

A guide to preventing uterine cancer in female NASA astronauts through physical activity during space travel

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ABSTRACT

Today, thanks to scientific advances, space travel is on the rise. However, astronauts encounter numerous challenges during their space voyages, including the effects of space radiation and microgravity. Interestingly, female astronauts experience a greater number of side effects compared to their male counterparts. Certain research has indicated that female astronauts are prone to various types of cancers, particularly uterine cancer, as a consequence of prolonged space journeys and exposure to space radiation and microgravity. Conversely, physical activity has long been recommended as a cost-effective measure for managing or preventing cancer. Therefore, the present study aims to provide a concise overview of the impacts of space radiation and microgravity on female astronauts. Furthermore, it seeks to emphasize, for the first time, the significance of physical activity specifically for the prevention of uterine cancer among female astronauts. This study serves as a brief review of previous findings, potentially opening a new avenue for NASA researchers and exercise physiologists to explore. Finally, this study proposes a concise guide outlining three sections of physical activity for female astronauts: before, during, and after space travel. This guide aims to assist female astronauts in maintaining their physical well-being and reducing the risk of uterine cancer.

Keywords: Cancer prevention, Physical activity, NASA, Female astronauts, Immune system.

Cite this article as:

Ahmadi Hekmatikar, A. H., Fernández-Lázaro, D., López Llorente, A., & Kazemi, A. (2025). A guide to preventing uterine cancer in female NASA astronauts through physical activity during space travel. *Physical Activity, Exercise and Cancer*, 2(2), 52-62. <https://doi.org/10.55860/MWMT2528>

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Submitted for publication August 13, 2025.

Accepted for publication September 30, 2025.

Published October 02, 2025.

[Physical Activity, Exercise and Cancer.](#)

©Asociación Española de Análisis del Rendimiento Deportivo. Alicante. Spain.

Identifier: <https://doi.org/10.55860/MWMT2528>

INTRODUCTION

Human space flights and deep space explorations have fuelled the curiosity of the National Aeronautics and Space Administration (NASA) scientists, pushing them to venture further into the cosmos in search of new discovery (Bromberg., 2000). Numerous national space agencies, such as the European Space Agency (ESA), the Japan Aerospace Exploration Agency (JAXA), NASA, and the Canadian Space Agency (CSA), dispatch numerous astronauts for scientific explorations in deep space (Bromberg., 2000). Presently, approximately half of the individuals undergoing astronaut training are women (Ronca et al., 2014). However, as of 2014, only 15% of NASA astronauts who completed missions were women (Ronca et al., 2014). In addition to the challenges associated with space travel, such as the stresses of reaching space and the forces of vibration and acceleration, microgravity and radiation pose the most significant risk (Cortés-Sánchez et al., 2021). Despite advancements in oncology research, which have identified cancer as the leading cause of death worldwide due to various factors (Siegel et al., 2018), the incidence of this disease is on the rise among female astronauts who are exposed to hazardous radiation and other contributing factors (Drago-Ferrante et al., 2022).

On the contrary, the significance of physical activity as a cost-effective remedy for various diseases has been emphasized in several studies, highlighting its role in preventing or managing cancer before its onset, as well as reducing treatment-related side effects and aiding in recovery. The relationship between physical activity and cancer has garnered attention from scientists approaching it from physiological and immunological perspectives, as it holds potential for cancer management (McTiernan et al., 2019; Friedenreich et al., 2010; Westerlind et al., 2003). However, despite the importance of physical well-being for female astronauts, there is a lack of studies recommending the importance of physical activity in the prevention or management of cancer specifically for this group. Therefore, the present study aims to propose physical activity guidelines that focus on immunological changes for female astronauts, enabling them to prioritize their physical health and cancer prevention. The objective is to provide a comprehensive overview of existing knowledge derived from studies conducted on Earth, while also identifying research questions and challenges that necessitate further investigation to pave the way for NASA astronauts.

FIRST PART: FACTORS AFFECTING CANCER IN FEMALE ASTRONAUTS

Several environmental factors, including space radiation and microgravity, may play a role in the potential elevation of tumour formation risk and the potential cellular mechanisms linked to space travel (Moreno-Villanueva et al., 2017). Additionally, several studies have indicated that female astronauts are susceptible to cancer as a result of their exposure to space radiation and microgravity (Nassef et al., 2019a, 2019b; Kopp et al., 2016; Deng et al., 2019; Dietz et al., 2019; Kennedy et al., 2018). It is established that space radiation can induce DNA damage, genomic instability, mutagenesis, chromosomal abnormalities, and neoplastic transformation in female astronauts, leading to biological effects (Blakely et al., 1998).

One of the crucial concerns regarding female astronauts pertains to their exposure to space radiation (Rose et al., 2022). Crew members traveling in minimally shielded spacecraft during interplanetary journeys are more susceptible to acute high-dose radiation exposure (Rose et al., 2022). It has been observed that the composition of cells, extracellular matrix, and tissue stroma is the primary determinant of radiation response in space (Rose et al., 2022). Generally, tissues rich in activated stem cells exhibit greater radiosensitivity, while predominantly differentiated tissues or those comprising substantial stromal and acellular components are relatively more resistant to radiation (So et al., 2007). In women, the ovaries are highly sensitive to radiation (So et al., 2007). Disruption of hormone production due to radiation exposure can increase the risk

of uterine cancer (So et al., 2007). Regarding radiation sensitivity, the vagina shares similarities with other mucous membranes, while the vulva, labia, and clitoris exhibit greater sensitivity to radiation (Prasad, 2020). A study investigating the impact of simulated radiation on female mice revealed a 32% incidence of uterine cancer in the group exposed to space radiation, compared to the control group. These findings indicate that heavy ion radiation can induce ovarian tumours in women (Watanabe et al., 1998a). In a separate investigation, the impact of heavy ion and X-ray radiation on tumorigenesis in B6C3F1 mice was examined by exposing them to 426 mg of carbon ion beam radiation at 290 MeV/U (LET 210-60 KeV/micron) with a dose rate of +400. Consistent with previous studies, this research demonstrated that space radiation can contribute to a 25-41% increase in ovarian and uterine cancer among women (Watanabe et al., 1998b). Supporting these findings, other studies also strongly affirmed the significant influence of simulated space and ion radiation on ovarian and uterine cancer in female mice (Nitta et al., 2003; Mishra et al., 2018). However, the results of these studies are predicated on the hypothesis that exposure to space radiation during space missions can lead to uterine and ovarian cancer upon returning to Earth (Nitta et al., 2003; Mishra et al., 2018). In one study, where fixed human cervical carcinoma (HeLa) cells were examined aboard the Russian MIR space station, researchers reported that space radiation could induce DNA damage in female astronauts, with the extent of damage contingent upon the duration of the flight and the specific space environment (Ohnishi et al., 2002).

One crucial operational procedure for female astronauts involves the utilization of hormonal contraception to suppress ovarian function, prevent pregnancy, and diminish menstrual flow or induce amenorrhea during preflight training and space travel (Jain et al., 2016). Consequently, considering the current lack of comprehensive knowledge in this area, the use of contraceptive and hormonal methods during long-term space missions may potentially contribute to cervical cancer in female astronauts (Jain et al., 2016). However, it has been reported that the use of these hormonal methods can increase the risk of human papillomavirus (HPV) infections in astronauts, and HPV infections can lead to cervical cancer (Maglennon et al., 2012). Immune dysregulation, impaired natural killer (NK) cell function, and reduced activation of T cells have been documented during spaceflight (Bigley et al., 2019; Martinez et al., 2015). Both short-duration and long-duration spaceflights can reactivate dormant herpesvirus infections (Rooney et al., 2019). Nevertheless, the compromised immune system function and the heightened susceptibility or activation of respiratory infections, particularly HPV, may impact the development of uterine cancer.

One of the primary challenges faced by female astronauts is the exposure to microgravity conditions (Rose et al., 2022). These conditions encompass the impact of weightlessness on gonadal function and fertility, as well as secondary stressors during spaceflight, such as sleep disruption, which may negatively affect uterine health during and after space missions (Rose et al., 2022). In addition to concerns regarding radiation-induced DNA damage, various molecular studies contribute to the hypothesis that individual susceptibility may increase under microgravity conditions, as crucial signalling pathways implicated in carcinogenesis can be dysregulated in such environments (Moreno-Villanueva et al., 2017, 2019). An illustrative example is the phosphoinositide-3 kinase (PI3K) signalling pathway, which plays a pivotal role in cellular metabolism, survival, and proliferation in response to growth factor stimulation (Dai et al., 2014; Najrana et al., 2016). In a simulation study, researchers reported that the combined effects of space radiation and microgravity, as observed in a simulated setting, can promote the growth of ovarian cancer cell lines. Specifically, a cell line named LN1 derived from a mixed molar ovarian tumour exhibited significant growth under the influence of space radiation and microgravity, providing favourable conditions for the proliferation of multipotent cell (Becker et al., 1993). Several other studies have similarly demonstrated that exposure to simulated microgravity can activate signalling pathways associated with tumour growth and cancer cells in relation to ovarian cancer (Becker et al., 1993; Przystupski et al., 2021).

Hence, the aforementioned studies present alarming findings indicating that female astronauts are susceptible to cancer development, necessitating the implementation of effective interventions and recommendations to mitigate or prevent this disease (Figure 1).

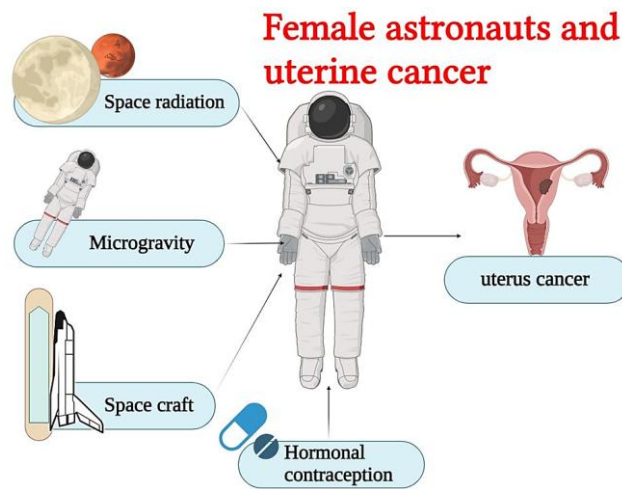


Figure 1. The effect of space travel on uterine cancer of female astronauts.

THE SECOND PART: APPROPRIATE TRAINING DOSE RESPONSE

Exercise immunology in female astronauts

One of the crucial aspects of the human body that exhibits significant responses to physical activity is the immune system (Mackinnon et al., 1986; 1987). Numerous studies have demonstrated the beneficial effects of sports activity on enhancing immune system functionality (Hoffman-Goetz et al., 1986; Hoffman-Goetz et al., 1988; Pedersen et al., 2000; Tvede et al., 1989; Nieman., 1994). When investigating the impact of sports interventions on the immune system, researchers consider two perspectives: the changes in the innate immune system and the acquired immune system (Shephard et al., 1991). The innate immune system represents the initial immune response triggered upon encountering pathogens or foreign substances, characterized by its rapid but non-specific nature (Maggini et al., 2018). Key components of the innate immune response include phagocytes like macrophages and monocytes, neutrophils, mast cells, eosinophils, among others. On the other hand, T and B cells are specialized cells responsible for long-term immunity (Maggini et al., 2018). These cells identify antigens and promptly initiate specific immune responses tailored to combat particular pathogens. Cytotoxic T cells, distinguished by the CD+8 receptor, eliminate infected or tumour cells, while helper T cells, identified by the CD+4 receptor, assist other immune cells in their functions (Maggini et al., 2018).

Today, studies in the field of exercise immunology emphasize the significance of the acquired immune system, as it plays a crucial role in combating cancerous tumours (Maggini et al., 2018; Lavín-Pérez et al., 2023). To illustrate, a meta-analysis study examined the impact of physical activity on CD+4 and CD+8 tumour-specific immune cells, as well as natural killer (NK) cells. The researchers concluded that breast cancer patients can enhance the performance of tumour-specific immune cells through moderate-intensity aerobic and resistance exercises (45-65% and 50-70% 1RM) (Lavín-Pérez et al., 2023). Although this particular study does not directly relate to the present research, its aim was to emphasize the improvement of tumour-specific immune cell function even in the presence of cancer. Additionally, an important aspect in the context of physical activity is the acute and chronic effects it has on the body's immune system.

Acute responses

The acute response of the immune system to exercise is influenced by the intensity and duration of the physical effort. Research indicates that during bouts of moderate and vigorous aerobic exercise lasting less than 60 minutes, there is an increase in the anti-pathogenic activity of tissue macrophages, as well as elevated levels of circulating immunoglobulins, pro-inflammatory cytokines, neutrophils, NK cells, cytotoxic T cells, and immature B cells (Bigley et al., 2019; Adams et al., 2011; Gupta et al., 2018; Simpson et al., 2012, 2015, 2017, 2020; Bigley et al., 2014). Studies demonstrate that acute exercise preferentially mobilizes NK cells and CD8+ T lymphocytes, which possess high cytotoxicity and the ability to migrate to tissues (Bigley et al., 2014). Moreover, stress hormones, which can suppress immune cell function, and pro-inflammatory cytokines, which indicate intense metabolic activity, do not reach high levels during short- to moderate-duration exercise sessions (Bigley et al., 2014). Nonetheless, these findings generally suggest that acute exercise plays a significant role in stimulating the continuous exchange of leukocytes between the circulation and tissues, thereby contributing to the immune system (Adams et al., 2011; Gupta et al., 2018; Simpson et al., 2012, 2015, 2017, 2020; Bigley et al., 2014). However, it is important to note that the positive effects of acute exercise, particularly moderate to intense exercises, are short-term and temporary in nature.

Heavy physical activity is prohibited

One concerning finding in exercise immunology studies is the limited attention given to the impact of intense sports activities on the decline of the body's immune system. The current body of evidence suggests that high-volume exercise training can induce physiological and immunological stress, ultimately leading to dysfunction within the system (Peake et al., 2015, 2017a). Examining the specifics of these studies reveals that heavy acute training can result in a decrease in the functionality of NK cells and T cells. Depending on the extent of the training, this decline in performance may persist for up to 24 hours in some cases, and in certain instances, up to 4 days (Peake et al., 2015, 2017a, 2017b). Other studies have also demonstrated that intense physical activity can cause significant disruptions in metabolites. These exercise-induced disturbances in metabolites, lipid mediators, and proteins are likely to have a direct impact on immune function (Nieman et al., 2018).

Acute exercise recommendations for female astronauts

Based on the reviewed studies, it appears that acute physical activity with moderate to intense intensity can serve as an immune strategy to enhance the functioning of the body's immune system (Adams et al., 2011; Gupta et al., 2018; Simpson et al., 2012 2015, 2017, 2020; Bigley et al., 2014). However, the drawback of acute exercise is that its immunological responses are short-lived and lack long-term immunological adaptation (Adams et al., 2011; Gupta et al., 2018; Simpson et al., 2012 2015, 2017, 2020; Bigley et al., 2014). From one perspective, implementing acute training for female astronauts prior to long-duration space flights may prove to be an ineffective strategy. From another perspective, following the return of female astronauts from space flights, where the function of the body's immune system is known to decline, engaging in acute exercises with moderate intensity based on non-space studies could potentially act as a positive immunological stress to restore the function of the body's immune system (Pedersen et al., 2000; Kaushik., 2024). However, high-intensity training raises concerns regarding potential further suppression of the body's immune system and increased vulnerability to viruses (Kaushik., 2024). Nevertheless, no studies have yet been conducted to fully elucidate the importance of this issue (Figure 2).

Chronic responses

The focal point of exercise immunology studies revolves around the realm of chronic responses resulting from sports training. Numerous studies strongly support the notion that regular physical activity with moderate intensity (55 to 65% VO₂MAX), conducted on a consistent basis (3-4 sessions per week, lasting 45 minutes

to 1 hour), can lead to improved immune system function (Wang et al., 2020; Keast et al., 2020; Scheffer et al., 2020). This improvement may manifest as an increase in the number and activity of T and NK cells, as well as anti-inflammatory cytokines, both in tissues and blood (Wang et al., 2020; Keast et al., 2020; Scheffer et al., 2020). Additionally, immunostaining characteristics include a reversed CD4+/CD8+ T cell ratio and an elevated frequency and proportion of senescent T cells. It has been hypothesized that regular exercise could promote the selective apoptosis of these senescent T cells, paving the way for their replacement with "younger" T cells capable of responding to new antigen. Examining the results of the studies, it appears that moderate-intensity aerobic exercises, such as running (conducted over 6 to 12 weeks, 3 to 5 sessions per week), can effectively enhance chronic immunological responses (Peake et al., 2017a, 2017b; Salimans et al., 2022). However, high-intensity resistance training (at 50 to 70% 1RM) can also yield positive effects on immunological responses (Salimans et al., 2022; Flynn et al., 1999), albeit not as substantial as those achieved through cardiovascular exercises (Figure 2).

Chronic exercise recommendations for female astronauts

It is evident that moderate-intensity aerobic exercises can result in long-term immunological adaptations, leading to improved functioning of the body's immune system (Mackinnon et al., 1986, 1987; R. Simpson et al., 2020; Wang et al., 2020; Keast et al., 2020; Scheffer et al., 2020). This enhancement can have a positive impact on tumour-specific immune cells, which is a significant milestone in cancer prevention or management (Mackinnon et al., 1986, 1987; R. Simpson et al., 2020; Wang et al., 2020; Keast et al., 2020; Scheffer et al., 2020). Based on previous studies, it appears that female astronauts can engage in moderate-intensity aerobic exercises, along with resistance training, for a period of 6 to 12 weeks prior to spaceflight (Mackinnon et al., 1986, 1987; R. Simpson et al., 2020; Wang et al., 2020; Keast et al., 2020; Scheffer et al., 2020). Although resistance training may not have a substantial effect on improving immune system function, the improvement in muscle tone and the secretion of myokines play a vital role in enhancing immune system performance. Additionally, moderate-intensity aerobic exercise during space travel can contribute to the optimization of immune system function. Finally, after returning from space, it seems that female astronauts are less likely to experience a decline in immune system function (Figure 2).

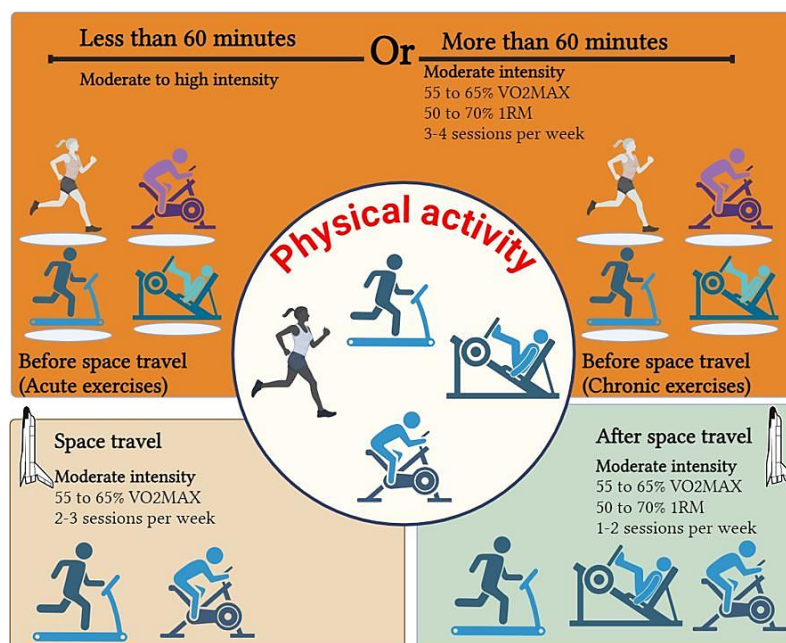


Figure 2. Physical activity guide for female astronauts.

DISCUSSION

Despite significant advancements in scientific research, there are still valuable gaps that need to be addressed in order to yield valuable results for future studies. This study aimed to provide a physical activity guide specifically tailored for female astronauts, with a focus on addressing the side effects of radiation and microgravity, particularly the risk of cancer. However, our current understanding of this subject is still in its early stages, and more comprehensive investigations are needed to unravel the underlying mechanisms. The present study highlighted several important points from different perspectives. Firstly, it emphasized that cancer can be a significant concern for female astronauts, warranting attention and proactive measures. Secondly, it underscored that acute physical activity is not a suitable strategy for space flights, as it does not lead to the desired immunological adaptations. Moreover, acute exercises upon returning to Earth from space travel may not be an effective approach. However, the study highlighted that intensive training before space travel can potentially lead to a decline in the immune system. Lastly, it emphasized that a period of 6 to 12 weeks of aerobic exercises can result in a substantial improvement in the body's immune system. Female astronauts can also incorporate aerobic exercise during space travel to maintain an enhanced immune system. Ultimately, the study emphasized the importance of the immune system in potentially mitigating the side effects of radiation and microgravity, including the development of cancer. It is crucial to acknowledge that this study provides a foundation for future research and sheds light on important aspects to be explored further.

CONCLUSION

The prevention of uterine cancer in female astronauts is a key issue that must be studied for the future, given that the presence of women in the aerospace field is constantly increasing. The immune system can mitigate the side effects generated by microgravity and radiation related to the development of uterine cancer. Therefore, it is necessary to implement long-term physical activity protocols focused on improving the immune system. In turn, further research is needed to determine the ideal amount of physical activity, as well as specific protocols for the prevention of uterine cancer in female astronauts.

AUTHOR CONTRIBUTIONS

Idea, conceptualization, project administration and editing, A.A.H., A.K.; writing—original draft preparation, A.A.H., D.F.-L.; analysis and editing, A.L.L. Authors have read and agreed to the published version of the manuscript.

SUPPORTING AGENCIES

This study has been financed by the Department of Education of the Junta de Castilla - León and the European Regional Development Fund (FEDER) by TCUE Plan 2024-2027; grant no. (067/230003 POC).

DISCLOSURE STATEMENT

No potential conflict of interest was reported by the authors.

ACKNOWLEDGMENTS

The authors would like to thank the Department of Education of the Junta de Castilla—León for funding the study. Also, the authors want to thank the Neurobiology Research Group, Faculty of Medicine of the University of Valladolid for their collaboration.

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