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Extraterrestrial Gynecology: Could Spaceflight Increase the Risk of Developing Cancer in Female Astronauts?

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COST is supported by the EU Framework Programme Horizon 2020

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Background

- Outer space is an extremely hostile environment for human life, due to ionizing radiation from galactic cosmic rays and microgravity.
- Spaceflight has also been shown to have an impact on established cancer hallmarks, possibly increasing carcinogenic risk.
- Terrestrially, women have a higher incidence of radiation-induced cancers.
- Females are permitted to spend significantly less time in space than men.

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Aims

- To focus on the effects of microgravity and radiation on the female reproductive system, particularly gynecological cancer
- To provide a summary of the research which has been carried out related to the risk of gynecological cancer
- To highlight what further studies are needed to pave the way for safer exploration class missions, as well as postflight screening and management of women astronauts following long-duration spaceflight

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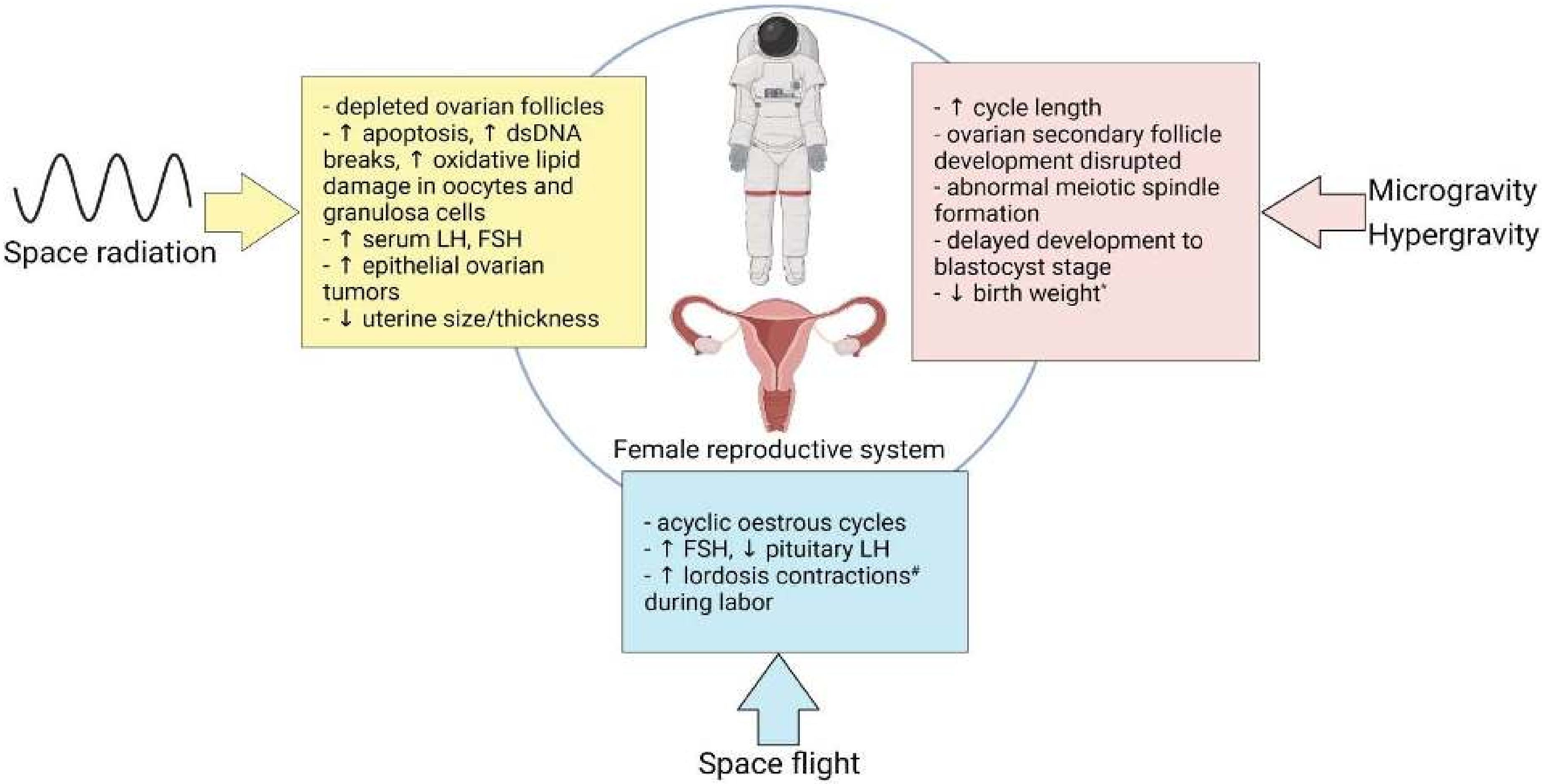
Radiation effects on female reproductive function		
Age	**Dose, mGy**	**Effect**
All ages	1700	Temporary sterility lasting 1-3 years
	1250-1500	Amenorrhea in 50%
	3200-6250	Permanent sterility
Ages 15-40	1250-2500	Temporary amenorrhea
	2500-5000	Ovulary suppression in 40-100%
	5000-8000	Permanent ovulary suppression in 40-100%
	8000-20000	Permanent ovulary suppression in 100%



- depleted ovarian follicles
- ↑ apoptosis, ↑ dsDNA breaks, ↑ oxidative lipid damage in oocytes and granulosa cells
- ↑ serum LH, FSH
- ↑ epithelial ovarian tumors
- ↓ uterine size/thickness
Space radiation
- ↑ cycle length
- ovarian secondary follicle development disrupted
- abnormal meiotic spindle formation
- delayed development to blastocyst stage
- ↓ birth weight*
Microgravity
Hypergravity
Female reproductive system
- acyclic oestrous cycles
- ↑ FSH, ↓ pituitary LH
- ↑ lordosis contractions# during labor
Space flight

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Space Radiation

What are the effects on carcinogenesis?

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List of studies showing effects of space radiation on cancer risk – Part 1				
Cell type	**Radiation model**	**Cell/animal model**	**Effect**	**Study**
Lung cells	Iron ion (Fe) beam (180 MeV/nucleon; LET 300 keV/µm) for 0.1 Gy	SV40-immortalized human bronchial epithelial cells (NL20)	Progeny of Fe-irradiated cells showed elevated micronucleus formation, increased markers for DNA double-strand breaks (γ-H2AX foci), reduced cell proliferation, persistent oxidative stress, and increased colony formation.	Cao et al., 2018
Lung cells	^{56}Fe (600 MeV/u at 0, 0.1, 0.3, 1.0 Gy) and ^{28}Si (300 MeV/u at 0, 0.3, 1.0 Gy) high-LET irradiation	Immortalized human bronchial epithelial cell line (HBEC3- KT)	Global differential CpG island methylation in response to ^{56}Fe and ^{28}Si ion exposure suggests a lasting impact on the epigenome relevant to lung cancer	Kennedy et al., 2018
Spleen cells	0.5 Gy Proton irradiation (1-GeV; LET 0.24-keV/µm)	Murine Lewis lung carcinoma (LLC) cells-bearing C57BL/6 mice	Upregulation of genes involved in DNA repair and cell cycle, including CDK2, MCM7, CD74 and RUVBL2	Wage et al., 2015

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List of studies showing effects of space radiation on cancer risk – Part 2

Cell type	Radiation model	Cell/animal model	Effect	Study
Hematopoietic stem cells	100 cGy of 1000 MeV/n protons (LET 0.23 keV/micron); ^{28}Si 300 MeV/n ions (LET 70 keV/micron)	$Mlh1^{+/-}$ mice (B6.129-$Mlh1^{tm1Rak}$/NCI) representing loss of MLH1 that occurs in human hematopoietic stem cells with age	High-LET ^{28}Si ion irradiation affected hematopoietic stem cell differentiation; high-LET irradiation caused early and higher incidence of tumorigenesis in Mlh1 heterozygous mice; Frequent occurrence of T-cell rich B-cell (TRB) lymphomas with altered mismatch repair pathway	Patel et al., 2020
Intestinal cells	^{56}Fe-irradiation (1.6 Gy; energy-1000 MeV/nucleon; LET-148 keV/μm)	Intestinal tissue from Female C57BL/6J mice	^{56}Fe-irradiation upregulated metabolites belonging to prostanoid biosynthesis and eicosanoid signaling pathways linked with cellular inflammation, which has been associated with intestinal inflammatory disease and colon cancer	Cheema et al., 2014
Liver cells	^{56}Fe ion irradiation (1 GeV/nucleon)	CBA/CaJ mice	Higher incidence of hepatocellular carcinoma than γ-irradiated mice	Weil et al., 2009

List of studies showing effects of space radiation on cancer risk – Part 3				
Cell type	**Radiation model**	**Cell/animal model**	**Effect**	**Study**
Kidney cells	^{56}Fe ions irradiation (1 GeV/amu, 151 keV/µm)	Aprt heterozygous ($Aprt^{+/-}$) B6D2F1 mice	Increased mutant frequencies leading to DNA damage	Turker et al., 2017
Normal human foreskin fibroblast cells	Kept at the International Space Station (14 days)	AG1522 cells	Larger size γ-H2AX foci suggest DNA damage	Lu et al., 2017
Normal human foreskin fibroblast cells	Kept at the International Space Station (14 days)	AG1522 cells	Downregulation of miRNA Let-7a, which was found to be downregulated to γ ray and UV ray radiation	Zhang et al., 2016

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Studies on effects of irradiation on gynecological tissues – Part 1

Tissue type	Radiation type	Cell/animal models	Effect	Study
Ovarian	0.439 Gy as a 290 MeV/u carbon-ion beam (LET 10 keV/micron)	B6C3F1 mice	Induction of ovarian tumors	Watanabe et al., 1998
	0.426 Gy heavy ion irradiation of 290 MeV/u carbon-ion beam (LET 60-210 KeV/micron) at the dose rate of 0.4 +/- 0.2 Gy/min; 0.5 Gy of X-ray irradiation at 0.1 Gy/min or 5 Gy of X-ray irradiation at 1 Gy/min	B6C3F1 mice	Tumorigenicity was lower for heavy ion than for 0.5 Gy and 5 Gy X-ray irradiation	Watanabe et al., 1998
	high and low LET radiations. 1.0 Gy monoenergetic neutrons (0.317, 0.525 and 1.026 MeV), 252Cf fission neutron (2.13 MeV) or 137Cs g-rays	C57BL/6N mice	Higher effectiveness of neutrons than g-rays to induce oocyte and pregranulosa cell apoptosis correlates with the inhibition of granulosa cell tumor development	Nitta & Hoshi, 2003
	HZE particles. 50 cGy iron ions	C57BL/6J	Induction of ovarian tumors	Mishra et al., 2018

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Studies on effects of irradiation on gynecological tissues –Part 2				
Tissue type	**Radiation type**	**Cell/animal models**	**Effect**	**Study**
Cervical	spaceflight (cells were flown on "Russian MIR space station or on the Space Shuttle)	HeLa human cervical cancer cells	Increased DNA damage	Ohnishi, et al., 2002
Endometrial	Monoenergetic protons (1–10 Gy; LET 8.35 keV/μm and 4.86 MeV) and γ-rays (0.2–1.6 Gy)	Human endometrial carcinoma cell lines (HEC1B and AN3CA cells)	Decreased cell survival	Palumbo et al., 2001

Microgravity

What are the effects on carcinogenesis?

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List of studies showing effects of microgravity on cancers – Part 1

Cancer type	Microgravity model	Model	Effect	Study
Breast cancer	6 min of r-µg*; PF** maneuvers	MCF-7 cell line	Rearrangement of F-actin and tubulin, appearance of filopodia- and lamellipodia-like structures; PF induced differential regulation of KRT8, RDX, TIMP1, CXCL8 (up), VCL, and CDH1 (down) genes	Nassef et al, 2019
Breast cancer	Exposure to an RPM##	MCF-7 cell line	Cells formed multicellular spheroids resembling epithelial ducts; Microgravity induced differential regulation of IL8, VEGFA, FLT1, ESR1 (up), ACTB, TUBB, FN1, CASP9, CASP3, PGR1 (down) genes	Kopp et al., 2016
Breast cancer	PF** maneuvers; incubator RPM#	MDA-MB-231 cells	Differential regulation of ICAM1, CD44, ERK1, NFKB1, FAK1 (up), ANXA2, and BAX (down) genes	Nassef et al, 2019
Glioma	Exposure to an RPM##	U251 cells	Induction of apoptosis, Reduced FAK/RhoA/Rock and FAK/Nek2 signaling events	Deng et al., 2019

* r-µg: real microgravity; # s- µg: simulated microgravity; ** PF: parabolic flight; ##RPM: Random Positioning machine (simulated microgravity)

List of studies showing effects of microgravity on cancers – Part 2

Cancer type	Microgravity model	Model	Effect	Study
Lung cancer (non small cell)	Exposure to an RPM##	NCI-H1703 (CRL-5889) cells	Formation of multicellular spheroids; spherical rearrangement of actin filaments in the outer region of cytoplasm; increased apoptosis, Upregulation of TP53, CDKN2A, RB1, PTEN, SOX2 in stimulated adherent cells	Dietz et al., 2019
Melanoma	Exposure to a 3-D Clinostat	A375 cells	Decreased cell viability; Increase in caspase 3/7 activity; reduced cell proliferation; change in cell morphology (presence of membrane blebbing lamellipodia, and stress fibers, absence of filopodia)	Przystupski et al., 2021
Thyroid cancer	Exposure to an RPM##	FTC-133 cells	Cells formed multicellular spheroids; Differential regulation of ERK1, EGF (up), CTGF, and CAV (down) genes in multicellular spheroids	Warnke et al., 2014
Thyroid cancer	10-day of r-µg*	FTC-133 cells	Differential expression of IL6, IL7, IL8, VEGF, TIMP1, MMP3, CCL4, B2M (up) proteins	Riwaldt et al., 2015

* r-µg: real microgravity; # s- µg: simulated microgravity; ** PF: parabolic flight; ##RPM: Random Positioning machine (simulated microgravity)

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Studies on effects of space flight and simulated gravity on gynecological tissues – Part 1				
Tissue type	**Microgravity/space flight**	**Cell/animal models**	**Effect**	**Study**
Ovarian	simulated microgravity RWV	LN1 human ovarian tumor cells	LN1 cells grew as spheroids free in suspension	Becker et al., 1993; Goodwin et al., 1997
	spaceflight (cells were cultured on the ISS)	LN1 human ovarian tumor cells	Cells showed reduced expression of vimentin and epithelial membrane antigen (EMA)	Hammond et al, 2005
	simulated microgravity 3D-C	SKOV-3 human ovarian cancer cells	Cells showed reduced proliferation, migration and higher sensitivity of cancer cells to the cisplatin	Przystupski et al., 2021
	microgravity	set of systems-biology tools and databases	identified several cancer related signatures induced by microgravity	Mukhopadhyay et al.,2016

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Studies on effects of space flight and simulated gravity on gynecological tissues – Part 2				
Tissue type	**Microgravity/space flight**	**Cell/animal models**	**Effect**	**Study**
Cervical	simulated microgravity RWV	Co- colture of HUVEC and tumor primary cells	Co-culture presented tubular structures penetrating the tumor cell masses	Chopra et al., 1997
	simulated microgravity hydrofocusing bioreactor (HFB) and rotary cell culture system (RCCS)	HeLa human cervical cancer cells	HFB exposure increased CD133-positive cell growth	Kelly et al., 2010
	spaceflight (cells were flown on ''Shen Zhou IV'' space shuttle mission)	Human cervical carcinoma CaSki cells	Cells exhibited morphologic differences, characterized by rounder, smoother, decreased, smaller and low-adhension cells. Furthermore, space-grown cells showed altered gene expression that generally corresponded to changes in genes regulating the cell cycle, cell morphology, apoptosis and signal transduction	Zhang, Z. J. et al., 2011; Guo, F. et al., 2012

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Studies on effects of space flight and simulated gravity on gynecological tissues – Part 3				
Tissue type	**Microgravity/space flight**	**Cell/animal models**	**Effect**	**Study**
Endometrial	simulated microgravity 3D-C	human endometrial stromal cells (eSCs)	Cells showed reduced proliferation and migration. This was accompanied by a simultaneous decrease in the phosphorylation of Akt and the level of matrix metalloproteinase (MMP)-2 and FOXO3a	Cho et al., 2019
	simulated microgravity RCCS	Human tumor primary cells	3D model endometrial cancer cell culture was established	Grun et al., 2009

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International Journal of
Molecular Sciences

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Extraterrestrial Gynecology: Could Spaceflight Increase the Risk of Developing Cancer in Female Astronauts? An Updated Review

Rosa Drago-Ferrante [1,†], Riccardo Di Fiore [3,4,†], Fathi Karouia [2], Yashwanth Subbannayya [5,†], Saswati Das [6,†], Begum Aydogan Mathyk [7,†], Shehbeel Arif [8], Ana Paula Guevara-Cerdán [9], Allen Seylani [10], Aman Singh Galsinh [11], Weronika Kukulska [12], Joseph Borg [13], Sherif Suleiman [3], D. Marshall Porterfield [14], Andrea Camera [15], Lane K. Christenson [16], April E. Ronca [17], Jon G. Steller [19], Afshin Beheshti [18,*] and Jean Calleja-Agius [3,*]

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Conclusion

- Currently, there is no evidence to suggest that female astronauts have an increased incidence of gynecological cancers.
- Scarce knowledge about the impact of space radiation and microgravity on gynecologic cancer as there have been insufficient numbers of female astronauts exposed to long duration, low-dose rate, proton and heavy ion radiation to reliably determine the impact on the female reproductive system.
- With the upcoming missions, there will be longer duration of exposures to both microgravity and space radiation, hence the influence of flight length on risks related to gynecological cancers will demand a larger focus in ensuring astronaut safety during flight and post-flight.
- Among all body tissues, the male and female gonads are among the most sensitive to radiation. Therefore these tissues are the best to study to determine space radiation related exposures.

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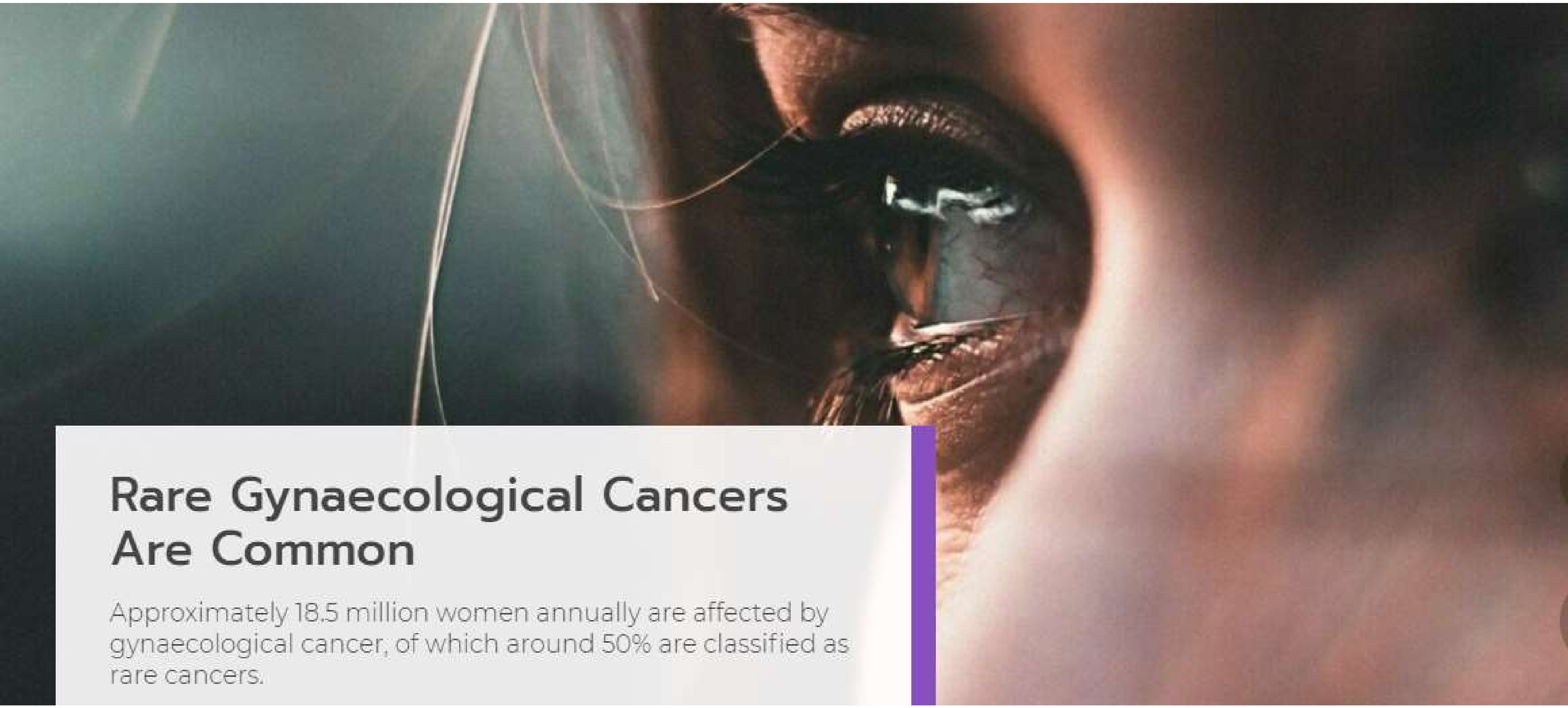
European network for Gynecological Rare Cancer research: From Concept to Cure (CA18117)



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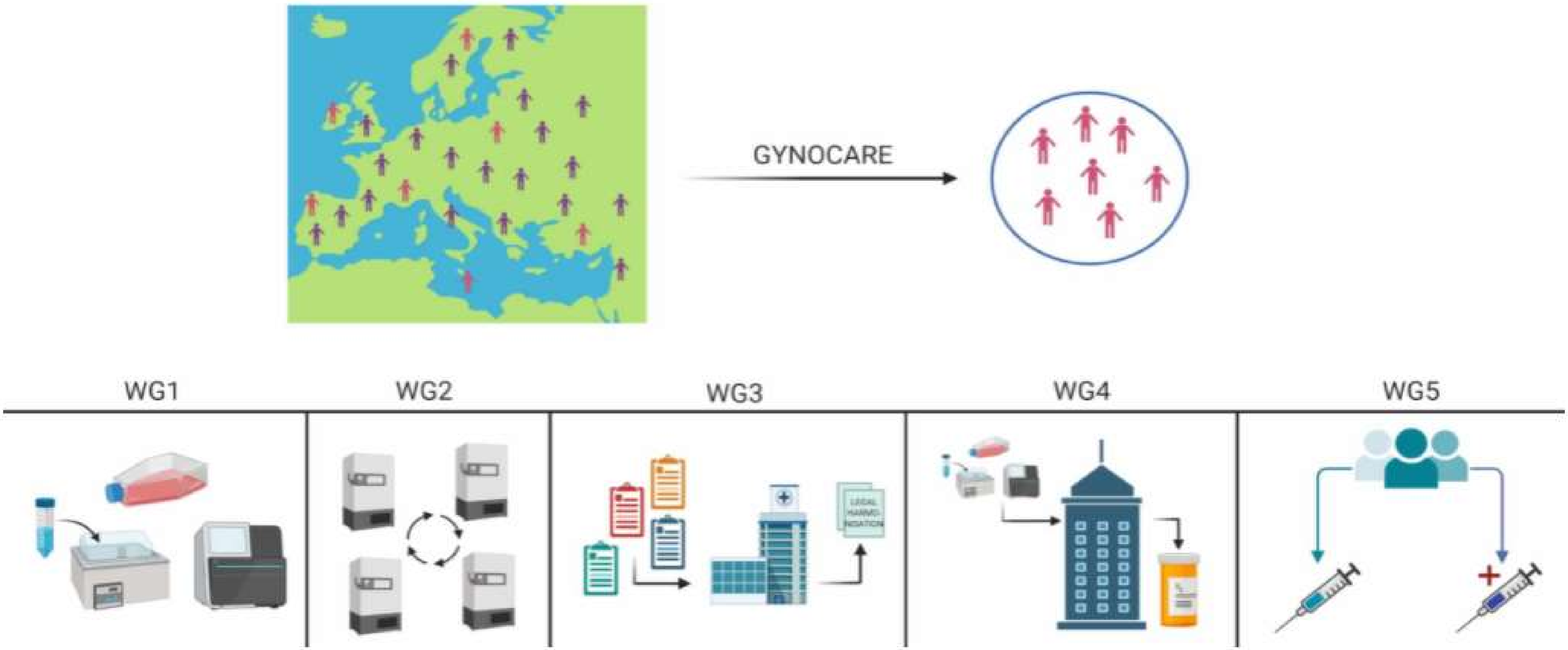

Acknowledgements

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Thank you!

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