carcinogenesis in individuals flying in space. There were no restrictions placed on the date of publication. Because the study aimed to use published peer-reviewed articles, a search of grey literature was not performed. The resulting search returned 369 results. To increase the amount of literature screened by the review, 313 articles were downloaded from 4 of the most contextually relevant reviews retrieved from the search (Chen et al., 2019; Drago-Ferrante et al., 2022; Grimm et al., 2020; Guo et al., 2022) and added to the pool of sources in EndNote to be screened. Finally, 38 additional articles deemed relevant to the research question by the lead researcher were selected from the results of a preliminary search performed before the initiation of the present review and added to EndNote. During title and abstract screening, articles were excluded for lack of relevancy as deemed by the lead researcher and co-author. Figure 1 presents the review process at each stage in more detail as a flow chart.

Selection of Sources of Evidence

Upon completion of the database search and article compilation, all articles were downloaded and exported to EndNote. The results were scanned twice for duplicates, first by EndNote's automatic duplicate scan function and again manually by the researcher. The titles and abstracts of the remaining articles were then manually screened for potential relevance to the

research question at the discretion of the authors using Rayyan.ai to quickly scan for keywords and analyze the contexts in which they were used. At the title and abstract level of screening, articles were deemed to be potentially relevant if they met established criteria for exclusion as outlined in Table 1.

Following title and abstract screening, all potentially relevant articles were retrieved and exported back to EndNote to be evaluated for full-text availability. Access to articles with no immediate full-text availability was formally requested via interlibrary loan. Following retrieval, articles were then screened at the full-text level according to the study's eligibility criteria in Table 2.

Data Charting Process

Data charting was conducted by taking narrative research notes for each article in EndNote. For each article, a detailed evaluation of study subjects, aims, methods, findings, results, and discussions were drafted. Statistics regarding various aspects of the nature of included articles were drawn from the data items extracted. Finally, data was extracted from the eligible articles (see Table 3 & Table 4).

Data Items

We extracted data relevant to the scoping review which included findings on risk factors and carcinogens in space that facilitate carcinogenesis (e.g. smoking, radiation exposure, infection, etc.), findings of the studies, characteristics of research subjects (e.g. humans or biological samples), and limitations either reported by the authors or determined by the researchers while reviewing the text.

Synthesis of Results

Based on the findings from the included articles, the findings were organized into two tables. Table 3 represents articles reporting carcinogens as potential risk factors and possible facilitators of carcinogenesis in space in three broad categories: radiation, microgravity, and environmental toxins. Table 4 displays the articles reporting alterations in physiology that could lead to an increased cancer risk and were also organized into three categories: altered immune system function, genetic variation, and genetic or DNA disruption. Both tables, although sharing some of the same specific probable causative catalysts for carcinogenesis (e.g. radiation), were kept separate for the convenience of data extraction and analysis.

Results

After screening through a total of 600 unique records, many deductions regarding the evidence and scope of cancer risk research can be formulated. Our review found 10 journals encompassing various disciplines with relevant publications. The majority of studies performed on living subjects were conducted on cell and tissue samples. This finding was expected given the ethical problems that would be associated with deliberate cancer induction in human subjects as well as the lack of present capabilities of observing human subjects in a true spaceflight environment beyond LEO. The bulk of research concerning human cancer risk in space is concentrated on DNA or genetic disruptions that occur as a consequence of the many environmental factors involved in space (see Table 4).

Nursing research is greatly underrepresented based upon the results of our review, and future directions for nursing research as it relates to space cancer risk research should involve the implementation of education into how the human body is affected by and adapts to exotic environments such as microgravity. Conversely, it is important to encourage research from nursing disciplines into the various aspects of care and management of cancer from toxic

substances, microgravity, radiation exposure, and the processes that can lead to carcinogenesis such as DNA disruption and altered immunity. As a gap in literature exists in our understanding of the pathophysiological processes behind carcinogenesis from spaceflight, nursing research would finally benefit from filling this gap in the future.

Hotspots of Publication & Scope of Research Literature

Articles deemed eligible for this review were published in 10 different journals: *Advances in Space Research*, *Cell Proliferation*, *Cell Reports*, *Cytogenic and Genome Research*, *Frontiers in Cardiovascular Medicine*, *International Journal of Molecular Sciences*, *Journal of Applied Physiology*, *Life Sciences in Space Research*, *Science of The Total Environment*, and *Scientific Reports*. Each journal contributed one publication to this review except for one, *Cell Reports*, which published 3 of the included articles.

The journals that published literature included in this review contributing to our understanding of cancer in space uncovered risks from many subjects and fields of study such as space & planetary sciences, cellular biology, life sciences, cytogenetics, cardiology, human physiology, astrobiology and radiation research, environmental sciences, and natural sciences. However, despite the wide multi-professional scope of literature covering space cancer risk research, there were no articles retrieved from any journals with nursing backgrounds.

Possible Facilitators of Carcinogenesis

In addition to determining the scope of the research being performed in regard to space cancer risks, this review also sought to identify potential carcinogens and risk factors that may lead to carcinogenesis in space and briefly review them.

Potential Carcinogens in Space

Specific carcinogens that could increase the likelihood of cancer were found in 42% (n = 5) of the included articles and are represented in Table 3. Radiation was identified as a carcinogen in 60% (n = 3) of the articles in Table 3 while environmental toxins (20%, n = 1) and microgravity (20%, n = 1) were in the remaining articles.

Eighty percent (n = 4) of these articles used specimens collected from human subjects to use as study samples while only 20% (n = 1) used actual human subjects. Collected specimens primarily consisted of blood samples, making up 75% (n = 3) of all the articles that took biological samples. Overall, our review found that radiation and microgravity destabilize genetic material in cells and can selectively allow for the propagation of carcinogenic mechanisms (George et al., 2004; Greco et al., 2003; Li et al., 2019; Nair et al., 2019) while carcinogenic toxins such as benzenes may pose a health risk to space travelers (Dai et al., 2018). A detailed presentation of the research subjects and key findings for each article where a specific carcinogen could be identified can be found in Table 3.

Potentially Carcinogenic Physiological Changes in Space

Several of the included articles (n = 7) had identified or discussed alterations in human or cellular physiology that could potentially lead to the onset of cancer. Fourteen percent (n = 1) of articles addressed altered immune function as a primary change induced by spaceflight. Another article studied how genetic variations within the individual could affect responses to radiation. Finally, the most well-researched alteration was genetic or DNA disruption, which made up 72% (n = 5) of the articles included in Table 4.

Our review determined that there is ample literature that draws a clear correlation between spaceflight and disturbance of the human condition. Spaceflight disrupts the genetics of cells by causing or increasing the number of abnormalities in chromosomal organization or

structure (Feiveson et al., 2021; Luxton et al., 2020), which can hold the potential to lead to pathologic manifestations. The ways in which space conditions such as radiation affect the human body vary considerably, as the presence of certain genes in the genome can influence the likelihood and severity of chromosomal damage (Sridharan et al., 2019). Additionally, spaceflight can evoke the presence of clonal hematopoiesis among cells (Mencia-Trinchant et al., 2020) and even disrupt small nucleolar RNAs (Rai et al., 2022). Furthermore, our review uncovered literature regarding the relationship between the immune system and its role in carcinogenesis from spaceflight. Natural killer (NK) cells curiously exhibit reduced effectiveness after flying in space, the reasons for which remain unknown (Bigley et al., 2019). An organized presentation of all articles included in this review that discussed pathophysiological changes that could result in cancer with the subject characteristics and key research findings can be found in Table 4.

Noteworthy Limitations Reported or Found in Current Research

Most articles discussed the limitations involved with their research. A frequent limitation of current research is that of all small sample sizes. Likewise, studies that utilized samples from astronauts took samples from more males than females. Researchers also have difficulty determining the underlying mechanisms behind many alterations in human health that can increase one's risk of developing cancer, thus, limiting the ability to identify exact causations of carcinogenesis and presenting a considerable gap in research literature. Additionally, no extended-duration spaceflights comparable to the length of time a Mars mission would take were completed in any of the studies included and all studies that involved astronauts used samples that were collected after missions to LEO.

Limitations

Our study, like any, was not without weaknesses. This review did not extract data directly from any review articles or grey literature, both of which may contain vital information pertinent to the research topic from a variety of different disciplines. The search was also not comprehensive given time constraints and the experience of the lead researcher. Search terms were also not entirely comprehensive regarding oncological terminology or pathophysiology which may have led to the exclusion of other studies that held relevance to the research question. During title and abstract screening, articles that did not mention cancer, did not potentially hold original research findings about cancer, or were not concentrated on cancer were excluded, which may have left out more studies with pertinent findings regarding oncogenesis in space. Our review only encompassed articles that had some relevance to spaceflight, as research findings from studies on individuals exposed to carcinogenic radiation through other means (e.g. Chernobyl nuclear accident, atomic bombs, etc.) were not included. Finally, the screening process was performed by two researchers with minimal discussion on exclusion, which although screened multiple times, may have allowed bias in article selection.

Discussion

In this review, we sought to briefly extract pertinent findings from and determine the scope of published peer-reviewed literature about cancer-related risks and facilitators of cancer in a spaceflight environment based on a systematic search through three databases. From our search, we determined that the research literature is still in its nascent stages, but that the spaceflight environment consists of a multitude of factors that can increase the likelihood of carcinogenesis following the conclusion or during the duration of the mission. Genetic and DNA disruption is the most extensively researched topic, making up the main potential factor for

carcinogenesis in five of the articles included and presenting itself in one way or another in the majority of the others. Other risk factors for cancer that space travelers face include microgravity itself, radiation, the presence of toxic compounds in the air, immune system disruption, and their own genetic variations.

Additionally, we sought to determine how nursing practice can contribute to future research in space cancer literature. Nursing research is highly underrepresented in this subject and it can contribute in a variety of ways, as nurses possess unique clinical decision-making skills and knowledge that prove to be beneficial in virtually every clinical environment (Pandian et al., 2022). Of all the academic journals that published relevant research about the risks of cancer in spaceflight, our scoping review found no published literature in any nursing journals. The inclusion of nursing in all aspects of space health will serve to be of vital importance in the future, particularly in the upcoming age of commercial spaceflight. In 2019, nurses made up 30% of total employees in U.S. hospitals, making them the single largest body of medically licensed personnel in the United States (U.S. Bureau of Labor Statistics, 2020). Therefore, it is reasonable to assume that they will also make up the majority of medical personnel aboard future commercial space missions with individuals who are much less healthy than astronauts, highlighting the urgency for nursing practice to extend into space. We identified a gap in the literature related to the pathophysiological processes involved with oncogenesis in space, presenting an opportunity for nursing research to further investigate how specific systems or variables may interact with one another to facilitate oncogenesis with the goal of gaining a better understanding of how to develop effective countermeasures in the future. Environmental toxins such as BTEX are carcinogens that can be greatly reduced but have little saturation in research literature, with very few references to them outside the study done by Dai et al. (2018). Nursing

research may, thus, benefit from studying the effects of spaceflight-related environmental carcinogens on the body.

More research must be done in true spaceflight environments, as radiation-related space cancer research on Earth has limited applicability to actual spaceflight due to the difficulty of simulating cosmic radiation which consists of heavier particles of much higher energy and charge than what is experienced terrestrially or near Earth (Freese et al., 2016). Furthermore, future research should concentrate on more diverse astronaut populations as well as extended-duration missions lasting over a year to gather more relevant information on how the human body adapts to an enhanced carcinogenic environment. NASA's Artemis program which aims to send humans back to the Moon for the first time since 1972 presents one such opportunity for research in long-term missions beyond Earth. However, evidence-based nursing science in space may remain limited until humans establish a more permanent extraterrestrial presence, so in the meantime, nursing can further contribute to research by producing literature about how the human body is affected by exotic environments such as spaceflight and then incorporating these findings into educational curriculums to encourage further exploration into how the body reacts to spaceflight. Altogether, the integration of nursing into space health research will help further benefit the field of nursing as well as all other medical disciplines involved in space health research activity.

Possible Facilitators of Carcinogenesis in Space

Radiation. A well-known risk factor for cancer associated with spaceflight due to the presence of various different types of ions otherwise not present within Earth's magnetosphere and atmosphere (Cucinotta & Durante, 2006), radiation is widely-researched, appearing as one of the primary carcinogens studied in more than half of the articles in which a specific carcinogen

was identified and mentioned in every article included in this review. Literature pertaining to radiation contains a mixture of articles that studied blood and samples from astronauts as well as studies that exposed blood samples to radiation *ex vivo*. Radiation is capable of causing chromosomal abnormalities within cells (George et al., 2004; Greco et al., 2003), particularly in those of astronauts older than 40 years of age (George et al., 2004). Radiation also increases the sensitivity of lymphocytes to irradiation, but it is unlikely that the number of previous flights affects the incidence of chromosomal abnormalities *in vivo* (Greco et al., 2003). Space travelers may be exposed to high linear energy transfer (high-LET) particles in the form of high atomic number and high energy (HZE) radiation, which is capable of inducing extensive DNA damage, particularly in low dose rates similar to those which would be encountered in a spaceflight environment (Hada et al., 2019; Nair et al., 2019). Although they were excluded from this review due to the vastly different approaches and methodologies used, radiation-cancer risk probability models are each unique and pose their own suggestions for improving risk prediction. One of the most recent studies suggested that the use of a multimodal ensemble framework should be used for future radiation risk predictions in deep space, as it is impossible to adequately reduce radiation exposure uncertainties associated with cancer risk with a single metric without a comprehensive understanding of the relationship between cancer risk and radiation dose (Simonsen & Slaba, 2021). No single model would provide sufficient risk prediction with current research. However, research should aim to incorporate these models into clinical practice and translate them into formats that can be understood by clinicians operating in space in the future.

Microgravity. Our review also found evidence that microgravity itself may have carcinogenic effects, a finding which holds significant ramifications for long-duration missions since it is a constant experience during spaceflight. In simulated microgravity, bone marrow stem

cells with deactivated apoptosis pathways and increased expression of pathways associated with tumorigenesis were more prevalent, indicating what the authors declare to be a selective proliferation of precancerous bone marrow cells (Li et al., 2019). The authors also state that over time, microgravity may selectively enable tumor cells to become more viable and invasive. Further research in the future should aim to study cellular mechanisms after exposure to true microgravity rather than a simulated microgravity environment.

Environmental Toxins. Although scarcely researched, certain environmental toxins can pose a mild risk for carcinogenesis during spaceflight. Dai et al. (2018) identified four environmental toxins that could potentially exist in a spaceflight environment: benzene, toluene, ethylbenzene, and xylenes (“BTEX”). Three of these toxins are recognized as being potentially carcinogenic, as individuals exposed to benzene, ethylbenzene, and o-xylene have an increased prevalence of cancer (Malik et al., 2022) with benzene in particular being a known carcinogen linked to leukemia (McHale et al., 2012). Cabins that had plants also had lower levels of these three carcinogens than cabins with no plants (Dai et al., 2018). Although the risk of developing cancer reduced as time progressed due to the reduction in ambient levels of BTEX via air purification, they remain carcinogens worthy of consideration in an enclosed environment.

Altered Immune System. Cells of the immune system are particularly sensitive to radiation (Nosel et al., 2013; Paganetti, 2023) and numerous studies have been done using human blood lymphocytes and other immune cells as samples, including several of the articles included in this review. The study by Bigley et al. (2019) which found that NK cells exhibit functional impairment after flying in space remains consistent with previous literature regarding immune system function in space. What makes Bigley et al. (2019)’s findings particularly concerning is that NK cells are one of the body’s primary defenses against altered cells

(Vishwasrao et al., 2021) and, according to the authors, reduced toxicity of NK cells is a likely contributor to the development of certain hematologic and skin cancers (Martner et al., 2015; Vineretsky et al., 2016). Bigley et al. (2019)'s finding that NK cells are most impaired in rookie flyers is also concerning given the context in which future missions to Mars will take place. Since a trip to Mars would likely already result in a total absorbed radiation dose that exceeds NASA's current 600 mSv career exposure limit (Ramos et al., 2023), it is possible that the Mars assignment will be the only time that group of astronauts will ever fly in space, making the whole crew consist of "rookie flyers" with little to no time spent in space prior to that mission. More research is needed to determine the process by which NK and other immune cells are inhibited by spaceflight as to develop countermeasures to protect against cancer.

Genetic Variation. An individual's genetic makeup is another potential risk factor that plays into one's risk of developing various cancers as a result of spaceflight. Carriers of oncogenes such as the breast cancer genes BRCA1 and BRCA2 within the genome may enhance an individual's risk of developing chromosomal aberrations secondary to high-LET radiation exposure (Sridharan et al., 2019). Interestingly enough, the presence of ATM, a tumor suppressor gene, also increased the likelihood of developing chromosomal abnormalities, albeit not to the same extent as the oncogenes. This may be because ATM is known to primarily suppress lymphoma and leukemia and has a much less understood role in suppressing solid tumor cancers such as breast cancer, potentially even acting as a facilitator for solid tumorigenesis (Liu et al., 2020). Perhaps unsurprisingly, carrier cells of the BRCA1 gene were more likely to be affected by irradiation than carriers of the BRCA2 gene, likely a consequence of the increased incidence of cancer observed in females with the BRCA1 mutation (Antoniou et al., 2003). Together, these results help to create a better picture of how genetic screening and identification of oncogenes

such as BRCA1 and BRCA2 in the genome are essential for determining the individual cancer risks of astronauts.

Genetic or DNA Disruption. Articles that studied genetic and DNA disruption in some way or another in cancer risk space research were plentiful. According to Pariset et al. (2020), the amount of pre-existing DNA damage within cells affects the cellular response to further damage induced by simulated galactic cosmic radiation, as they determined that cells with less extensive baseline damage were most capable of repairing DNA damage. Similar to the findings by Pariset et al. (2020), Feiveson et al. (2021) found that cells of astronauts who had more chromosomal alterations experienced more chromosomal damage after spaceflight and their cells exhibited higher sensitivity to ex vivo radiation. Age may certainly play a role in one's risk of developing cancer due to the accumulated damage done to DNA naturally over time, as older astronauts tend to have more chromosomal abnormalities than younger ones (Feiveson et al., 2021; George et al., 2004). Clonal hematopoiesis is yet another alteration seen in some astronauts that is related to genetic disruption (Mencia-Trinchant et al., 2020), a phenomenon linked to an increased incidence of hematologic cancers (Genovese et al., 2014). Research literature from our review also suggests that telomere length shortened after spaceflight (Luxton et al., 2020), which can predispose astronauts to the development of gastrointestinal, head, and neck cancers (Zhu et al., 2016). Since Luxton et al. (2020) claim it is not known what exactly caused the astronauts' shortened telomeres in their study, additional research should be conducted to determine the extent to which oxidative stress causes this alteration in spaceflight, as the authors found a possible correlation between oxidative stress and telomere length.

Limitations of Scoped Literature

While all articles reviewed held good methodological content and produced valuable research data, a common limitation among studies that utilized astronauts as subjects was an inability to find a large sample size. While there are many explanations for this, the most significant reason is most likely related to the difficulty of accessing astronaut populations for research purposes. There also exists a discrepancy between the number of male subjects and female subjects, which is a consequence of astronaut demographics as there are fewer female astronauts than male to include in studies. Beyond astronaut demographic limitations, no long-term spaceflights were completed in any of the studies included in this review, as even the longest spaceflights across all studies fell far short of the expected duration of Mars missions (Shen et al., 2022). Furthermore, all astronauts from whom samples were collected flew only to LEO, which possesses a very different environment than that of space beyond near-Earth space (Freese et al., 2016).

Future Directions for Research

Environmental toxins such as BTEX are carcinogens that can be greatly reduced but have little saturation in research literature, with very few references to them outside the study done by Dai et al. (2018). More research must also be done in true spaceflight environments, as radiation-related space cancer research on Earth has limited applicability to actual spaceflight due to the difficulty of simulating cosmic radiation which consists of heavier particles of much higher energy and charge than what is experienced terrestrially or near Earth (Freese et al., 2016). Furthermore, future research should concentrate on more diverse astronaut populations as well as extended-duration missions lasting over a year to gather more relevant information on how the human body adapts to an enhanced carcinogenic environment. NASA's Artemis program which

aims to send humans back to the Moon for the first time since 1972 presents one such opportunity for research in long-term missions beyond Earth.

Another opportunity exists for future research to understand how microgravity, radiation, and environmental toxins all interact together with one another to compound cancer risks. Finally, there is a gap in many studies in regard to the pathophysiology of different processes that could cause cancer from spaceflight.

Implications to Nursing Practice

Our review determined that nursing science is absent in much of space cancer research literature, indicating a gap in the scope of nursing practice in general. By including nursing in space health research, future career prospects and breakthroughs in our understanding of how spaceflight affects the human condition as a whole can be achieved and explored with evidence-based practice expanding into space travel contexts.

Conclusions

Human health in space is a healthcare topic that is growing in relevance and has many aspects and opportunities for future research. Cancer risk is one such aspect of space health that is of utmost importance for study. It is studied by a wide variety of medical disciplines and has publications in many different journals. However, research in the present day is limited primarily by the difficulty of accessing astronauts as well as by the current near-Earth, short-term state of space travel. Altogether, it can be concluded that no single variable results in an increase in the risk of cancer development, as multiple interacting factors exist simultaneously which may then produce a variety of different pathophysiological mechanisms that can further increase the risk of cancer.

Nursing practice can greatly benefit space health literature by becoming more involved with studies that relate to space travel or other exotic environments. A few ways in which nursing can contribute are by mapping out how each system is changed and evaluating the extent to which each contributes to an increased risk of developing conditions such as cancer, establishing courses in nursing education programs to familiarize new nurses with how the human body is affected by exotic conditions, and by helping to establish policies and procedures for space-specific health assessment and care implementation.

The general purpose of nursing is to improve the experience of the human condition regardless of where one is, whether be on or off the Earth and as populations continue to get more diverse, so will the individualization of nursing practice (Rogers, 1992). The era of space flight promises an opportunity to discover new ways in which patients can be treated for various conditions and for nursing practice to expand into a new frontier. The understanding and, ultimately, prevention of long-term complications associated with spaceflight such as cancer is an area of great significance. With the cooperation of all specialties in healthcare, nursing contributions to human health research in space can greatly expand the horizons of what is possible to achieve by human beings.

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Dissemination of Scholarly Work

- Honors Capstone Research Program Poster Presentation
- Peer-reviewed academic journal (TBD)

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Figures, Illustrations, and Tables

Figure 1

Systematic Study Flow Chart

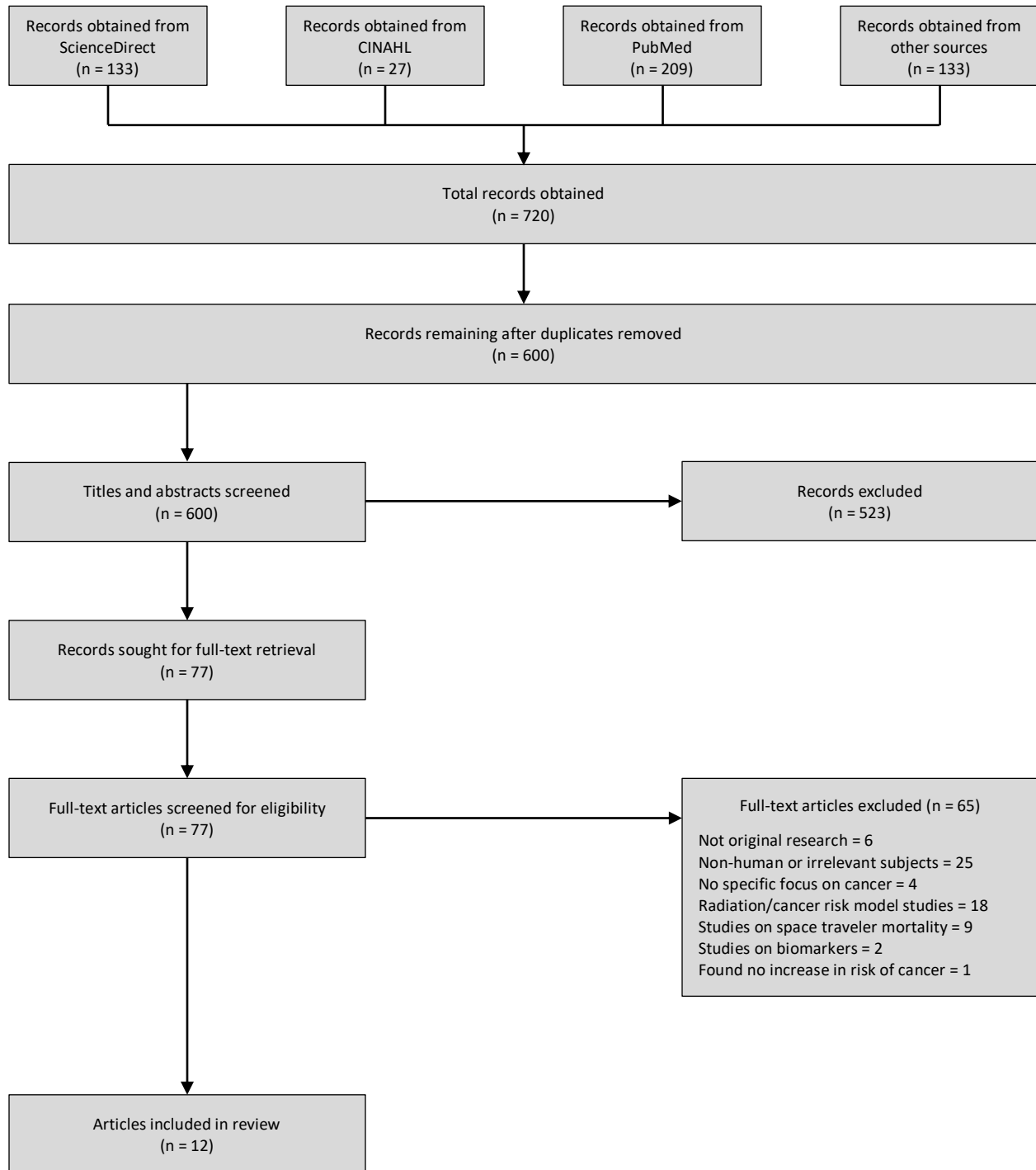


Table 1

Reasons for Exclusion at the Title and Abstract Level of Screening

1. Not published in English
2. Involved non-human cells or research subjects
3. No relevance to cancer risk and spaceflight due to lack of contextually relevant keywords
4. Total irrelevance to the research question
5. Evaluation of a device or tool
6. Study of cancer treatment or treatment of complications from cancer treatment
7. Engineering or design-focused study
8. Not original research
9. Retracted publication
10. Comparison study of exposure effects of different radioactive particles
11. Study of cancer risk countermeasures
12. Use of already-cancerous cells as study subjects

Table 2

Scoping Review Exclusion Criteria at the Full-Text Level of Screening

Criteria for Exclusion	Rationale for Exclusion
<i>No Specific Focus on Cancer or Possible Cancer Pathogenesis</i>	<ul style="list-style-type: none"> • Radiation exposure leads to a multitude of different pathologies including cataract formation, neurocognitive effects, cardiovascular disease, and radiation sickness (Freese et al., 2016). • While important considerations for space missions, articles that do not specifically determine possible risks that can lead to oncogenesis or find data relevant to cancer in spaceflight were not relevant to the present review's aims.
<i>Use of Irrelevant Subjects or Specimens</i>	<ul style="list-style-type: none"> • Studies that involved the use of non-humans, specimens from non-human subjects, or immortalized cells taken from cell lines were not included. • Animal studies provide important insights into various pathologies, but genetic and physiological differences greatly limit the feasibility of transferring many findings from animals to humans (Akhtar, 2015). • Immortalized cells are cells manipulated in a way that makes them proliferate indefinitely which is achieved in a variety of ways (Irfan Maqsood et al., 2013). While providing great benefit in the understanding of pathogenesis and processes involved in diseases such as cancer, some findings may not represent what would otherwise be observed in specimens taken directly from a living subject because of their altered phenotypic expression and physiological processes (Kaur & Dufour, 2012).
<i>Not Original Research</i>	<ul style="list-style-type: none"> • Reviews of existing data can potentially depart from the research question and have limited ability to contribute new findings to research literature, thus, failing to answer our research question of where the current original research is centered for space cancer risk. • This criterion was applied at the title and abstract level of screening, but some articles produced uncertainty regarding their classification as original research or not. These articles were carried to the full-text level for final screening before removal.
<i>Radiation/Dose Risk Model Evaluations or Assessment Methodologies</i>	<ul style="list-style-type: none"> • Some recovered literature aimed to quantify absorbed doses of radiation or make predictions of radiation dosages. • Articles written to propose models for future studies, risk assessment, or analysis of radiation dose were deemed irrelevant as this review was designed to scope literature about the risks of cancer faced by individuals in spaceflight environments. • These articles make little contribution to existing literature on what factors may cause cancer in space and focus more on estimation of risk, monitoring, or evaluation of methods quantifying cellular damage instead. • Research into methodologies and models would be best fitted for a future study centered more around countermeasure or assessment research.
<i>Studies on Mortality of Space Travelers</i>	<ul style="list-style-type: none"> • Astronauts are routinely monitored for any medical conditions or diseases that they develop for the rest of their lives (Hamm et al., 1998), allowing for research into what causes death in those who have flown in space. • Articles that studied the mortality or risks of mortality from diseases such as cancer in spaceflight populations were excluded due to their primary focal point on risk or prevalence of death rather than the risk of developing cancer.
<i>Studies on Biomarkers</i>	<ul style="list-style-type: none"> • Studies that focused on the discovery of biomarkers contain a lack of evaluation of risks posed to astronauts, as some biomarkers are the result of carcinogenic processes rather than causes. • However, studies finding pathological consequences of spaceflight that alone could increase the risk of cancer development while also serving as biomarkers by technicality (e.g. presence of altered immune cells, etc.) were included.
<i>Studies Finding no Increase in Risk of Cancer</i>	<ul style="list-style-type: none"> • There exist many factors in the spaceflight environment that do not or with one's health that do not increase the likelihood of developing cancer. • Studies that reported a factor with little effect or could decrease the risk of carcinogenesis in spaceflight failed to address the research question.

Table 3

Data Extraction Table for Articles Reporting Carcinogens as Cancer Risks

Study	Title	Subject	Carcinogen Identified	Key Findings	Notable Study Limitations
Dai et al., 2018	Aromatic hydrocarbons in a controlled ecological life support system during a 4-person-180-day integrated experiment	4 human researchers	Environmental toxins	<p>Incineration or drying of biological waste increased aromatic concentration of toxic aromatic hydrocarbons benzene, toluene, ethylbenzene, and xylenes (“BTEX”) within the cabin.</p> <p>Cabins with plants present had higher ambient levels of toluene and xylenes whereas cabins without plants had more ethylbenzenes and xylenes.</p> <p>BTEX levels were significantly higher in cabins without plants where the crew spent most of their time, indicating that individuals who do not work around plants such as engineers are at a higher risk of inhaling BTEX than those who do.</p> <p>Other sources of BTEX included solvents, oil paint, detergents, sewage treatment, furniture, and construction materials.</p> <p>Health risks from BTEX inhalation would be most significant at the start of a mission since overall air BTEX concentration decreases as time progresses and the air is purified.</p>	Modules not perfectly airtight to one another as to allow individuals to travel between one module to another – risk for cross-contamination
George et al., 2004	Chromosome aberrations of clonal origin are present in astronauts' blood lymphocytes	Blood samples collected from 12 astronauts	Radiation	<p>3 subjects exhibited chromosomal abnormalities in the form of clonal exchanges, suggesting that chromosomal changes in blood lymphocytes may be very prevalent.</p> <p>Chromosomal aberrations were no longer detectable from lymphocytes of 2 of the astronauts after 240 and 182 days. In the third, one became undetectable after 72 days and the other became more and more rare in lymphocytes over 735 days.</p> <p>All 3 astronauts who exhibited clonal chromosome aberrations were age 40 or older.</p> <p>Sample from one astronaut with a previous history of flying in space possessed a clonal chromosome aberration before the study flight.</p>	Small sample size
Greco et al., 2003	Biological dosimetry in Russian and Italian astronauts	Blood samples collected from 9 cosmonauts (8 Russian, 1 Italian)	Radiation	<p>Aberrations were present in 6 samples after landing, the most frequent abnormality being simple exchanges.</p> <p>There was no correlation between the number of previous flights a participant had had and the number of chromosomal aberrations found in blood samples.</p> <p>There was no correlation between the length of extra-vehicular activity (EVA) and cell damage.</p> <p>Blood lymphocytes exhibited increased sensitivity to irradiation after spaceflight.</p> <p>The cause of increased radiosensitivity of blood cells was inconclusive, though it was speculated to be due to microgravity and radiation exposure.</p>	<p>Unequal number of cells were examined for each cosmonaut blood sample (subject 1 n = 397; subject 2 n = 1,174; subject 3 n = 811; etc.)</p> <p>Flight duration varied considerably (subject 1 n = 198 days; subject 3 n = 73 days; subject 9 n = 10 days; etc.)</p>
Li et al., 2019	Effects of simulated microgravity on the expression profiles of RNA during osteogenic differentiation of human bone marrow mesenchymal stem cells	Human bone marrow mesenchymal stem cell (hBMSC) samples collected from 3 healthy donors (1 male, age 23; 2 females, ages 19 & 34)	Microgravity	<p>The most enriched pathways in middle and late-stage osteogenic differentiation in hBMSCs included cytokine-cytokine receptor interaction and cancer pathways.</p> <p>Genes associated with cancer tumor formation and propagation (tumor formation, growth factor, blood vessel formation, etc.) were upregulated while genes associated with apoptosis were downregulated.</p>	<p>Not an actual space mission – simulated microgravity exposure</p> <p>Small sample size</p>
Nair et al., 2019	The Impact of Dose Rate on DNA Double-Strand Break Formation and Repair in Human Lymphocytes Exposed to Fast Neutron Irradiation	Blood samples collected from 4 healthy donors	Radiation	<p>Biomarkers of DNA double-strand breaks took longer to disappear after low dose rate than from a higher dose rate, indicative of more extensive DNA damage for low dosages.</p>	<p>Not an actual space mission</p> <p>No clear consensus exists on what constitutes as “low dose rate” outside the confines of this study</p>

Table 4

Data Extraction Table for Articles Reporting Changes in Physiology as Cancer Risks

Study	Title	Subject	Risk Factor or Health Alteration Identified	Key Findings	Notable Study Limitations
Bigley et al., 2019	NK cell function is impaired during long-duration spaceflight	Natural killer (NK) cells derived from blood samples of 9 astronauts (8 male, 1 female; ages 37-57) and 8 healthy sex-matched ground-based controls	Altered immune system function	<p>NK cell cytotoxicity was decreased in blood samples from astronauts relative to their controls, indicating impaired immunity.</p> <p>First-time flyers had considerably greater reductions in NK cell cytotoxicity when compared to veteran crewmates, indicating the body may adapt over repeated exposures.</p> <p>Immune system impairment takes longer to return to baseline in first-time flyers than in experienced flyers.</p>	<p>Disproportionate representation of male subjects compared to female subjects</p> <p>Age differences between astronauts</p> <p>No clear cause of impaired immune system function found</p>
Feiveson et al., 2021	Predicting chromosome damage in astronauts participating in international space station missions	Blood samples collected from 38 astronauts (28 male, 10 female)	Genetic/DNA Disruption	<p>Astronauts who had more chromosomal aberrations in their blood cells and higher radiosensitivity to ex vivo gamma irradiation experienced more chromosomal damage from spaceflight than did others with less radiosensitivity and who had flown in fewer flights.</p> <p>Most of the damage from radiation was likely the result of damage to bone marrow cells given the lifespan of T cells and the time period of collections following the astronauts' return to Earth.</p> <p>Older astronauts had more chromosomal aberrations than did younger astronauts</p>	<p>Not all blood samples collected after landing were able to be collected from all astronauts.</p> <p>Too few female subjects to gather adequate data on whether sex affects likelihood of developing chromosomal damage from radiation exposure.</p> <p>Assumptions made while establishing predictions for chromosome aberration rate may have slightly altered results.</p>
Luxton et al., 2020	Telomere Length Dynamics and DNA Damage Responses Associated with Long-Duration Spaceflight	Blood samples collected from 11 astronauts and 11 age and sex-matched ground-based controls	Genetic/DNA Disruption	<p>The telomeres in cells in astronaut blood samples were dramatically shorter when compared to healthy controls regardless of mission duration.</p> <p>The mechanisms behind telomere shortening are not understood but may be caused by radiation, microgravity, and oxidative stress from spaceflight.</p> <p>More chromosomal aberrations occurred during and after spaceflight. Telomere length correlated with oxidative stress.</p>	<p>Definitive causation could not be determined due to the presence of multiple factors that cause oxidative stress in space and inability to separate them all in a controlled study in space.</p>
Mencia-Trinchant et al., 2020	Clonal Hematopoiesis Before, During, and After Human Spaceflight	Blood samples collected from a pair of twin astronauts	Genetic/DNA Disruption	<p>Clonal hematopoiesis was present in both astronauts</p>	<p>Mechanisms underlying generation of clonal hematopoiesis could not be determined</p>
Pariset et al., 2020	DNA damage baseline predicts resilience to space radiation and radiotherapy	Blood samples collected from 674 healthy human donors (47% male, 53% female) and 30 samples from males with prostate cancer after radiation therapy	Genetic/DNA Disruption	<p>The extent of pre-existing DNA damage in mononuclear cells before exposure to simulated galactic cosmic radiation affects cellular responses after radiation-induced DNA damage.</p> <p>Less extensive baseline DNA damage was correlated with more effective recruitment of DNA damage repair proteins.</p> <p>Age of subjects had far more effect on cells' abilities to repair radiation-induced DNA damage than did sex or body mass index (BMI).</p>	<p>Not an actual space mission</p> <p>Some authors had patents related to the work of the study</p>
Rai et al., 2022	Spaceflight-Associated Changes of snoRNAs in Peripheral Blood Mononuclear Cells and Plasma Exosomes-A Pilot Study	Blood samples collected from 5 astronauts	Genetic/DNA Disruption	<p>Astronauts exhibit disruptions in small nucleolar RNAs (snoRNAs) after short flights in space.</p>	<p>Small sample size</p>

Study	Title	Subject	Risk Factor or Health Alteration Identified	Key Findings	Notable Study Limitations
Sridharan et al., 2019	Genetic variation and radiation quality impact cancer promoting cellular phenotypes in response to HZE exposure	Mammary epithelial cells of varying genotypes from female donors	Genetic Variation	<p>Cells of heterozygous carriers of BRCA1, BRCA2, and ATM gene mutations developed more chromosomal abnormalities after exposure to high-LET radiation than did the wild-type non-carrier.</p> <p>BRCA1 mutation led to greater haploinsufficiency than did BRCA2 or ATM mutations.</p> <p>Genetic background plays a role in one's susceptibility to chromosomal damage from radiation.</p>	<p>Not an actual space mission</p> <p>Small sample size</p>

Appendix A

Full Scoping Review Search Strategy

Database & Search Terms	Additional Search Information & Rationale
<p>ScienceDirect</p> <p><i>Title, Abstract, Keywords:</i> (astronaut OR cosmonaut OR “space travel” OR “space flight” OR “space exploration”) <u>AND</u> (cancer OR “cancer risk” OR tumorigenesis OR oncogenesis)</p>	<p>Results were restricted to records containing the search terms in the title, abstract, and keywords due to the higher likelihood of the search returning more results relevant to the research question and fewer results containing only the search terms within the text.</p>
<p>Cumulative Index to Nursing and Allied Health Literature (CINAHL)</p> <p><i>Subject Terms:</i> astronaut OR cosmonaut OR “space travel” OR “space exploration”</p> <p><u>AND</u></p> <p><i>Title:</i> cancer OR “cancer risk” OR tumorigenesis OR oncogenesis</p>	<ul style="list-style-type: none"> • Search expanded to apply equivalent subjects • Searched all available databases <p>Results were restricted to records containing the subject terms due to their relevance to the research question when combined with the terms searched within the titles of articles.</p>
<p>PubMed</p> <p><i>Title, Abstract:</i> (astronaut OR cosmonaut OR “space travel” OR “space flight” OR “space exploration”) <u>AND</u> (cancer OR “cancer risk” OR tumorigenesis OR oncogenesis)</p>	<p>Results were restricted to records containing the search terms in the title or abstract to maximize the yield of relevant results as opposed to articles containing the search terms with no relevance to the research question.</p>

Appendix B

Honors Capstone Research Poster Presentation



COLLEGE OF NURSING

Honors Capstone Research (HCR) Summer Program 2023

Cancer Risk in Human Spaceflight & Directions for Space Nursing: A Rapid Scoping Review

Brighton B. Krejci, mentor Dr. Azita Amiri
College of Nursing

Introduction

Humans will have a higher risk of developing cancer during future missions into deep space as they travel beyond the magnetosphere.

- 650-day mission to Mars likely to result in radiation dose beyond NASA's current 600 mSv career limit [1]

It will be important to understand all the risks associated with cancer in space to facilitate research of health-based countermeasures in the future and application of future nursing practice beyond Earth.

Research Aims:

- Determine the general scope of research activity in spaceflight cancer risk research
- Find out what is known from literature about causes and risk factors of carcinogenesis in spaceflight
- Discuss how nursing can contribute to space health and space cancer research in the future

Preliminary Results - Full-Text Level

- Potentially eligible articles found in 35 different journals
 - Life Sci Space Res with most publications (n = 10)
- 77 unique publications screened at full-text
- Most studies dealt with cell samples
- Many different types of studies done
- No published literature from nursing backgrounds

Potential Risk Factors for Cancer in Space

- Radiation
 - Extensive but localized DNA damage from heavy, high-charge (HZE) particles common in space [2]
- Microgravity
 - Microgravity and radiation interact to produce more chromosomal aberrations than each alone [3]
- Environmental toxins
 - Benzene and ethylbenzene elevated in areas where crew spent time and produced by waste disposal [4]
- Impaired immune system function
 - Cytotoxicity of NK cells reduced in space, significantly inhibited in rookie crewmembers [5]

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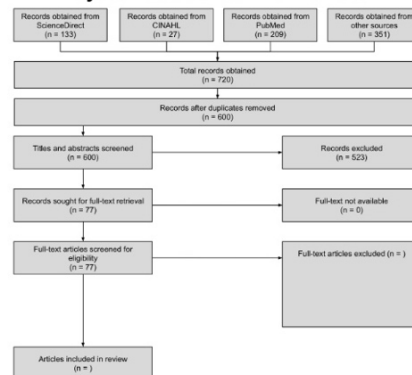
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Methods

We used PRISMA-ScR guidelines to perform a scoping review of literature.

- Search conducted in June 2023 across 3 databases using keywords based on common terms for cancer and spaceflight
- Results subjected to a systematic review process and screened for relevance
- Once screened at title and abstract level, full-text requested via interlibrary loan and screened again
- Data regarding type of study, study findings, subjects, and journal of publication were extracted

Systematic Screen Flow Chart



Impact & Conclusions

Cancer risk research in space is multifaceted and has many ongoing inquiries. New deep space exploration endeavors such as NASA's Artemis program promise opportunities to generate new understandings of and develop new treatments for health risks including cancer.

- Nursing research can contribute by collaboration with other health disciplines
- Study of therapeutic approaches to risk reduction and endorsement of educational programs or classes to encourage nursing involvement in space health research

