UNIVERSITAT DE BARCELONA

Advancing in Endometrial Cancer Prevention: Exploring the Role of Circadian Disruption Factors and the Sensitivity of Cervicovaginal Cytology for its Detection

Jon Frias Gomez

PHD THESIS

Advancing in Endometrial Cancer Prevention: Exploring the Role of Circadian Disruption Factors and the Sensitivity of Cervicovaginal Cytology for its Detection

Doctoral thesis dissertation presented by

JON FRIAS GOMEZ

to apply for the degree of doctor at the University of Barcelona

September 2024

Doctoral programme in Medicine and Translational Research
Faculty of Medicine and Health Sciences
University of Barcelona

Supervised by

Laura Costas Caudet

Cancer Epidemiology Research Programme, Catalan Institute of Oncology,
IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain.

&

Ramon Cleries Soler

Cancer Plan, Catalan Institute of Oncology,
IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain.

Tutor: **Jordi Ponce Sebastià**, Department of Gynecology, IDIBELL, Hospital Universitari de Bellvitge,
L'Hospitalet de Llobregat, Barcelona, Spain.

Cover page

Eroriz ikasten

da oinez

ACKNOWLEDGEMENTS

La experiencia de poder realizar este doctorado ha sido muy gratificante, me ha permitido poner en práctica los conocimientos adquiridos durante mis años de carrera y máster, y seguir aprendiendo de mis compañeros. Esta aventura, que comenzó años antes, cuando decidí venirme de Euskadi a Barcelona a estudiar el grado de Ciencias Biomédicas, se consolidó en 2019 con mi matriculación en el doctorado. Y en todo este camino hay mucha gente a la que tengo que agradecerles su compañía.

Lehenik eta behin, nere ***familixiai***: ***ama, aita*** *eta* ***Laura***, **mila esker** bihotz-bihotzez nere onduan egotiagatxik. Sobre todo, en los momentos de bajón y dudas, cuando no sabía si estaba tomando el camino correcto. Por confiar siempre en mí, y animarme a seguir adelante. Y como no, también por alegraros de mis triunfos y celebrar conmigo todos mis logros. Kriston zorte ona daukat tokatu jaten ***familixiakin***. **Eskerrik asko!**

También quiero dar las gracias al equipo de Tumores Viejos: ***Bea, Laia A., Marisa, Miren*** y en especial, a ***Sara T.***, por su paciencia conmigo durante mis prácticas. Muchas gracias a todas por acogerme super bien cuando llegué al ICO a realizar mi TFM, involucrarme en vuestro grupo y hacerme disfrutar con la investigación. Fue un placer realizar el TFM con vosotras, y a partir de aquel TFM surgió después la oportunidad de poder realizar esta tesis.

Trabajar en el ***PREC*** ha sido una experiencia muy guay. He tenido la oportunidad de conocer a mucha gente muy TOP. Todas las compañeras que he tenido en el ***ZULO*** y en el grupo ***ParquecICO: Carlota, Laura M, Valerie, Esther, Lucia, Mercedes, Jazmin, Anna S., Sara H., Pili, Vicky, Carol, Xin,*** etc. Ha sido un placer compartir ratitos para desconectar, tomar el café y las comidas en el ***ParquecICO*** con muchas de vosotras. También, se merecen especial mención todas mis compañeras del ***Screenwide (Magda, Paula, Blanca, Gemma, Patricia, Álvaro*** *y* ***Marta)*** que han estado encargándose del trabajo de campo, sin vuestro trabajo esta tesis no existiría, **¡Mil gracias!** Trabajar codo con codo con vosotras ha sido muy fácil e incluso divertido. Dentro del grupo ***Screenwide***, también quiero agradecer a ***Yolanda***, por sus consejos estadísticos, siempre has estado dispuesta a ayudar y hacías que fuera muy fácil solicitarte consejo/ayuda con diferentes dudas estadísticas.

Mención aparte se merecen mis dos directores de tesis: ***Laura Costas*** *y* ***Ramon Cleries***. Ha sido un placer realizar esta tesis bajo vuestra supervisión, habéis hecho que lo complicado termine siendo más fácil, **¡Gracias!** Pero en especial, quiero agradecer a ***Laura***, por aguantarme todos estos años, estar siempre ahí para discutir mis dudas, y ayudarme a convertirme en un mejor científico. A largo de todos estos años hemos tenido nuestras pequeñas diferencias, ¿y quién no? Pero siempre hemos sabido superarlas y creo que esto me ha servido no solo para crecer como científico, sino también como persona. Ha sido un placer ser tu doctorando. Eso sí, con tu *toc* sigo teniendo una relación *amor/odio*. Al principio odio todos los pequeños fallos que eres capaz de detectar xd, pero al final, después de dedicarles tiempo y esfuerzo, tengo que reconocer que es verdad que el resultado final siempre termina mejorando mucho. Muchas gracias por haberme acompañado en todo este camino, esta tesis no sería ni la mitad de lo que es si no te hubiera tenido como directora. **¡Gracias Laura!**

Durante todos estos años que llevo viviendo en Barcelona, también he tenido la oportunidad de hacer no solo amigos, sino muy buenos amigos. Personas que siempre han estado ahí, dispuestas a tomar una cerveza, después de un mal día para mejorarlo, o después de un muy buen día para celebrarlo. ***Olalla***, te conocí nada más llegar a Barcelona y desde entonces siempre has estado ahí. **¡Muchas gracias!** También quiero agradecer a mis ***queridas María, Natalia*** *y* ***Vicky***, tres chicas estupendas y un poquito locas, pero que, sin vuestra compañía, mi vida hubiera sido más tranquila, pero también mucho más aburrida xd. Una mención especial se merecen también ***Richard, Héctor, Quim, Jorge*** *y* ***Jandro***, por ser compañeros de aventuras, de fiestas, de risas y de llantos. Me cuesta imaginarme una Barcelona sin todos vosotros. **Muchas gracias por ser tan buenos amigos**. También quiero agradecer a todos los amigos que hice gracias al ***Pink Spot***. Sois tantos que no tiene sentido mencionaros a todos uno a uno. Pero gracias a vosotros la pandemia del COVID fue mucho más llevadera. Los martes, jueves y sábados, y en todos los planes que surgían, siempre era un placer estar con vosotros. Y hoy en día, muchos seguimos siendo buenos amigos, ***¡Gracias!***

Kuadrilla be eskertu behar dot. 14 urte noia ja Bartzelonan bizitzen, baina Bergara bueltatzen naizen bakoitzian denboria ez dala pasau ematen dau. Kriston zorte ona daukat zuek lagun bezala eukitziagatxik, zuen alde on eta txar guztiekin, ez diela gutxi (broma xd). Askotan esaten dogun moduan: "*sois la familia que se elige*"; bueno, gure gurasoek aukeratu zebena

ikastola berdinian apuntatzian. Hala eta be, horrenbeste urte eta gero (eta askoz gehiaxau izatia espero dot) pentsatzia nahi dot, lagun onak izaten jarraitzen bou, guk ere zertxobait aukeratu izan dogula. **Mila esker** hain lagun onak izatiagatxik; zorte haundixa daukat **kuadrilla** honekin!

Ahora que me encuentro escribiendo estos agradecimientos desde Laredo, también quiero agradecer a mi ***kuadrilla de Laredo***. Sois muy buenos amigos, y aunque no nos veamos mucho a lo largo del año, los veranos sin vosotros, sin los paseos por la playa, la marmita y las fiestas por la puebla no serían lo mismo. **¡Muchas gracias por estar ahí!**

Y, por último, a ***todas las mujeres*** que han decidido participar en los diferentes estudios que integran esta tesis, y en particular, a todas aquellas que han formado parte del estudio ***Screenwide***. Gracias por vuestra generosidad al decidir participar en el estudio, compartir muestras biológicas y contestar la larga encuesta epidemiológica. Sin vuestra colaboración, esta tesis no hubiera sido posible. **¡Gracias!**

Mila esker guztioi!

Pd: También quiero agradecer a mi yo del pasado por todo el trabajo realizado. Por habérselo currado durante todos estos años y haber sabido mirar siempre el lado positivo de las cosas para motivarse y seguir hacia delante. **Zorionak**!

FUNDING

Jon Frias Gomez:

-SLT006/17/76 - Funds from University and Research Grants Management Agency (AGAUR) for instrumental action of incorporation of scientists and technologists (PERIS). 2016-2020.

-FI20/00031 - Funds from the Health Ministry of Spain for a Pre-doctoral Training Contracts in Health Research (PFIS). 2021-2024.

-MV21/00061 - Funds from the Health Ministry of Spain for researcher mobility within the AES framework (M-AES) to conduct a stay at the National Cancer Institute (NCI) USA between August 15, 2022, and December 18, 2022. Unfortunately, this stay did not take place.

Screenwide project funding:

-2017 SGR 1085 - Funds from University and Research Grants Management Agency (AGAUR). Project: "Group of Molecular Epidemiology and Genetics in Infections and Cancer". (SGR 2017-2019).

-PI19/01835 - Funds from the Health Ministry of Spain. Project: "Environmental, occupational, and serological risk factors associated with endometrial cancer, within the framework of the Screenwide study and the E2C2 consortium". 2020-2022.

-2021 SGR 01354 - Funds from University and Research Grants Management Agency (AGAUR). Project: "Group of Molecular Epidemiology and Genetics in Infections and Cancer. (Screenwide)."

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS AND ACRONYMS

ASR	Age-Standardized Rates
BMI	Body Mass Index
BSO	Bilateral Salpingo-Oophorectomy
CT	Computed Tomography
E2C2	Epidemiology of Endometrial Cancer Consortium
EAH/EIN	Endometrial Atypical Hyperplasia/Endometrioid Intraepithelial Neoplasia
EBRT	External Beam Radiation Therapy
EC	Endometrial Cancer
EDCs	Endocrine Disrupting Chemicals
EECs	Endometrioid Endometrial Carcinoma
EmGD	Endometrial Glandular dysplasia
ER	Estrogen Receptor
ESGO	European Society of Gynaecological Oncology
ESP	European Society of Pathology
ESTRO	European Society for Radiotherapy and Oncology
FIGO	International Federation of Gynecology and Obstetrics
HPV	Human Papilloma Virus
IARC	International Agency for Research of Cancer
IHC	Immunohistochemistry
LVSI	Lymphovascular Space Invasion
MMI	Myometrial Invasion
MMR	Mismatch Repair
MMRd	Mismatch Repair Deficient
MRI	Magnetic Resonance Imaging
NSPM	No Specific Molecular Profile
OCs	Oral Contraceptives
OS	Overall Survival
PARP	Poly (ADP-ribose) polymerase
PMB	Postmenopausal Bleeding
POLE	Polymerase-ε
PR	Progesterone Receptor
PRT	Pelvic Radiotherapy
ProMisE	Proactive Molecular Risk Classifier for Endometrial Cancer
SCC	Squamous Cell Carcinoma
SEGO	Spanish Society of Gynecological Oncology
SEIC	Serous Endometrial Intraepithelial Carcinoma
SHBG	Sex Hormone-Binding Globulin
TCGA	The Cancer Genome Atlas
TVS	Transvaginal Sonography
WHO	World Health Organization

LIST OF ARTICLES COMPRISING THE THESIS

This thesis is a compilation of five research articles, all published in peer-reviewed journals. It addresses three main research objectives, with four articles presenting original research and one dedicated to a systematic review and meta-analysis.

Articles, by publication date:

1) **Frias-Gomez J**, Benavente Y, Ponce J, Brunet J, Ibáñez R, Peremiquel-Trillas P, Baixeras N, Zanca A, Piulats JM, Aytés Á, Matias-Guiu X, Bosch FX, de Sanjosé S, Alemany L, Costas L; Screenwide Team. Sensitivity of cervico-vaginal cytology in endometrial carcinoma: A systematic review and meta-analysis. Cancer Cytopathol. 2020 Nov;128(11):792-802. doi: 10.1002/cncy.22266. Epub 2020 Mar 23. PMID: 32202704.

   Impact factor at publication, Quartile (Subject category): 5.284, Q1 (Pathology)

2) **Frias-Gomez J**, Peremiquel-Trillas P, Alemany L, Ameijide A, Marcos-Gragera R, Ponce J, Brunet J, Matias-Guiu X, Galceran J, Izquierdo Á, Borràs JM, Costas L, Clèries R. Predicting the rising incidence and mortality of endometrial cancers among women aged 65-74 years in Catalonia. Maturitas. 2021 Feb;144:11-15. doi: 10.1016/j.maturitas.2020.09.006. Epub 2020 Sep 30. PMID: 33358202.

   Impact factor at publication, Quartile (Subject category): 5.11, Q1 (Obstetrics & Gynecology)

3) **Frias-Gomez J**, Tovar E, Vidal A, Murgui L, Ibáñez R, Peremiquel-Trillas P, Paytubi S, Baixeras N, Zanca A, Ponce J, Pineda M, Brunet J, de Sanjosé S, Bosch FX, Matias-Guiu X, Alemany L, Costas L; Screenwide Team. Sensitivity of cervical cytology in endometrial cancer detection in a tertiary hospital in Spain. Cancer Med. 2021 Oct;10(19):6762-6766. doi: 10.1002/cam4.4217. Epub 2021 Sep 4. PMID: 34480514; PMCID: PMC8495290.

   Impact factor at publication, Quartile (Subject category): 4.711, Q2 (Oncology)

4) Costas L, **Frias-Gomez J**, Benavente Moreno Y, Peremiquel-Trillas P, Carmona Á, de Francisco J, Caño V, Paytubi S, Pelegrina B, Martínez JM, Pineda M, Brunet J, Vidal A, Matias-Guiu X, Bosch X, Ponce J, Kogevinas M, De Sanjosé S, Alemany L. Night work, chronotype and risk of endometrial cancer in the Screenwide case-control study. Occup Environ Med. 2022 Feb 24:oemed-2021-108080. doi: 10.1136/oemed-2021-108080. Epub ahead of print. PMID: 35210289.

   Impact factor at publication, Quartile (Subject category): 4.9, Q1 (Public, Environmental & Occupational Health)

5) **Frias-Gomez J**, Alemany L, Benavente Y, Clarke MA, de Francisco J, De Vivo I, Du M, Goodman MT, Lacey J, Liao LM, Lipworth L, Lu L, Merritt MA, Michels KA, O'Connell K, Paytubi S, Pelegrina B, Peremiquel-Trillas P, Petruzella S, Ponce J, Risch H, Setiawan VW, Schouten LJ, Shu XO, Trabert B, Van den Brandt PA, Wentzensen N, Wilkens LR, Yu H, Costas L. Night shift work, sleep duration and endometrial cancer risk: A pooled analysis from the Epidemiology of Endometrial Cancer Consortium (E2C2). Sleep Med Rev. 2023 Dec;72:101848. doi: 10.1016/j.smrv.2023.101848. Epub 2023 Sep 7. PMID: 37716022; PMCID: PMC10840870.

Impact factor at publication, Quartile (Subject category): 11.2, D1 (Clinical Neurology)

THESIS SUMMARY IN SPANISH

Título: Avanzando en la Prevención del Cáncer de Endometrio: Explorando el Rol de los Factores de Disrupción Circadiana y la Sensibilidad de la Citología Cervicovaginal para su Detección.

Introducción: El cáncer de endometrio (CE) es el tumor ginecológico más frecuente en los países desarrollados, con una incidencia en aumento debido al envejecimiento de la población y la obesidad creciente. Este cáncer es dependiente de estrógenos, por lo que factores que alteran el ritmo circadiano, como el trabajo nocturno o la duración del sueño, podrían influir en su riesgo al alterar la producción y metabolismo de estas hormonas. Identificar factores de riesgo modificables es crucial para desarrollar estrategias preventivas. A pesar de la evidencia limitada y contradictoria, es importante seguir investigando el impacto de la disrupción circadiana en el desarrollo del CE.

El CE se manifiesta principalmente a través del sangrado uterino anormal, especialmente en mujeres postmenopáusicas. De hecho, el 90% de las mujeres con este tipo de cáncer experimentan este síntoma. La evaluación diagnóstica estándar incluye ultrasonografía pélvica y biopsia endometrial si se detecta un aumento en el grosor endometrial. La falta de un programa de cribado para el CE ha impulsado la búsqueda de nuevas herramientas de detección de este cáncer. Investigaciones recientes se han centrado en la sensibilidad del análisis molecular en la citología cervicovaginal para la detección del CE. Aunque los resultados preliminares sugieren que este enfoque podría ser más sensible que la evaluación morfológica tradicional, la sensibilidad exacta de la evaluación morfológica en la citología cervicovaginal para el diagnóstico del CE es desconocida. En consecuencia, su precisión en la detección del CE sigue siendo discutible.

Hipótesis: Planteamos que el CE en Cataluña podría aumentar para 2030 debido a factores como el envejecimiento poblacional y la obesidad. Asimismo, postulamos si la disrupción circadiana y la citología cervicovaginal podrían desempeñar un papel en el desarrollo y detección de esta enfermedad.

Objetivos: La tesis tiene tres objetivos principales: 1) Proyectar la incidencia y mortalidad del CE en Cataluña hasta 2030; 2) Determinar si la alteración del ritmo circadiano, medida a través del trabajo nocturno y la duración del sueño, incrementa el riesgo de desarrollar CE; y 3) Evaluar la sensibilidad de la evaluación morfológica de la citología cervicovaginal para detectar el CE.

Métodos: Para proyectar la incidencia y mortalidad por CE en Cataluña hasta 2030, se utilizaron registros de cáncer de Girona y Tarragona (1994-2012) y datos de mortalidad del Registro de Mortalidad Cataluña (1994-2013). Los datos se agruparon en intervalos anuales para 18 grupos de edad y se vincularon con datos demográficos del Instituto Catalán de Estadística (1995-2017), proyectados hasta 2030. Las tasas específicas por edad de Girona y Tarragona se extrapolaron para Cataluña. Se emplearon modelos bayesianos autorregresivos de edad-periodo-cohorte, ajustados y validados, para proyectar la incidencia y mortalidad, estandarizando tasas según la población europea de 2013 y proporcionando intervalos de predicción del 95% más allá del 2012.

Para evaluar la disrupción del ritmo circadiano y el CE, se realizaron dos estudios independientes. Primero se realizó un estudio con 180 casos y 218 controles del estudio Screenwide, estimando odds ratios (ORs) e intervalos de confianza (IC) al 95% mediante modelos de regresión logística ajustados por posibles factores de confusión. Después, se llevó a cabo un estudio de mayor tamaño muestral en el cual se realizó un análisis agregado utilizando datos individuales del E2C2, con un total de 11 estudios realizados entre 1976 y 2021 en EE. UU. y Europa, centrado en 6,335 mujeres posmenopáusicas con CE y 18,453 controles. Primero se calcularon ORs e IC 95% utilizando regresión logística para cada estudio ajustando por factores de confusión relevantes y después se realizó un meta-análisis con los datos de cada estudio.

Finalmente, para evaluar la sensibilidad de la evaluación morfológica de la citología cervicovaginal en la detección del CE, se llevó a cabo un estudio retrospectivo en el Hospital Universitario de Bellvitge. Se incluyeron pacientes diagnosticadas con CE entre 1990 y 2020 con resultados previos de citología cervicovaginal y se calculó la sensibilidad de esta para la detección del CE. Después, en un segundo estudio se realizó una revisión sistemática de la literatura científica para identificar estudios que evaluaran la citología cervicovaginal en la

detección del CE. Se calculó la sensibilidad de la citología cervicovaginal para cada estudio y se realizó un meta-análisis de efectos aleatorios para obtener una estimación global.

Resultados: El estudio proyecta que para 2030 en Cataluña, las mujeres de 65 a 74 años experimentarán un aumento en la incidencia y mortalidad por CE, mientras que en las mujeres jóvenes se espera una disminución. Respecto a la prevención primaria, no se mostró una asociación estadísticamente significativa entre el trabajo nocturno y el CE, ni asociaciones según el tipo o la duración del turno. Tampoco se encontró una asociación estadísticamente significativa entre la duración del sueño y el riesgo de CE. En cuanto a la prevención secundaria, la revisión morfológica de citología cervicovaginal demostró una sensibilidad entre 26-45% para detectar el CE.

Conclusiones: El aumento previsto en la incidencia y mortalidad del CE en mujeres mayores resalta la necesidad de un enfoque multifactorial para su prevención (prevención primaria) y detección temprana (prevención secundaria). Los resultados de esta tesis sugieren que ni el trabajo nocturno ni la duración del sueño están fuertemente asociados con el riesgo de CE. Por otro lado, la revisión morfológica de la citología cervicovaginal muestra sensibilidad insuficiente en la detección del CE. Por lo tanto, es esencial continuar con los esfuerzos en ambos ámbitos para abordar la futura carga del CE.

INTRODUCTION

INTRODUCTION

1. Anatomy of the Uterus

The primary female reproductive organs in humans encompass the ovaries, fallopian tubes, uterus, and vagina. The uterus, a muscular, pear-shaped organ, occupies a central position within this system. Located between the bladder and rectum, its size and weight vary depending on a woman's hormonal status and pregnancy history. In nulliparous women, the uterus typically measures around 7.5 cm long, 5 cm wide, and 2.5 cm thick, weighing approximately 40-50 grams. The uterus itself can be further divided into four sections: fundus (top), body, cervix (lower narrow part), and isthmus (narrow region connecting the body and cervix) (1–3) (Figure 1).

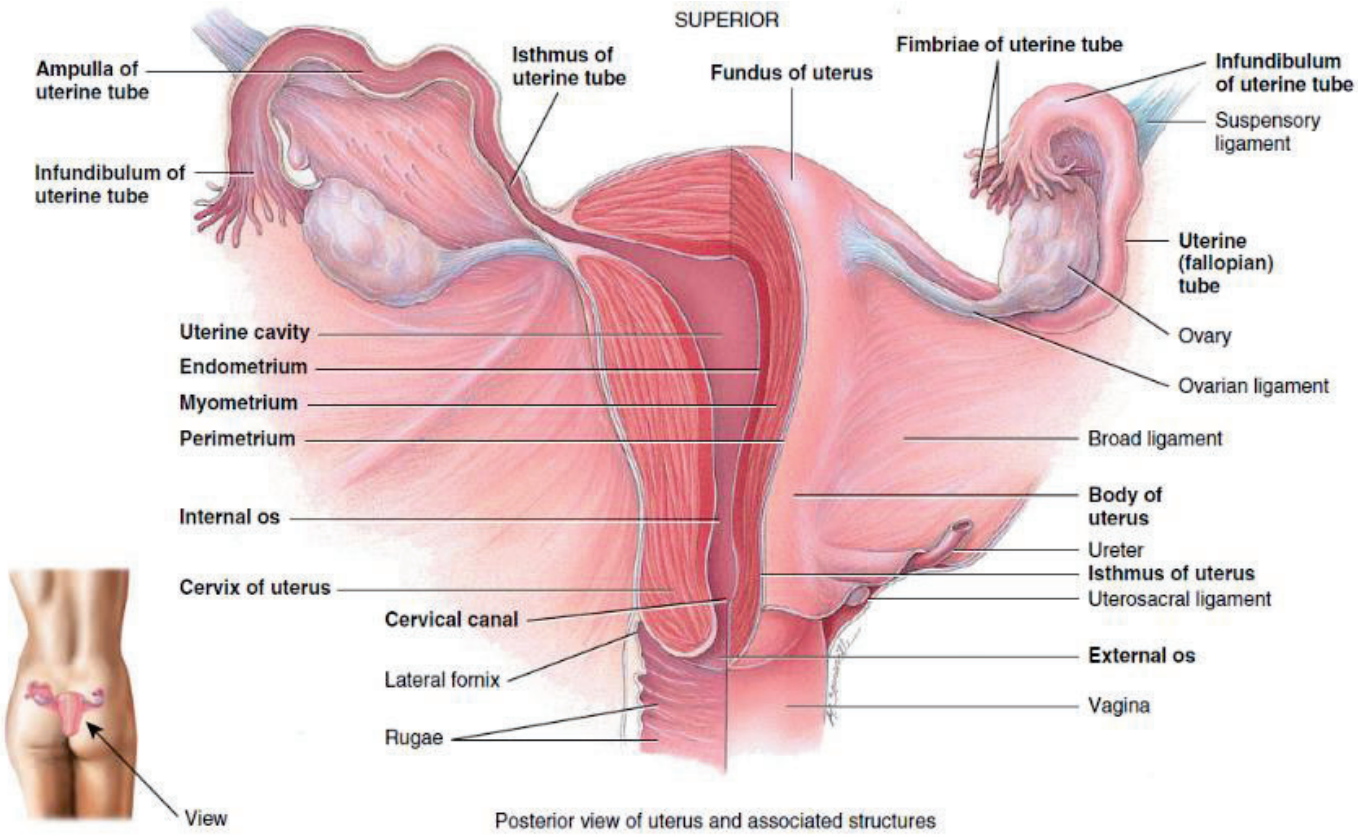


Figure 1. Anatomy of the uterus and the associated structures.
Image from Tortora GJ and Derrickson BH, 2018 (1).

Histologically, the human uterus is composed of three distinct layers (Figure 2):

-The **perimetrium** represents the outermost layer. This thin, delicate membra is intimately adherent to the underlying myometrium, constituting the visceral perimetrium (2).

-The **myometrium**, the most robust layer, is composed of three muscle layers with poorly defined boundaries: the subvascular, vascular and supravascular layers. It plays a crucial role in responding to hormonal stimuli (2).

-The **endometrium**, also known as the mucosa, forms the innermost layer. This highly vascular and glandular epithelium undergoes cyclical changes throughout the menstrual cycle mediated by hormonal signals originated from the ovaries. During the menstruation, this layer sheds, resulting in menstrual bleeding (2).

1.1. The Endometrium

The endometrium, a multicellular tissue that lines the uterus, undergoes monthly cycles of physiological tissue injury and repair during the menstrual period (4). Remarkably, this process is marked by rapid repair, leaving no residual scarring or loss of function (5). After the reproductive phase, the endometrium in postmenopausal women becomes inactive, free from cyclical changes, and typically atrophies (6).

The endometrium is composed of the epithelial layer and cell-rich connective tissue layer known as the lamina propia. Functionally, the human endometrium consists of two layers:

-The **basal layer** constitutes the lower third of the endometrium, situated adjacent to the myometrium. Unlike the rest of the endometrium, it does not shed during menstruation, remaining constant throughout the menstrual cycle. This layer primarily consists of stem cells, which are instrumental in regenerating the functional layer. Its crucial role involves initiating the formation of a new functional layer after the completion of each menstrual cycle (7,8).

-The **functional layer** constitutes the upper two thirds of the endometrium and consists of columnar surface epithelium overlaying a multicellular stroma. Positioned near the uterine cavity, it features a single layer of columnar epithelium. The stroma contains connective tissue with fibroblast-like stromal cells, specialized spiral arteries, tissue-resident endometrial immune cells, and a cyclical influx of innate immune cells. Endometrial leukocytes, including both cyclical and tissue-resident immune cells, dynamically regulate tissue breakdown and repair during menstruation (9,10). This layer undergoes shedding and renewal with each menstrual cycle. Conversely, in the event of pregnancy, the endometrium transforms into a thick, blood vessel-rich, glandular tissue layer (7,8). During the postmenopausal period, in the absence of estrogen stimulation, the endometrium appears thin on gross examination. The functional layer is absent, leaving only the basal layer visible (6).

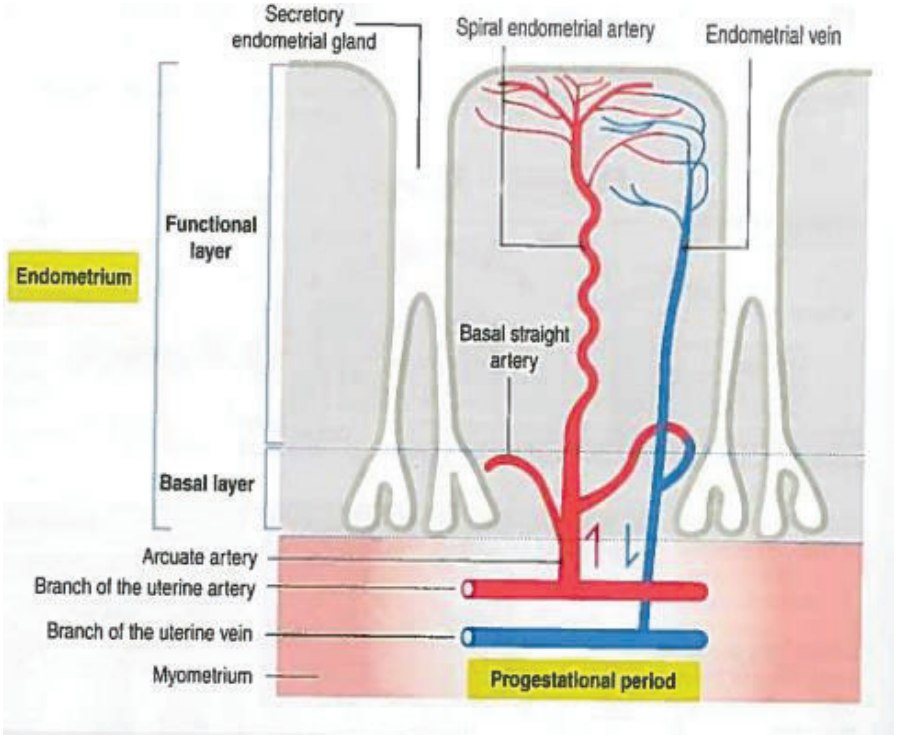


Figure 2. The two functional layers of the endometrium: the functional and the basal layers. Image from Kierszenbaum AL, 2019 (7).

The primary role of the endometrium is to create an optimal environment for embryo implantation, and to menstruate in the absence of pregnancy (4,8,11). Additionally, it serves to prevent adhesions between the opposing walls of the myometrium and maintains the patency of the uterine cavity. The functional endometrium has a lifespan equivalent to the reproductive period of an adult, spanning from menarche to menopause (12). To prepare for potential implantation, the endometrium undergoes monthly cyclical changes in response to fluctuating ovarian sex steroids, which regulate its growth and differentiation throughout the menstrual cycle. If fertilization does not occur, the functional layer of the endometrium is shed and expelled, leading to menstruation, which typically occurs approximately every 24-38 days (8).

1.2. Endometrial Stages

Throughout a woman's reproductive years, the functional endometrium undergoes distinct stages, including three phases associated with the menstrual cycle (menstrual, proliferative and secretory), and another one specific to pregnancy (13,14). Later, following the menopause, the endometrium enters a final phase where it gradually becomes atrophic (15). Each stage is characterized by unique histological, molecular, and time-specific features.

1.2.1. The Menstrual Cycle

The menstrual cycle is a regular physiological process for most women, occurring approximately every 28 days, which starts with the menarche and finishes with the menopause. Women in high-income countries are estimated to experience roughly 400-500 menstrual ovulations throughout their lifetime, influenced by factors such as the median age at menarche and menopause, as well as the number of children conceived (8,16,17). The menstrual cycle consists of three main phases: the proliferative, secretory, and menstrual phases (1) (Figure 3).

During the proliferative phase, the endometrium undergoes extensive growth in response to high levels of estrogen. Ovulation marks the release of the oocyte from the dominant ovarian follicle, which transforms corpus luteum, secreting progesterone and initiating the progesterone-dominant secretory phase, typically lasting 14 days. During this secretory

phase, characterized by high levels of estradiol and progesterone, the endometrial cells undergo decidualization. Decidualization encompasses the functional and morphological changes within the endometrium that create the decidual lining essential for blastocyst implantation. This process is progesterone-dependent and occurs spontaneously, independent of embryo presence (18). If pregnancy does not occur, progesterone levels decline, triggering spontaneous decidualization and leading to menstrual shedding and cyclic endometrial regeneration (18). At the end of the secretory phase, with the demise of the corpus luteum, both progesterone and estrogen levels decrease, causing the endometrial cells to stop being maintained. This withdrawal of progesterone results in menstrual bleeding, accompanied by endometrial apoptosis, inflammation, and the expression of matrix metalloproteinases (19). The peri-menstrual phase encompasses the transition from the secretory phase, through menstrual breakdown and repair, to regeneration in the proliferative phase (4).

1.2.2. Endometrium at Pregnancy

Implantation, vital for species survival, involves initial adhesion, attachment, and invasion (20). Its success relies on complex molecular interactions between a viable blastocyst and a properly primed endometrium (20). Each menstrual cycle presents a critical implantation window of 24-36 hours, maximizing endometrial receptivity. Failure to implant during this period results in either pregnancy failure or increased risk of adverse outcomes (21). Endometrial vascular development and thickness have been linked to successful implantation outcomes in women (22). Furthermore, endometrial glands are proposed as a source of nutrients, growth factors, and cytokines throughout the first trimester of pregnancy in women (23,24).

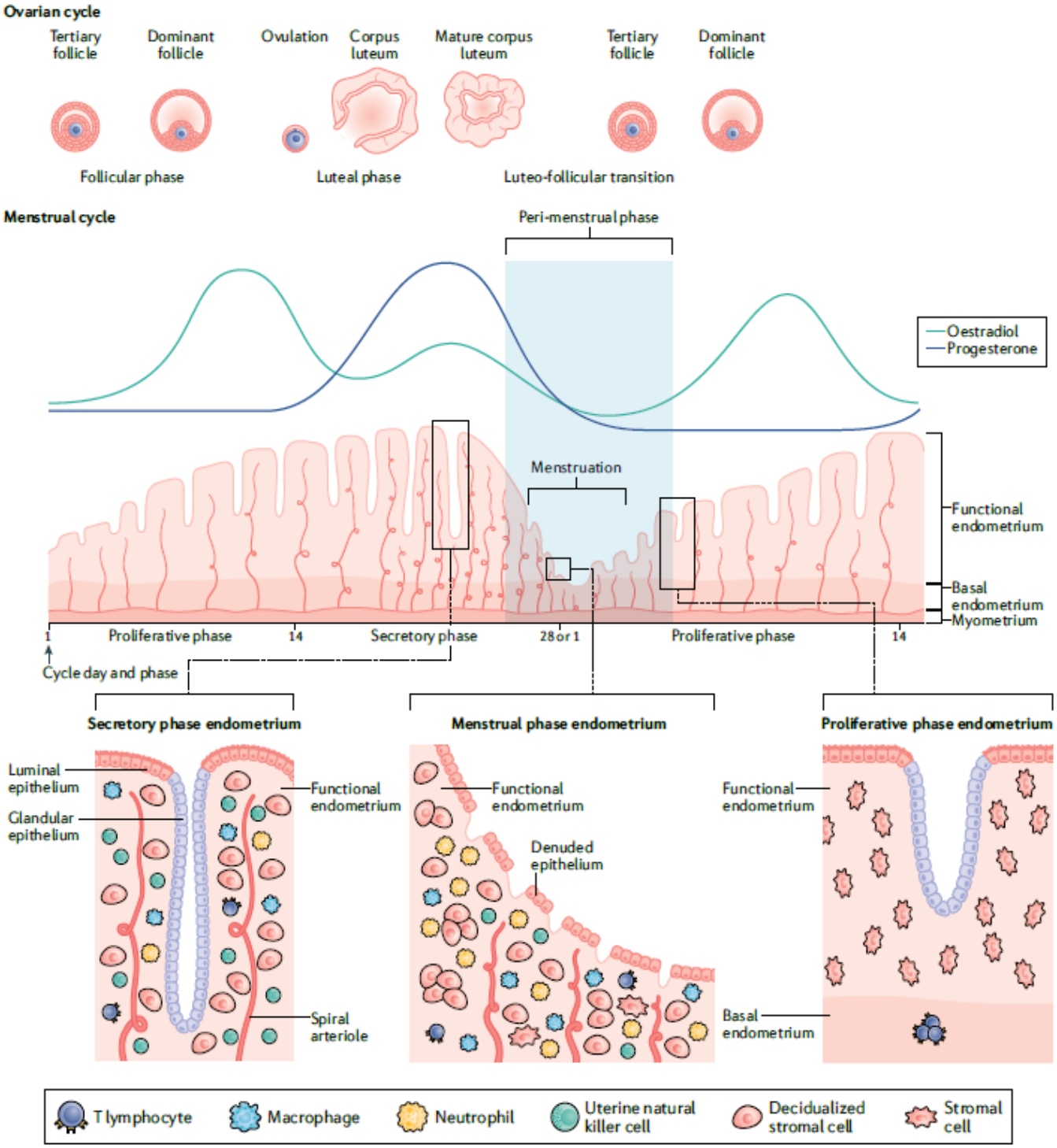


Figure 3. The female menstrual cycle.
Image from Jain V et al., 2022 (8).

1.2.3. Atrophic Endometrium at Postmenopause

Atrophic endometrium, a term describing endometrial tissue that is smaller and less active than normal, is a non-cancerous condition commonly found in postmenopausal women. After menopause, endometrial tissue becomes atrophic due to the cessation of ovulation and ovarian estrogen and progesterone secretion. At this point, there is a loss of the functional layer. The endometrial glands adopt a simple tubular or low cuboidal, often cystic, form, showing neither proliferative nor secretory activity, while the endometrial stroma becomes fibrotic. The glands typically have a diameter of 0.1 mm, and the endometrial thickness on transvaginal sonography (TVS) is less than 4 mm. In the absence of sufficient estrogenic stimulation, the epithelium becomes quiescent and may appear atrophic (25).

Atrophic endometrium is classified into four histological subtypes: inactive atrophic, weakly proliferative (non-inactive) atrophic, mixed (inactive and non-inactive), and cystic atrophic, which is often associated with tamoxifen use (26,27).

The most common cause of postmenopausal bleeding (PMB) is endometrial atrophy, found in approximately 45–50% of patients with PMB. The exact cause of bleeding from the atrophic endometrium is unknown. The etiology is postulated to involve either anatomic vascular anomalies or local disturbances in hemostasis, characterized by thin-walled veins and fragile stromal support within these superficial vessels (26).

2. Endometrial Cancer

2.1. Natural History

Endometrial cancers (EC) originate from various precursor lesions (Figure 4). Type I endometrioid endometrial carcinoma (EEC) typically arises from endometrial atypical hyperplasia/endometrioid intraepithelial neoplasia (EAH/EIN), often linked to estrogenic stimulation. While most cases of simple hyperplasia without atypia regress to normal endometrium (28,29), one quarter to one third of women with EAH/EIN are diagnosed with carcinoma within the first year (30,31). Progression risks vary based on the presence of atypia (32); for instance, the cumulative 20-year progression risk is <5% for hyperplasia without atypia compared to 28% for atypical hyperplasia (33).

Type II EC usually develops on an atrophic endometrium or within an endometrial polyp. Serous endometrial intraepithelial carcinomas (SEIC) exhibit similar morphology to endometrial serous carcinoma but lack stromal invasion. Although SEIC may precede widely invasive serous carcinoma, it is not considered a precancerous lesion due to its high potential for extrauterine spread (34).

Endometrial glandular dysplasia (EmGD), a newly defined entity, has been proposed as a precursor lesion for type II EC (35). However, EmGD terminology is not universally accepted, and there is limited understanding of its natural history, compounded by poor interobserver agreement among pathologists. Questions remain regarding whether all type I cancers follow the hyperplasia model, and the association between type I EC in Lynch syndrome and EIN lesions or de novo development (36).

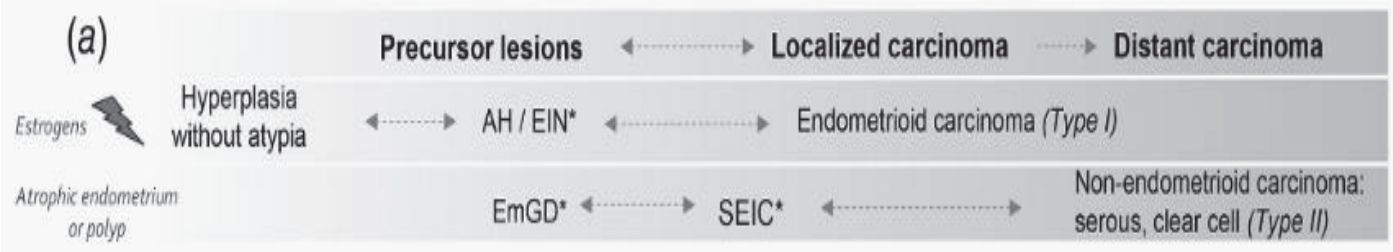


Figure 4. Natural history of endometrial cancer.
Image from Costas L et al. 2019 (37).

2.2. Precursor and Tumor-Like Endometrial Lesions

2.2.1. Endometrial Hyperplasia Without Atypia

Endometrial hyperplasia without atypia involves the proliferation of endometrial glands with irregular size and shape but lacks significant cytological atypia (38). It results from prolonged exposure to estrogen unopposed by progesterone or progestational agents, affecting the entire endometrial field (39). Commonly diagnosed in perimenopausal women experiencing abnormal non-cyclical vaginal bleeding, it often presents with increased endometrial thickness on TVS. Principal risk factors include perimenopause, obesity, polycystic ovarian syndrome, and prolonged exposure to unopposed estrogen (39,40). Progression to well-differentiated EC occurs in 1-3% of women with hyperplasia without atypia (29,38).

2.2.2. Endometrial Atypical Hyperplasia/ Endometrioid Intraepithelial Neoplasia (EAH/EIN)

EAH/EIN signifies cytological alterations and heightened glandular proliferation within a specific region of the endometrium (38). Typically emerging among women aged 50 to 55, its manifestation commonly involves postmenopausal or perimenopausal bleeding, often linked with heightened estrogen levels (39,40). EAH/EIN shares genetic affinities with EEC and exhibits associations with hereditary conditions such as Cowden and Lynch syndrome (41,42). Notably, approximately one quarter to one third of women with endometrial atypical hyperplasia biopsies may transition to cancer either immediately or within the initial year of follow-up (31).

2.2.3. Endometrial Polyps

Endometrial polyps are abnormal growths in the uterus, ranging from few millimeters to several centimeters and can be either single or multiple (43). They are made up of endometrial glands, stroma, and blood vessels (44). Several factors such as age, hypertension, obesity, and tamoxifen use contribute to their development (45–47). While they can often be asymptomatic

(48), they may cause abnormal uterine bleeding (49), or, less commonly, infertility (50,51). Malignant transformation of these polyps is rare, occurring only in a small percentage of cases (between 0% and 12.9%) based on extensive studies (52,53).

2.3. Endometrial Cancer Classification

In recent years, the classification of EC has transitioned from traditional clinical and morphological distinctions to a molecular-based approach. This transformation, driven by advancements in molecular research, particularly insights from The Cancer Genome Atlas (TCGA) analysis (54), has revolutionized the classification system beyond the conventional type I and type II categorization (55). While molecular insights continue to drive classification, histological classification remains indispensable for precise diagnosis and patient management, particularly considering the obstacles to accessing molecular testing in many world regions.

2.3.1. Histological Classification

According to the new World Health Organization (WHO) classification, published in 2020, endometrial epithelial tumors are categorized in the following groups (Table 1) (38):

2.3.1.1. Endometrioid Endometrial Carcinoma (EEC)

EEC is a malignant epithelial tumor characterized by a combination of glandular, papillary, and solid architectural patterns, with the neoplastic cells demonstrating endometrioid differentiation. Predominantly observed in postmenopausal women (90% occurring in those older than 50 years) with a median age of 63 years, EEC commonly manifests with abnormal or PMB. It accounts for the majority, approximately 80%, of uterine corpus malignancies in Europe (38,56), which is approximately 70% of all ECs.

2.3.1.2. Serous Endometrial Carcinoma

Serous endometrial carcinoma is characterized by significant nuclear pleomorphism, often presenting with diffuse papillary and/or glandular growth patterns (38). PMB is a common presenting symptom among most patients. In surgically staged cases, approximately 40-50%

exhibit extra-uterine metastasis, frequently involving lymph nodes, peritoneal sites, and the omentum (57,58). Although serous endometrial carcinomas represent about 10% of all ECs, they contribute to a disproportionately high percentage, up to 40%, of deaths related to EC (57,58). Additionally, the incidence of serous endometrial carcinoma is notably higher among Black women compared to other populations (59).

2.3.1.3. Clear Cell Endometrial Carcinoma

Clear cell endometrial carcinoma is characterized by papillary, tubolocystic, and/or solid architectural patterns, accompanied by variably pleomorphic polygonal, cuboidal, flat, or hobnail cells displaying clear or eosinophilic cytoplasm (38). Patients typically present in their seventies (60,61), with PMB being the most common initial symptom. Abnormal cervicovaginal cytology screening, particularly in advanced-stage disease, may also be observed (62). Notably, around 50-60% of cases are diagnosed at an early stage (60,63,64). This tumor is rare, comprising less than 10% of all EC (63,64). The 5-year overall survival (OS) rate ranges from 55% to 78% (60,61).

2.3.1.4. Undifferentiated and Dedifferentiated Carcinoma

Undifferentiated carcinoma of the endometrium is a malignant epithelial tumor characterized by a lack of identifiable cell lineage differentiation. Dedifferentiated carcinoma presents with both an undifferentiated carcinoma component and a differentiated component, often resembling International Federation of Gynecology and Obstetrics (FIGO) grade 1 or 2 EEC. Most affected patients are either perimenopausal or postmenopausal, with a median reported age of approximately 55 years (ranging from 30 to 80 years). PMB is the primary presenting symptom, although some patients may also experience abdominal pain. Undifferentiated carcinomas are rare, comprising only about 2% of ECs. There is a suggested association with Lynch syndrome. These tumors are typically highly aggressive, with recurrence or disease-related mortality occurring in 55-95% of cases (38,65).

2.3.1.5. Mixed Carcinoma of the Uterine Corpus

A mixed carcinoma is characterized by the presence of two or more distinct histological types

of EC, with at least one component being either serous or clear cell (38). The previous arbitrary threshold of 5% for a serous component has been eliminated, as evidence suggests that any percentage of high-grade carcinoma, whether serous or clear cell, carries a poorer prognosis. Mixed EC are rare, with mixed endometrioid and serous carcinomas constituting approximately 10% of all ECs (66). The behavior of these tumors is determined by the highest-grade component present. Consequently, these tumors are classified as high-grade carcinoma regardless of the relative proportions of serous or clear cell carcinoma components (67).

2.3.1.6. New Entities

The 2020 WHO classification introduces four new categories of endometrial epithelial tumors (38):

-Mesonephric and Mesonephric-like Adenocarcinoma: These two tumors exhibit numerous morphological, immunohistochemical, and molecular similarities. However, mesonephric carcinoma presents distinct evidence of mesonephric remnants, while such remnants are not identifiable in mesonephric-like carcinoma. These tumors typically display small tubules with dense eosinophilic colloid-like material, alongside a diverse array of morphologies including papillary, ductal, retiform, solid, and spindled architecture (38,68).

-Squamous Cell Carcinoma (SCC): Primary SCC of the endometrium, though well recognized, was unintentionally omitted in the fourth edition. Similar to mesonephric carcinomas, SCC is exceptionally rare in the uterine corpus. Risk factors include chronic inflammatory conditions, previous irradiation, and human papilloma virus (HPV) infections. Morphologically, these tumors resemble SCC found elsewhere in the body but may display less cytological atypia and broader invasive fronts (38,68).

-Mucinous Carcinoma, Gastrointestinal Type: This type of carcinoma has only recently been described, with previous attention focused on tumors of this morphology arising in the cervix, where it is more prevalent. Histologically, it features glandular architecture with mucin-secreting epithelium, potentially including goblet cells. Accurate recognition is crucial, first to differentiate from cervical or gastrointestinal tract origin, and second, as these tumors

are associated with aggressive clinical behavior, avoiding misdiagnosis as low-grade EEC (38,68,69).

-Carcinosarcoma: Carcinosarcoma, a biphasic tumor comprising both high-grade carcinomatous and sarcomatous components (38), typically presents with symptoms such as vaginal bleeding, uterine enlargement, or the presence of a pelvic mass (70,71). At the time of diagnosis, approximately 45% of cases are already classified as stage III or IV (72,73). Carcinosarcomas represent about 5% of all uterine malignancies (74). Patients affected by this condition are typically postmenopausal and share similar predisposing risk factors as those for EC. The 5-year disease-specific survival rate for patients with FIGO stage I-II disease is approximately 60%, whereas for those with stage III and IV disease, the rates drop to 25% and 10%, respectively (72,75). In addition to advanced stages, several independent factors are associated with a poor prognosis, including tumor size exceeding 5 cm, myometrial invasion (MMI) of over 50%, presence of lymphovascular space invasion (LVSI), and predominance of sarcomatous elements (74,76).

Table 1. Incidence of endometrial carcinomas by histological types

Histological type of EC	EC Percentages
Endometrioid Endometrial Carcinoma	70%
Serous Endometrial Carcinoma	10%
Clear Cell Endometrial Carcinoma	<10%
Undifferentiated and Dedifferentiated Carcinoma	2%
Mixed Carcinoma of the Uterine Corpus	10%
Other Endometrial Carcinomas	<5%

Table information from Female Genital Tumours (38).

2.3.2. Classical Classification

In 1983, Bokhman proposed a classification system for EC based on clinical, endocrine, and epidemiological features (55). This widely recognized system, known as Bokhman's classification, differentiates between type I and type II tumors primarily based on their clinical, metabolic, and endocrine features, as outlined in Table 2 (77).

Table 2. Dualistic classification of epithelial endometrial cancer, including clinical and pathological correlates

	Type I	Type II
Clinical, endocrinological, and morphological components (Bokhman classification)		
Distribution	60-70%	30-40%
Reproductive function	Decreased	No disturbances
Onset of menopause	After age 50 years	Younger than age 50 years
Background endometrium	Hyperplasia	Atrophy
Estrogen associated	Yes	No
Associated obesity, hyperlipidemia, and diabetes mellitus	Yes	No
Tumor grade	Low (grade 1-2)	High (grade 3)
Myometrial invasion	Superficial	Deep
Potential for lymphogenic metastatic spread	Low	High
Prognosis	Favorable	Unfavorable
Sensitivity to progestogens	High	Low
Outcome (5-year survival)	86%	59%
Clinicopathological and molecular correlates		
Prototypical histological type	Endometrioid	Serous
Estrogen-receptor or progesterone-receptor expression	High	Low
Stage at diagnosis	Early (FIGO stage I-II)	Advanced (FIGO stage III-IV)

FIGO, International Federation of Gynecology and Obstetrics.
Table from Murali et al. 2014 (77).

-Type I (Endometrioid Adenocarcinomas): Type I EC, the most common subtype, is characterized by low-grade, endometrioid tumors that are hormone-receptor-positive. These cancers typically carry a favorable prognosis, with a 5-year OS rate of 85% (78). Often estrogen-dependent and linked to endometrial hyperplasia, type I tumors are associated with conditions such as estrogen excess, obesity, and hormone-receptor positivity. They tend to be moderately or highly differentiated, contributing to their favorable outcomes (77,79).

-Type II (Non-Endometrioid Adenocarcinomas): Type II tumors account for 10-15% of ECs. These high-grade carcinomas, predominantly of serous and clear cell histologies, exhibit a poor prognosis. Unlike their type I counterparts, type II tumors are considered estrogen-independent and are often associated with endometrial atrophy (77,79).

Extensive evidence consistently shows significant overlap between type I and type II EC tumors characteristics, along with notable heterogeneity within each category. Additionally, the histopathological classification of EC presents a considerable challenge, even for expert gynecopathologists, leading sometimes to poor interobserver agreement among pathologists. This lack of agreement has resulted in inaccuracies in EC risk assessment, potentially causing both over- and under-treatment.

2.3.3. Molecular Classification

In 2013, TCGA Research Network conducted an in-depth analysis of ECs, employing advanced sequencing technologies and assessing various molecular aspects, including DNA methylation, reverse-phase protein array, and microsatellite instability (54). The study focused on prevalent EC histological types: endometrioid (n=307), serous (n=53), and mixed endometrioid and serous (n=13) carcinomas. ECs were categorized into four prognostically relevant groups based on mutational burden and somatic copy-number variations: Ultramutated, hypermutated, copy-number high and copy-number low (Figure 5).

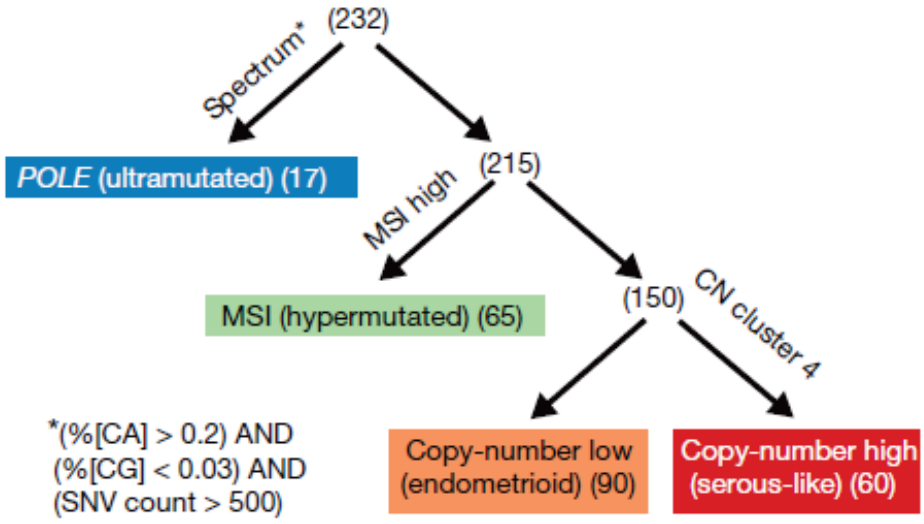


Figure 5. Endometrial cancer tumor stratification diagram.
Image from Cancer Genome Atlas Research Network, et al. 2013 (54).

The initial TCGA study utilized whole-genome sequencing for assessment, which is impractical on a large scale, both clinically and economically. However, subsequent studies have validated comparable molecular analyses using more accessible techniques, such as immunohistochemistry (IHC) and Sanger next-generation sequencing (80–82). In particular, the ProMisE (Proactive Molecular Risk Classifier for Endometrial Cancer) classification, which is based on IHC markers and polymerase-ε *(POLE)* sequencing, has demonstrated reliability in categorizing tumors into the four subtypes identified by TCGA (82,83). The four molecular prognostic groups identified by surrogate test are *POLE*-mutated, mismatch repair (MMR)-deficient, p53-abnormal, and "no specific molecular profile" (NSMP).

-Ultramutated (*POLE*-mutant) Carcinoma: TCGA Research Network study revealed that all ultramutated ECs exclusively displayed pathogenic mutations in the exonuclease domain of *POLE*, establishing it as a reliable indicator of ultramutated status (54). *POLE* mutations are present in approximately 5-10% of ECs, representing the least common molecular subgroup in TCGA (54). Patients within this subgroup tend to be younger, have lower body mass index (BMI), and present with earlier FIGO stages compared to other TCGA groups. Additionally, these tumors demonstrate a favorable prognosis, with an overall progression-free survival ranging from 92% to 100% (54,82,83). Intriguingly, despite their good prognosis, approximately half of *POLE*-mutant ECs are high-grade (54). Notably, *POLE* mutations are significantly more prevalent in high-grade EEC (12.1%) compared to low-grade ones (6.2%) (84). Consequently, this suggests that many *POLE*-mutant ECs might be overtreated based solely on their histological characteristics (85). *POLE* mutations have a prognostic significance that surpasses both MMR deficiency and p53 mutations, making it the primary surrogate test conducted for ECs (86–88).

-Hypermutated (Mismatch Repair Deficient [MMRd]) Carcinoma: The hypermutated group, comprising 28% of EC cases in TCGA, universally displayed high microsatellite instability, often attributed to MMR deficiency (54,89). IHC for MMR proteins (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) serves as a surrogate test for identifying this group, with Lynch syndrome accounting for a portion (3-5%) and somatic defects, including epigenetic *MLH1* silencing, constituting the remainder. Histologically resembling *POLE*-mutated tumors, they are predominantly endometrioid (85.8%) with a notable frequency of high-grade cases

(47.4%) (85). MMR deficiency is more prevalent in high-grade compared to low-grade EEC (39.7% vs. 24.7%) (90) and is frequently observed in undifferentiated/dedifferentiated carcinomas (44%) (91) and mixed ECs with an endometrioid component (16-66%) (92–94), but less so in clear-cell carcinoma (9.8%) (90) and carcinosarcoma (7.3%) (95). Prognostically, MMR deficiency supersedes p53 abnormalities but is inferior to *POLE* mutations, hence it is assessed as a surrogate test once *POLE* mutation is ruled out (86–88). The overall prognosis of MMRd ECs is intermediate, varying by stage.

-Copy Number-High (p53-abnormal) Carcinoma: The copy number-high group, mainly characterized by a high prevalence of *TP53* mutations (85%) and serous morphology (73.3%) (54). This group is alternatively referred to as the p53-abnormal group, as p53 IHC serves as a cost-effective surrogate for *TP53* molecular testing (82,83,86). However, around 5% of *TP53*-mutant tumors do not exhibit p53 expression abnormalities, requiring molecular analysis for identification (96). Additionally, there exists a subset of copy number-high ECs lacking *TP53* mutations, necessitating molecular analysis for classification (54). Despite its imperfection as a surrogate for copy-number analysis, p53 IHC demonstrates sufficient accuracy for common practice (83,86,97). This group represents the prototypical "type II" EC, associated with older age, non-endometrioid morphology, advanced stage, and poor prognosis, typically exhibiting high-grade features and striking nuclear atypia (54,85,98,99). The p53-abnormal signature is significantly more prevalent in high-grade than low-grade EECs (21.3% vs. 4.7%) (84), dominating carcinosarcomas (73.9%) (95) and a substantial portion of clear cell ECs (42.5%) (100). Across different histotypes, p53-abnormal ECs consistently display aggressive biological behavior (82,83,86,97,99). The European Society of Gynaecological Oncology (ESGO), the European SocieTy for Radiotherapy and Oncology (ESTRO), and the European Society of Pathology (ESP) guidelines classify all p53-abnormal ECs (excluding non-myoinvasive cases) within the high-risk group (101).

-Copy Number-Low (No Specific Molecular Profile [NSMP]) Carcinoma: The remaining TCGA group, lacking high mutational load or significant copy-number variations, is termed the "copy number-low/endometrioid group," representing the prototypical type I EC (54). Identified by the absence of molecular signatures from other groups, it is also known as "NSMP" (86,101). The NSMP group, the most common TCGA group (~40% of cases),

exhibits intermediate prognosis similar to the MMRd group (54,82,83,86,97). Although predominantly low-grade endometrioid tumors (84.4%) (85), NSMP can manifest across various EC hystologies, including mesonephric-like ECs (100%) (102), clear cell ECs (40.9%) (91), neuroendocrine ECs (36%) (93), high-grade EECs (28%) (84), undifferentiated/dedifferentiated ECs (25%) (91), and carcinosarcomas (13.5%) (95). However, the NSMP group appears to be more prognostically heterogeneous and influenced by other clinicopathological factors than the MMRd group (86). Non-endometrioid NSMP ECs exhibit a bad prognosis similar to p53-abnormal ECs, while NSMP EECs display highly variable prognoses, ranging from good to poor (54,97).

3. Epidemiology

3.1. Incidence, Mortality, and Survival

In 2022 EC was the 6th most common female cancer, with an incidence of 420,368 cases and a mortality of 97,723 cases, worldwide (78) (Figure 6). Moreover, it stands as the most prevalent gynecological cancer in high-income countries, with a rising global incidence attributed to increasing risk factors, notably the aging population and the prevalence of obesity (103). The lifetime risk of EC for women is approximately 3%, with a median age of diagnosis at 61 years. Most cases manifest between the ages of 65 and 75 (79).

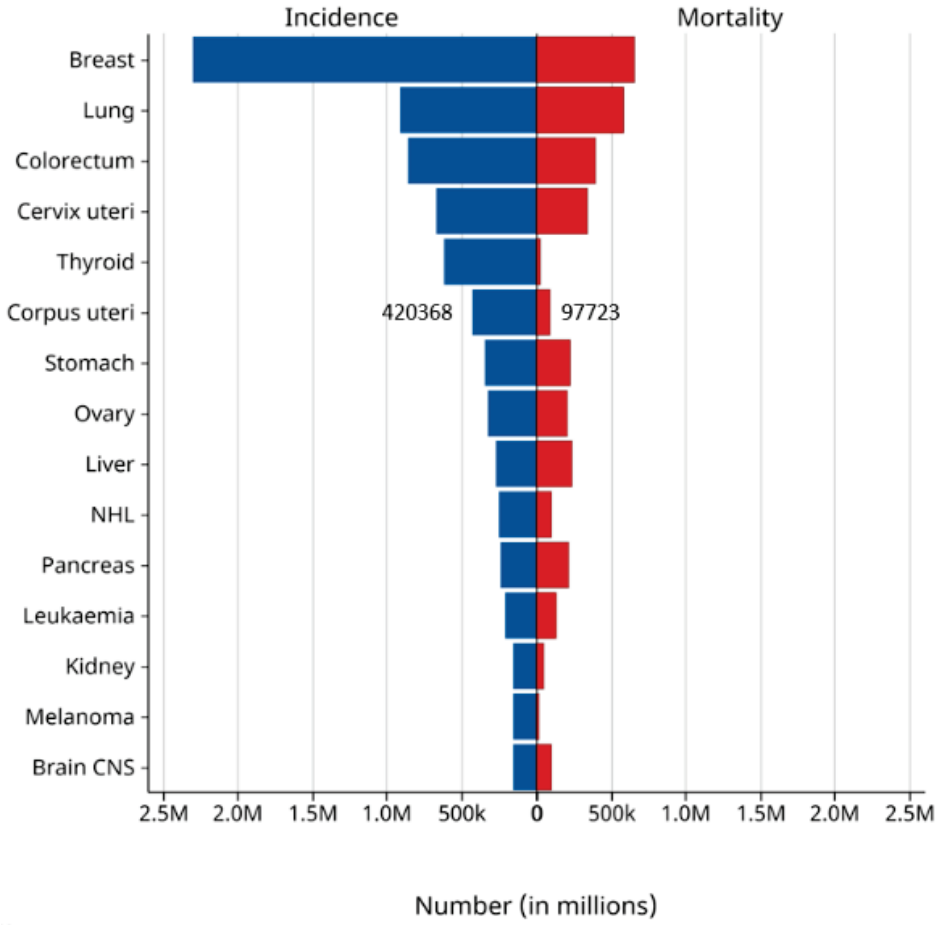


Figure 6. World absolute numbers, incidence and mortality, females in 2022. (Top 15 cancer sites).
Image from Globocan 2022 (78).

World age-standardized incidence and mortality rates (ASR) of EC in 2022 varied significantly across regions. Globally, the ASR for incidence was 8.4, while the ASR for mortality was 1.7. Across continents, ASR for incidences ranged from 3.5 in Africa to 22.3 in North America (Figure 7). In terms of mortality, ASR varied from 1.1. in Africa to 3.2 in North America (78) (Figure 8) .

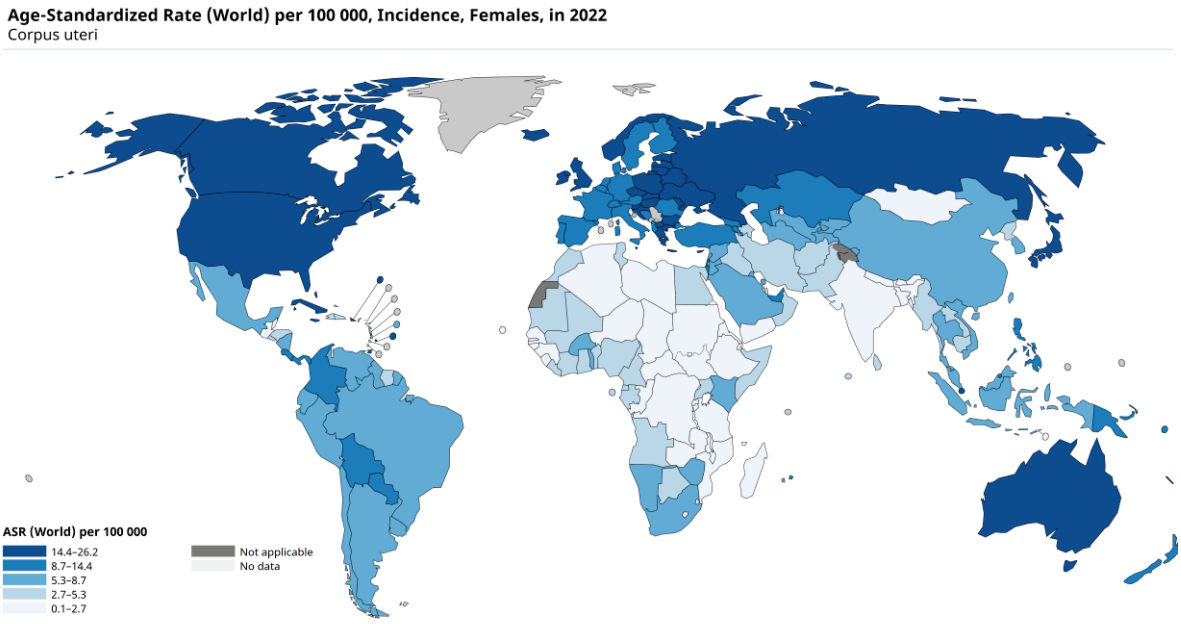


Figure 7. Age-standardized incidence rates of corpus uteri cancer worldwide.
Image from Globocan 2022 (78).

In 2022, Europe accounted for 29.7% of the total new cases of EC worldwide, with a total 124,874 reported cases. Additionally, 31.0% of the total world deaths attributed to EC occurred in Europe, amounting to 30,272 deaths (78). Specifically, in 2022 Spain reported 6,698 new EC cases and 1,625 deaths, with a crude incidence rate of 28.2 per 100,000 population, according to Globocan 2022 estimates (78). Moreover, Spain's ASR incidence and mortality for EC were 12.9 and 2.1 per 100,000 population.

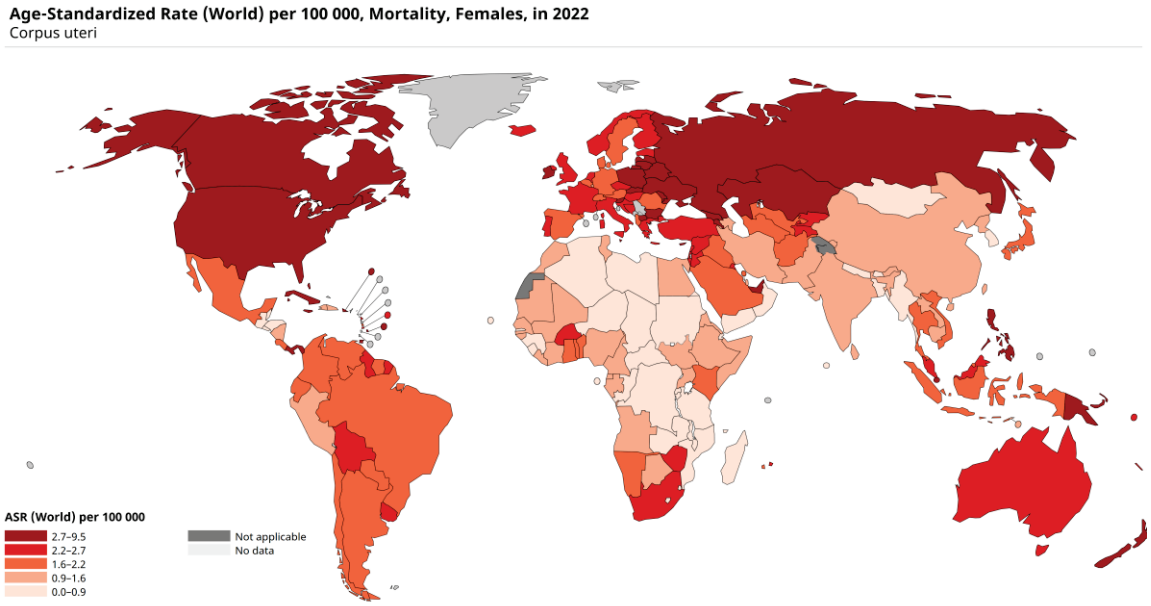


Figure 8. Age-standardized mortality of corpus uteri worldwide.
Image from Globocan 2022 (78).

Due to aging population and increasing obesity rates, similar to trends observed over recent decades, global EC cases are projected to rise from 420,368 new cases in 2022 to 676,296 new cases in 2050, marking a 60.9% increase. In Spain, a 21.4% increase is expected, from 6,698 new cases in 2022 to 8,129 in 2050 (78).

Despite increasing incidence, most EC cases have a favorable prognosis, with 67% of new cases being diagnosed at early-stages, where, following treatment, exhibiting an 81% 5-year OS rate (104). However, survival rates decline with advanced stages: for FIGO stage III, the 5-year OS drops to 60%, and for stage IV disease, it decreases further to 20% (78). Furthermore, there are notable disparities in survival rates based on race. White women exhibit a 5-year relative survival rate of 84%, whereas Black women with the disease show a significantly lower rate of 64%. Primarily, this discrepancy is attributed to the higher likelihood of Black women being diagnosed with more aggressive and advanced ECs (104). However, survival is lower for Black women for every stage at diagnosis (105,106). Additionally, 5-year disease-free survival varies across different patient groups: it is approximately 90% in patients without lymph node metastasis, around 60–70% in those with pelvic lymph node metastasis, and approximately 30–40% in individuals with para-aortic lymph node involvement (107).

Survival outcomes are influenced by various predictive factors including tumor grade, age, comorbidities, tumor diameter, LVSI, and postoperative complications (108,109). Nomograms predict survival effectively (108,110) and can guide patient counseling, personalize postoperative management, and improve quality of life.

3.2. Risk and Protective Factors

Numerous studies have identified several risk and protective factors associated with EC (Table 3) (111).

3.2.1. Modifiable Risk Factors

Modifiable risk factors refer to environmental, lifestyle, or acquired factors that can increase the likelihood of developing a specific condition or disease. These factors are not directly associated with genetic predispositions passed down through generations. Within this group, we can find the following risk factors associated with EC:

-Obesity: Obesity, defined as a BMI of 30 kg/m² or higher, is characterized by excessive fat accumulation that impairs health (112). The prevalence of obesity has increases during the last decade in every country achieving pandemic dimensions (113). Nowadays, the prevalence of obesity surpasses that of underweight in the global population, except in certain regions of sub-Saharan Africa and Asia (114).

Increasing BMI escalates the risk of EC, with a 54% higher risk for every 5 kg/m² rise in BMI (115). Obesity can elevate the risk of EC through several mechanisms. These include the conversion of androgens to estrogens via heightened aromatase activity, leading to increased concentrations of endogenous sex hormones. Additionally, chronic inflammation, mediated by proinflammatory adipokines and hyperinsulinemia, plays a significant role. Furthermore, obesity may contribute to epigenetic changes, among other factors. Therefore, obesity drives EC by boosting estrogen production, disrupting signaling pathways, and fostering chronic inflammation and hormonal imbalances (116–118). In postmenopausal

women, the combination of progesterone deficiency and excess estrogen due to obesity may be a contributing factor in EC development (119).

Box 1. Estrogens and Endometrial Cancer

In a normal menstrual cycle, estrogen's proliferative effects on the endometrium are counterbalanced by progesterone, which stabilizes the endometrial lining and prepares it for potential pregnancy (18). However, when estrogen is not balanced by progesterone, condition known as "unopposed estrogen", it can lead to excessive proliferation of endometrial cells, increasing the risk of mutations and cancer development (120). Prolonged exposure to unopposed estrogen can cause endometrial hyperplasia, a condition where the endometrium becomes excessively thick (39). Hyperplasia can be a precursor to EC if left untreated (29,38) (Figure 9).

Circulating estrogens and their metabolites have been consistently linked to EC (121–123), as well as genetic variants in sex hormone-related genes like *CYP19* (124,125). Mendelian randomization studies further solidify the causal link between estrogen exposure and EC risk (125–127). Both type I and type II ECs are influenced by estrogenic factors, although to differing degrees (128,129). Factors contributing to unopposed estrogen exposure and the subsequent EC risk include hormone replacement therapy, obesity, polycystic ovary syndrome, early menarche, and late menopause (130–134).

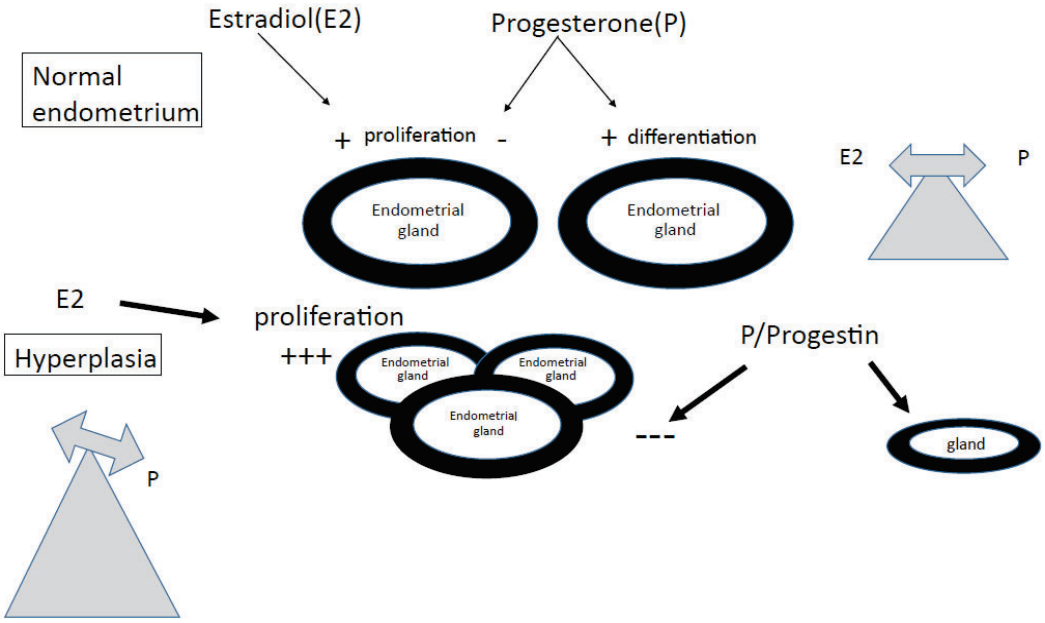


Figure 9. Estrogens and endometrial cancer.
Image from Gompel A. 2020 (120).

-Physical Activity: The WHO defines physical activity as any movement by skeletal muscles that requires energy, encompassing activities during leisure, transport, work, or domestic tasks (135). Both moderate and vigorous physical activities enhance health. Specifically, physical activity decreases EC risk by lowering levels of sex steroids, insulin resistance, and chronic inflammation (136). Additionally, physical activity may indirectly decrease EC risk by reducing obesity (137). Moreover, a meta-analysis suggests that the impact of physical activity is more pronounced in postmenopausal women (137), potentially lowering EC risk by reducing excess estrogen levels after menopause, either directly or indirectly through the reduction of peripheral adipose tissue (138,139). The study also indicates that physical activity seems to be more beneficial for overweight/obese women compared to those of normal weight (137). This protective effect may be attributed to physical activity's ability to counteract obesity-related risk factors for EC, including elevated estradiol, reduced sex hormone-binding globulin (SHBG), insulin resistance, and chronic inflammation (136,140). Therefore, physical activity appears to be a critical modifiable factor in preventing EC.

-Type 2 Diabetes: Type 2 diabetes is a chronic condition where the body struggles to use or produce enough insulin, resulting in high blood sugar levels (141). It is often linked to lifestyle factors like diet and exercise, alongside genetic and environmental influences. The incidence is swiftly rising, particularly among children and young adults up to 40 years old. Currently, approximately 537 million adults globally live with diabetes, predominantly type 2, and this figure is projected to climb to 783 million by 2045 (142).

Regarding type 2 diabetes and EC risk, it seems that hyperinsulinemia, a common phenomenon preceding diabetes onset, may be associated with EC mechanism. This connection could occur directly through its mitogenic effect or indirectly by reducing SHBG levels and subsequently increasing bioavailable estrogen levels, potentially raising EC risk (143,144).

-Tobacco Smoking: Smoking tobacco is a highly prevalent habit worldwide, with nearly 1 billion smokers globally (145). Many countries are implementing effective policies to reduce smoking prevalence, with projected declines over the next decade. However, the total number of smokers is not decreasing due to the increasing global population (145).

While numerous studies have observed a potential reduction in EC risk associated with smoking (111), the precise biological mechanism remains unclear. It is hypothesized that smoking may decrease EC risk due to its anti-estrogenic effects (146), although no consistent association has been established with lower circulating levels of estradiol (147). Conversely, smoking may increase EC risk through exposure to polycyclic aromatic hydrocarbons in cigarette smoke, which may elevate anticarcinogenic estradiol metabolites while simultaneously suppressing estrogen receptor function (148).

-Coffee Consumption: Coffee is among the most widely consumed beverages worldwide in adult population (149), with substantial implications for public health. Coffee consumption has been inversely associated with EC risk in several studies (111,150,151). The protective effect of coffee may be attributed to its potential to lower circulating estrogen and insulin levels, key hormones implicated in endometrial carcinogenesis (152). Additionally,

several bioactive compounds found in coffee, recognized for their antioxidant and chemo preventive properties, also appear to exert anticarcinogenic effects (153).

-Modifiable Reproductive Factors: Several modifiable reproductive factors can increase a woman's risk of EC by extending the overall lifetime exposure to unopposed estrogen (154).

-Parity: Parity, a key reproductive factor that refers to the number of times a woman has given birth, can influence EC risk by impacting estrogen and progesterone levels. Studies indicate a positive association between nulliparity (not having given birth) and an increased risk of developing EC (155).

-Breastfeeding: Breastfeeding is the practice of feeding an infant with milk from a woman's breast, providing essential nutrients and antibodies for their growth and development. Breastfeeding is considered a protective factor for EC due to the suppression of estrogen levels by progesterone during lactation (156).

-Hormonal Contraceptives: Hormonal contraceptives, introduced in the early 1960s, have become the dominant form of female contraception in most developed countries, with over 300 million users (157). Hormonal contraceptives contain synthetic version of estrogen and progesterone, potentially influencing female hormone balance and some cancer risk. Regarding EC, hormonal contraception seem to be associated with alterations in the mitotic activity of the endometrium, impacting the development of EC (158).

Oral contraceptives (OCs) stand as one of the most prevalent birth control methods used by women at reproductive age. Comprising a blend of estrogen and progestin, these formulations have evolved significantly since their inception. Initial formulations contained estrogen doses as high as 150 µg in the 1960s, but modern iterations have significantly reduced these doses to as low as 20 µg (159,160). The protective mechanism of OCs against EC stems from their ability to mitigate exposure to unopposed estrogen during the follicular phase of the menstrual cycle. By doing so, they effectively curtail estrogen-induced cell proliferation, a hallmark of endometrial

carcinogenesis (161,162). Furthermore, incorporating a progestin into OCs has demonstrated efficacy in mitigating the adverse effects of estrogen on EC risk (163,164).

3.2.2. Non-Modifiable Risk Factors

Non-modifiable risk factors are inherited genetic traits that cannot be altered through lifestyle changes or medical interventions. These inherited genetic risk factors can significantly influence the development of various diseases, including cancer, cardiovascular disease, neurological disorders, and metabolic conditions.

-Age: The global trend of increased longevity is evident, with a growing proportion of individuals reaching their sixties and beyond. In 1950, no country had over 11% of its population aged 65 and beyond; by 2000, this had risen to 18%. Projections suggest a dramatic rise to 38% by 2050. By mid-century, the population aged 60 or older is expected to surpass the number of adolescents aged 10–24, with estimates at 2.1 billion versus 2.0 billion, respectively (165). Advanced age is a significant risk factor for cancer, with individuals over 60 accounting for 55% of new diagnoses and 75% of cancer-related deaths (78).

The accumulation of somatic mutations in the endometrium increases with age (166–168). A recent study examining the presence of somatic driver mutations in histologically normal endometrium found that the prevalence of these mutations increased with patient age (169). The likelihood of a woman having a somatic mutation increased by 5% per year (169). However, the aging of the population increases the risk of this cancer not only by accumulating somatic mutations in the endometrium (166–168), which elevate the chance of developing EC, but also due to the hormonal changes associated with the postmenopause. As the population ages, women will spend more years in a postmenopausal state, increasing their risk of developing EC. For more details, refer to section ***Menopause***.

-Non-Modifiable Reproductive Factors: Some reproductive factors that cannot be modified can increase a woman's risk of EC by extending the overall lifetime exposure to unopposed estrogen (154).

-Menarche: Menarche refers to the first occurrence of menstruation in a woman's life, marking the onset of reproductive maturity. It typically occurs during puberty, signaling the beginning of the menstrual cycle and the ability to become pregnant.

A later menarche could decrease EC risk by reducing the total number of ovulations in woman's lifetime, thereby decreasing exposure to endogenous estrogens and periods of progesterone deficiency (133).

-Menopause: The postmenopausal period is defined as the absence of menstrual periods for 12 consecutive months without a pathological cause (170). Worldwide, menopause typically occurs between the ages of 49 and 52, with an average age of 50 (171). In developed countries, where nearly one-third of a woman's lifetime is spent in the postmenopausal phase, over 80% of ECs develop during this period (172).

Following menopause, the ovaries cease the production of estrogen and progesterone, though a minimal amount of estrogen continues to be naturally synthesized in adipose tissue (173). The influence of estrogen becomes more pronounced at postmenopause due to the absence of compensatory progesterone levels produced by the ovaries before menopause, leaving hyperestrogenism unopposed and increasing the risk of developing EC (134).

The postmenopausal state is a well-known risk factor for EC; however, the onset of menopause varies among women. Consequently, several studies have investigated whether the age at which menopause occurs affects EC risk. A recent meta-analysis of 18 studies found that a later age at menopause is associated with an increased EC risk (134). A potential biological explanation for the increased EC risk in women with delayed menopause is the extended exposure to endogenous estrogens and progesterone deficiency associated with a greater number of ovulations throughout their lifetime (134). Additionally, later menopause may heighten the risk through increased spontaneous and environmentally induced mutations in endometrial stem

cells (174). Progesterone deficiency, which is common in anovulatory cycles associated with later menopause, may also contribute to this risk (175).

-Lynch Syndrome: Lynch syndrome, an autosomal dominant inherited condition, results from germline pathogenic variants in MMR genes such as *MLH1, MSH2, MSH6,* or *PMS2*. These mutations significantly increase EC risk, with lifetime risks ranging from 13% to 49% (176). According to the Prospective Lynch syndrome Database, the cumulative risk of EC by the age 75 for women with mutations in *MLH1, MSH2, MSH6* and *PMS2* is estimated to be 37.0%, 48.9%, 41.1% and 12.8%, respectively (176).

Lynch syndrome associated EC is characterized by early onset at a young age (177), lower BMI (178), EEC histology (179), and involvement of the lower uterine segment (180). This type of EC is the most common extraintestinal sentinel cancer (40%) in women with Lynch syndrome (181). Significant advances have been made in the screening, diagnosis, surveillance, prevention, and treatment of Lynch syndrome-related EC. Universal screening for Lynch syndrome among patients with EC is widely supported, utilizing a combination of traditional clinical criteria and molecular techniques, such as MMR-IHC, microsatellite instability testing, *MLH1* promoter methylation testing, and gene sequencing (182). The efficacy of endometrial biopsy and TVS in monitoring asymptomatic Lynch syndrome carriers remains inconclusive. Consequently, prophylactic strategies such as hysterectomy and bilateral salpingo-oophorectomy (BSO) are recommended once childbearing is complete (183).

-Cowden Syndrome: Cowden syndrome, also known as multiple hamartoma syndrome or *PTEN* hamartoma tumor syndrome, is a rare autosomal-dominant condition caused by mutations in the *PTEN* tumor suppressor gene (184). These mutations result in uncontrolled cell proliferation, leading to the formation of multisystem hamartomas and malignancies. Individuals diagnosed with Cowden syndrome are at an increased risk of developing breast, thyroid, colon, kidney, and endometrial malignancies (184). Specifically, individuals with Cowden syndrome have a 20-30% lifetime risk of developing EC (185).

-Family History: A woman's risk of developing EC nearly doubles if she has a first-degree relative with the disease. Additionally, having a first-degree relative with colon cancer

increases a woman's risk of developing EC by 17% (186). Some studies suggest that the association between family history and EC is stronger under certain conditions: when multiple relatives are affected, when the affected relatives are more closely related, when the affected relative is a sister, and when the age of diagnosis is younger (187–189).

Table 3. Summary of risk and protective factors for endometrial cancer

Modifiable		
Factor	**Contrast**	**RR (95% CI)[1]**
Body mass index	For every 5kg/m2	1.54 (1.47-1.61) (115)
Physical activity	High Vs. Low	0.80 (0.75-0.85) (137)
Diabetes mellitus	Present Vs. Absent	1.89 (1.46-2.45) (190)
Tobacco smoking	Yes Vs. No	0.81 (0.74-0.88) (191)
Coffee consumption	Drinkers Vs. No drinkers	0.87 (0.79-0.95)[2,3] (150)
Reproductive factors		
Parity	Parous Vs. Nulliparous	0.69 (0.65-0.74) (155)
Breastfeeding	Longest Vs. Shortest total duration	0.61 (0.44-0.85) (192)
Oral contraceptives	Ever Vs. Never	0.57(0.43-0.77)[2] (193)
Non-Modifiable		
Factor	**Contrast**	**RR (95% CI)[1]**
Age	Cumulative risk by age 74 in Europe	1.90% (0.98%-3.00%)[4] (78)
Reproductive factors		
Menarche	Age at menarche	0.68 (0.58-0.81) (133)
Menopause	Highest Vs. Lowest age at menopause	1.89 (1.58-2.26) (134)
Lynch syndrome	MMR mutations carrier	24%-51%[5] (194)
Cowden syndrome	*PTEN* mutations	20%-30% [6] (185)
Family history	First degree relative with EC	1.82 (1.65-1.98) (186)

RR, Relative Risk; CI, Confidence Interval.
[1]Data obtained through meta-analysis.
[2]Odd Ratio (OR) (95% CI).
[3]Data obtained through pooled analysis.
[4]Cumulative risk of endometrial cancer by age 74 in Europe (Range).
[5]Cumulative incidence by age of 70 (Range).
[6]Lifetime susceptibility.

3.2.3. Potential New Risk Factors

Numerous risk and protective factors, comprising both modifiable and non-modifiable elements, have been well-established in relation to EC risk (111). Potential risk and protective factors are variables or conditions being investigated for their association with specific health outcomes. These factors are considered based on preliminary findings or potential biological mechanisms, but future research is necessary to establish a definitive link to disease development and gain widespread acceptance within the scientific community.

Typically, these factors are identified through ongoing research, epidemiological studies, or advancements in technology that allow for more nuanced understanding of the complex relationships between various factors and outcomes. They often require further investigation to determine their precise impact on health outcomes. Identifying novel risk factors can contribute to developing new prevention strategies and identifying high-risk populations. This increased awareness may facilitate EC early detection if the malignancy does develop.

These are some potential new risk and protective factors for EC that have been analyzed in recent studies:

-Endocrine Disrupting Chemicals (EDCs): According to the WHO definition, EDCs are exogenous substances or mixtures that alter the functions of the endocrine system, consequently causing adverse effects in an intact organism, its progeny, or (sub)populations (195). EDCs encompass a diverse group of chemicals, including persistent contaminants, pesticides, industrial substances, and natural compounds. They have been linked to various women's health issues, such as fertility problems, endometriosis, and endometrial and breast cancer (196). Regarding EC, although exposure to estrogens is a well-established risk factor (121,122), little is known regarding the effect of EDCs in relation to EC risk.

The epidemiological literature on EDCs and EC risk is sparse. Studies assessing exposure to individual organochlorines and polychlorinated biphenyls, using serum biomarkers (197,198) and dietary assessments (199), consistently reported null associations. Conversely, initial findings of a positive association between dietary cadmium and EC risk in a meta-

analysis of two studies (200) were not replicated in larger subsequent studies (201,202). A recent investigation of 139 case-control sets examining urinary levels of bisphenol A, parabens, and phthalate metabolites found most chemicals showed no significant associations with EC risk. However, mono-n-butyl phthalate and dibutyl phthalate exhibited statistically significant associations, suggesting a potential inverted-U risk pattern (203). Conflicting results emerged for parabens; one study reported no associations (203) while another found positive associations (204). Additionally, a study utilizing urinary biomarkers in 49 EC cases observed positive associations with alkylphenol exposures above median levels (205).

Furthermore, studies have explored not only the direct relationship with specific EDCs but also mixtures of EDCs. In a recent case-control study involving 156 EC cases and 150 controls, researchers investigated the relationship between serum xenoestrogen burden and EC risk. They identified an inverted-U risk trend, indicating a potential increase in EC risk with higher categories of total serum xenoestrogen burden (206). Also, a recent study investigating the association between the use of hair products and EC risk found a significant link with the use of straightening products, and the association was even stronger among frequent users (207). Studies examining the relationship between pesticides and EC risk have generated controversy, with conflicting findings across various assessments of their potential carcinogenicity (208–210). However, it is important to notice that most studies investigating the relationship between EDCs and EC risk have been limited by modest sample sizes. Therefore, further studies with larger sample sizes are needed to better understand the potential links between various EDCs and EC risk.

-Circadian Disruption (Night Shift Work and Sleep Duration): EC is an estrogen-dependent cancer (121,122), and there is a connection between circadian disruption and hormonally-related cancers. Night shift work was classified as probably carcinogenic to humans by the International Agency for Research on Cancer (IARC) in 2019, based on limited evidence from epidemiologic studies and sufficient evidence from animal models (211). Exposure to light at night during night shifts has been linked to a decrease in serum melatonin levels (212,213), and shorter sleep duration is also associated with lower melatonin urinary levels (214). Melatonin has demonstrated significant anti-tumor effects in various studies, affecting apoptosis, anti-growth signaling, inflammation, angiogenesis, and sex hormone levels

(215,216). Exposure to light at night during sleep deprivation or night shifts can disrupt melatonin production (212), potentially raising cancer risk (217–219). However, the link between sleep duration, night shift work, and EC is unclear, with conflicting study results. Two studies have investigated the connection between night shift work and EC risk with discordant results (220,221). Additionally, three studies investigating the link between sleep duration and EC risk reported no significant associations (222–224). Consequently, further research is necessary to evaluate the relationship between circadian disruption, specifically night shift work and sleep duration, and EC risk.

- Vitamin D: The role of vitamin D in reducing cancer incidence and mortality has been extensively studied over the years (225,226). Vitamin D, particularly in its active form, 1,25(OH)2D, is a powerful hormone that regulates cell growth by promoting differentiation, inhibiting proliferation, and fostering apoptosis in cancer cells (227,228). It also plays a role in reducing angiogenesis and metastasis, potentially aiding in cancer prevention and control (227–229). Vitamin D is primarily obtained from sunlight (227,230). Recent ecological studies have examined the relationship between cancer mortality rates and indices of total solar or UVB radiation, around the world (231–234). However, research on the relationship between sun exposure or vitamin D and EC remains limited. Three studies have investigated the association between vitamin D intake and EC risk, yielding inconsistent results (235–237).

-Microbiome: Recent findings indicate that the uterus is not a sterile cavity (238). Furthermore, emerging research indicates that the composition of microbiome could wield significant influence, potentially acting as a notable risk factor owing to its inflammatory profile in EC. However, although several emergent studies have begun to investigate the composition of the endometrial microbiome and its role in EC (239–244), the composition of endometrial microbiome in EC remains poorly studied. Therefore, future studies in this field are needed to improve the knowledge about the relationship between the endometrial microbiome and EC.

-Dietary Factors: The connection between obesity and EC suggests that diet might influence cancer development by affecting estrogen levels (119). Various studies have examined the impact of specific diets on EC risk, particularly focusing on fruit and vegetable

consumption, adherence to the Mediterranean diet, and the dietary inflammatory index, all showing a protective effect (245,246). The components of these diets may act synergistically, resulting in an overall effect greater than the sum of their individual contributions. The biological mechanisms by which these diets may reduce EC risk are multifaceted. High vegetable intake may lower EC risk by modulating steroid hormones levels, activating antioxidant mechanisms, and stimulating the immune system (247). Both the Mediterranean diet and a low dietary inflammatory index are rich in antioxidants with significant anti-inflammatory properties, which have been inversely related to EC risk (248,249). Additionally, the Mediterranean diet is rich in phytoestrogens, which have estrogen-like effects that may compete for estrogen receptors binding, potentially exerting anti-estrogenic effects (249). While previous studies support possible associations between some specific diets and EC risk (246,248,249), further research is essential to continue clarifying specific dietary connections and perform effective prevention strategies.

Beyond dietary patterns, research has explored the role of specific micro- and macronutrients in EC risk, though findings remain inconsistent. While food frequency questionnaires are commonly used in nutritional epidemiology, their susceptibility to self-reporting bias is a limitation (250). A recent Mendelian randomization study suggests potential links between EC risk and genetically predicted vitamin C levels, as well as macronutrient dietary patterns (251). Specifically, higher fat intake may elevate EC risk, while higher carbohydrate or sugar intake might reduce it (251). In addition, red and processed meats, classified as Group 2A (probably carcinogenic to humans) and Group 1 (carcinogenic to humans) by the IARC in 2015 (252), respectively, have been linked to an increased risk of EC in systematic reviews and meta-analyses (253). Studies on beverages have produced inconsistent findings regarding their impact on EC risk (254). For instance, milk contains detectable levels of steroid hormones, including estrogens (255), which could theoretically influence EC risk. Although some epidemiological studies have explored this potential link, the results remain inconclusive (235,256–261). Similarly, daily alcohol consumption has been associated with higher circulating estrogen levels in postmenopausal women (262,263), which could exacerbate estrogen levels in those undergoing estrogen replacement therapy, suggesting a possible connection to EC risk (264). This suggests a plausible association between alcohol consumption and EC risk. However, limited epidemiological research has explored this

relationship, yielding inconclusive results (265–267). To comprehensively understand the relationship between diet and EC risk, larger-scale studies incorporating detailed data on known risk factors are essential.

Considering all the above, in relation to the epidemiology of EC, it is important not only to analyze the true connection between potential new risk factors and the disease, but also to discover new ones. The discovery of new risk factors can have significant implications for public health. Aspects such as night shift work, sleep hours, dietary factors, sun exposure, or exposure to pesticides affect a large portion of the population. Therefore, investigating their potential relationship with EC risk could significantly contribute to developing preventive strategies, mitigating the expected increase in these tumors, and identifying high-risk populations.

Worldwide epidemiological studies are essential for understanding diseases. However, individual studies often face challenges due to the high costs, time commitment, and difficulty in recruiting sufficient participants to detect meaningful associations between risk factors and disease. To adress these challenges, epidemiological consortia have become essential in cancer research. By pooling data from multiple studies, researchers can increase sample sizes and gain deeper insights into disease pathology.

4. Screening, Clinical Presentation, Diagnosis, and Treatment

4.1. Screening and Early Detection

Currently, there is no general population screening test available for EC. Therefore, developing a screening test for EC is pivotal. Early detection is crucial for improving outcomes and quality of life post-treatment, as it allows for less aggressive treatment and better prognosis. The optimal screening or early detection tool should be minimally invasive, cost-effective and easy to administer while accurately detecting both pre-invasive and early-stage disease (268).

Several research groups are investigating minimally invasive sampling methods to identify a potential screening or early detection test for EC. Uterine samples, like uterine lavage and brushings, offer an excellent source of EC specific biomarkers, but their collection is invasive, painful, and poorly tolerated by some patients (269,270), limiting their suitability for widespread screening. Other minimally invasive samples, such as cervical or vaginal, could benefit from the anatomical continuity between the endometrium and the cervix, potentially allowing the identification of signs of disease originating from the upper genital tract. Cervicovaginal cytology stands out as it is routinely obtained to detect cervical cancer and precursors (271). However, although different studies have observed morphological abnormalities in cervicovaginal cytology from EC cases, its accuracy to detect EC remains a topic of debate (272). Moreover, taking advantage of the continuity between the endometrium and the cervix, molecular analyses of samples like vaginal swab or tampons are also being explored for EC detection (273–280). Blood (280–284) and urine samples (280,285–288) are also under investigation for various molecular tests related to this purpose.

The following table and figure summarize the latest studies being conducted to find a minimally invasive test for EC detection (Figure 10 & Table 4).

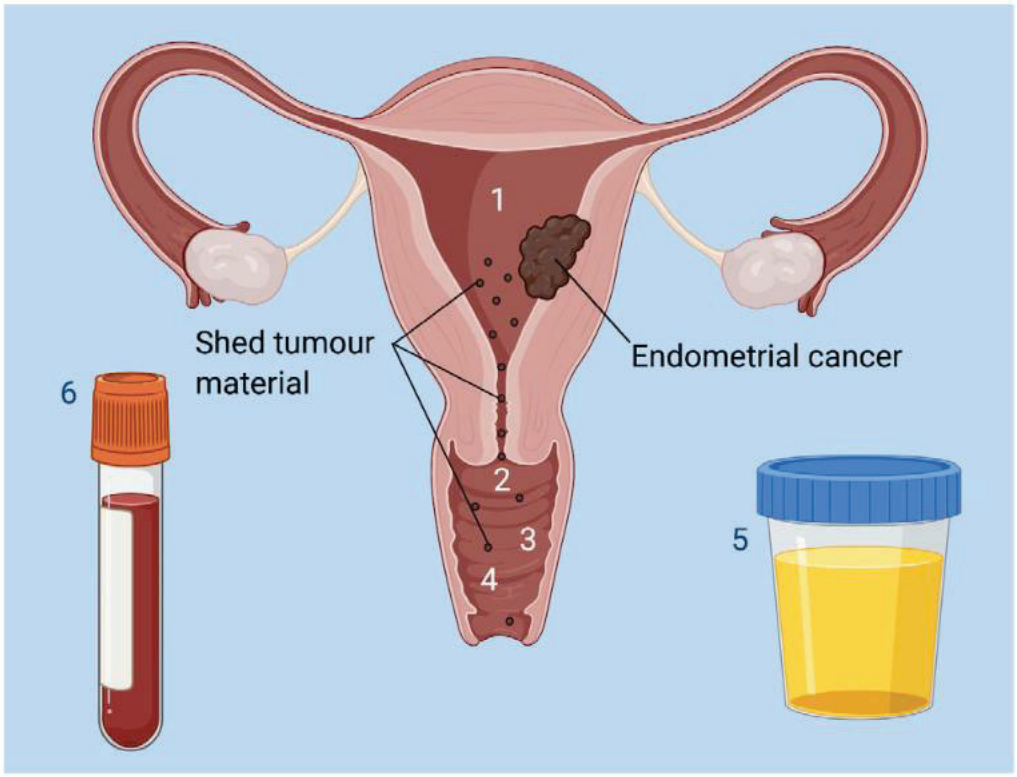


Figure 10. Sampling methods for novel detection tools.
1) Uterine lavage and brushings. 2) Cervical brush sample. 3) Vaginal tampon.
4) Vaginal swab. 5) Urine sample. 6) Blood sample.
Image from Jones ER et al. 2021 (289).

Table 4. Novel minimally invasive sampling methods for endometrial cancer detection

Sampling method	Biomarker	Advantages	Disadvantages
Cervicovaginal specimens (37,272,280,289–291)			
Cervical brush	Cytology Genomic- DNA mutations or methylation Microbiome Proteins	Non-invasive	Current thresholds insufficiently sensitive for early (pre) cancer detection
Vaginal tampon	Genomic- DNA mutations or methylation	Non-invasive Suitable for self-collection at home	Uncomfortable for elderly women
Vaginal swab	Metabolomic Genomic- methylated DNA Proteins	Non-invasive Suitable for self-collection at home	Proof-of-principle data only
Other liquid biopsies			
Urine (272,280,289,292)	Genomic- microRNA , DNA mutations Metabolites Proteins and peptides Hormones Cytology Spectroscopic	Non-invasive Suitable for self-collection at home	Proof-of-principle data only
Blood (272,280,289,290,293)	Genomic- ctDNA, cfDNA, miRNA Proteins and peptides Metabolomic Spectroscopic	Routinely available	Low concentrations of cancer-specific biomarkers in early cancer

ctDNA, Circulating tumor DNA; cfDNA, Cell free DNA; miRNA, microRNA.

4.2. Clinical Presentation

Currently, strategies to diagnose EC focus on symptomatic women. PMB, defined as vaginal bleeding occurring 12 months or more after menopause, is the most common symptom of EC. While 90% of individuals diagnosed with EC experience PMB, only 9% of women experiencing PMB are ultimately diagnosed with EC (294) (Table 5). The probability of developing EC varies with age, increasing from less than 1% in women under 50 with PMB to 24% in those over 80 (295). In case of premenopausal women with EC the main symptoms are heavy irregular menses or intermenstrual bleeding. However, 5-20% of women diagnosed with EC are asymptomatic (294), potentially leading to delayed diagnoses.

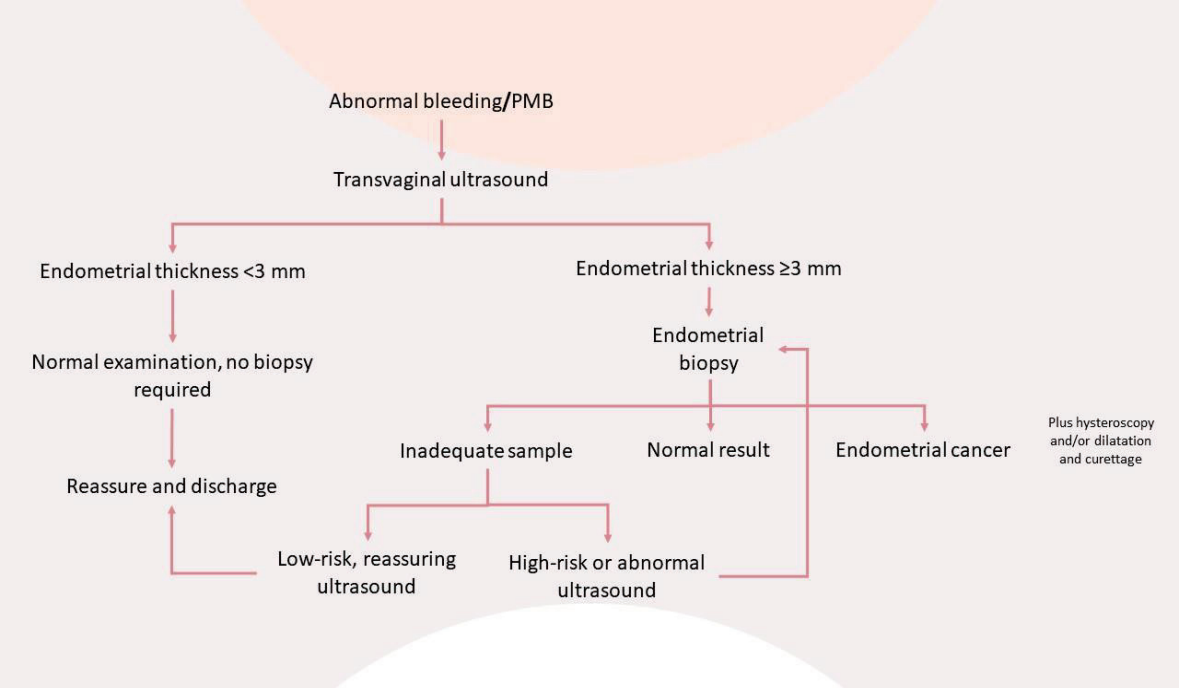
Table 5. Postmenopausal bleeding etiologies

Causes	Estimated percentages (%)
Atrophic endometrium/atrophic vagina	60-80%
Endometrial cancer	7-10%
Endometrial hyperplasia	5-10%
Endometrial/cervical polyps	2-12%
Hormone replacement therapy	15-25%
Others	<10%

Table adapted from Hurtado S et al. 2023 (296)

Performing invasive diagnostic tests on asymptomatic patients has not shown clinical benefit (297,298), thus endometrial histological examination should only be conducted when clinical suspicion arises. Therefore, the diagnostic approach for symptomatic women experiencing PMB typically encompasses the following steps (Figure 11): TVS is typically performed as a first-line investigation. The TVS provides a non-invasive assessment of double-layered endometrial thickness, which can be used to triage women for further investigation. The diagnostic accuracy of TVS for EC detection depends on the endometrial thickness cut-off used. As the endometrial thickness cut-off increases, sensitivity tends to decrease while specificity rises (299). In accordance with this, the Spanish Society of Gynecological Oncology (SEGO) in their 2023 guide for EC recommends a 3mm cut-off for endometrial thickness (300). An endometrial biopsy is indicated for woman with PMB and thickened endometrium (≥3mm) on TVS. However, endometrial biopsy is an invasive procedure with potential risks,

such as failure (11%; range 1–53%), inadequate samples (31%; range 7–76%), pain, bleeding, infection, and rare cases of perforation (301). Given the blind nature of endometrial sampling and its associated failure rate, hysteroscopy is often considered when biopsy results are inconclusive, or symptoms persist despite benign biopsy findings and suspicious TVS results (302). Hysteroscopy involves visualizing the uterine cavity using a thin, lighted scope. This allows for detailed endometrial examination and targeted biopsies of suspicious areas during the same procedure. According to a systematic review, hysteroscopy seems to have a sensitivity of 86.4% and specificity of 99.2% for EC detection, but with moderate accuracy for endometrial hyperplasia (303). Magnetic resonance imaging (MRI) is a valuable tool for assessing deep myometrial invasion, cervical involvement, and lymph node metastasis in EC. However, expert transvaginal ultrasound often provides comparable accuracy for evaluating myometrial invasion and cervical involvement (101,304). For detecting extrauterine disease or metastases in high-grade EC, a computerized tomography (CT) scan of the thorax, abdomen, and pelvis is standard practice (101,304,305).



Algorithm adapted from "Oncoguía SEGO: Cáncer de endometrio 2023" (300).

Figure 11. Diagnostic process of endometrial cancer.

4.3. Preoperative Endometrial Cancer Risk Evaluation

Preoperative risk assessment aims to determine surgical candidacy, extent of disease, and optimal surgical approach based on factors such as histological type, grade, MMI, LVSI, extrauterine spread, and molecular profile. The 2021 ESGO/ESTRO/ESP risk stratification incorporates clinical, pathological, and molecular data for improved prognostication and personalized treatment (101). While age and comorbidities also influence surgical decisions, the accuracy of preoperative risk assessment can be limited by the concordance between biopsy and final diagnosis, highlighting the need for careful consideration.

4.3.1. Histological Type

The histological type of the tumor is a crucial prognostic factor in EC. The 5th edition of the *WHO Classification of Tumours, Female Genital Tumours* (38) is used to classify EC cases histology. For more details, see section "2.3.1 Histological classification."

4.3.2. Tumor Grade

Histological grading of tumors, primarily based on architectural features (306), holds significant importance in both initial biopsy and final hysterectomy specimens, especially for EECs and NSMP group (307). While non-endometrioid carcinomas are inherently high-grade, EECs are classified using a binary system adapted from the *WHO Classification of Tumors, Female Genital Tumors* (38). Low-grade EECs are categorized as grades 1 and 2, displaying up to 5% and 6-50% solid non-glandular growth respectively, while high-grade EECs (grade 3) exhibit at least 50% solid components (Table 6) (306). This binary system not only holds prognostic significance but also streamlines clinical decision-making and improves reproducibility in clinical practice (308).

Table 6. Endometrial cancer tumor grade classification

Binary System	Grade	Description	Differentiation %
Low grade	Grade 1	Well differentiated	≤5%
	Grade 2	Moderately differentiated	(5-50%]
High grade	Grade 3	Poorly differentiated	>50%

4.3.3. Myometrial Invasion (MMI)

MMI extent is a key prognostic risk factor (309). It is recommended to assess the percentage of myometrium involved, categorizing it as none, <50%, or ≥50% of the overall myometrial thickness infiltrated by carcinoma (310,311).

4.3.4. Lymphovascular Space Invasion (LVSI)

LVSI assessment should focus on the invasive front of the tumor (312). It is crucial to differentiate between "substantial" or "extensive" LVSI and "focal" or "absent" LVSI (313,314).

4.3.5. Imaging Guidelines

The choice of imaging technique for assessing prognostic factors depends on the disease's extent and histological characteristics: For patients with early preoperative stages (apparently confined to the uterus) and low-grade histology, pelvic MRI and/or TVS are recommended to evaluate the local uterine extent of the disease (315). In contrast, for patients with advanced preoperative stages (suspected extrauterine involvement) and/or high-grade histology, contrast-enhanced thoraco-abdominopelvic CT is recommended to rule out distant metastases (316).

4.3.6. Molecular Classification

Molecular profiling has emerged as a promising tool for enhancing pre-operative risk classification, providing accurate insights into tumor characteristics from biopsy samples.

Molecular features can be used to estimate recurrence risk and survival (81,82). For more details, see section “2.3.3 Molecular classification”.

4.4. 2023 FIGO Staging

Significant advancements in pathology, molecular findings, treatments, clinical trials, and prognostic data have emerged since the 2009 FIGO staging system for EC (306). To incorporate these developments, the FIGO Committee on Women's Cancer revised the staging system in 2023, resulting in the updated 2023 FIGO staging for EC (317) (Figure 12 & Table 7).

Due to advancements in molecular classification, the 2023 FIGO staging system incorporates molecular subtypes (*POLE*-mutated, MMRd, NSMP, and p53abn) to enhance prognostic prediction and inform treatment decisions (317). Comprehensive molecular classification is encouraged for all EC cases to facilitate risk-group stratification. In early EC, the presence of pathogenic *POLE* mutations or p53 abnormalities now modifies the FIGO stage. For stage I and II tumors based on surgical/anatomical and histological findings, a *POLE*-mutated endometrial carcinoma, confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histological type, is now classified as stage IAm *POLE*-mutated. In contrast, a p53abn endometrial carcinoma confined to the uterine corpus with any MMI, with or without cervical invasion and regardless of the degree of LVSI, is classified as stage IICm p53abn (317) (Table 8).

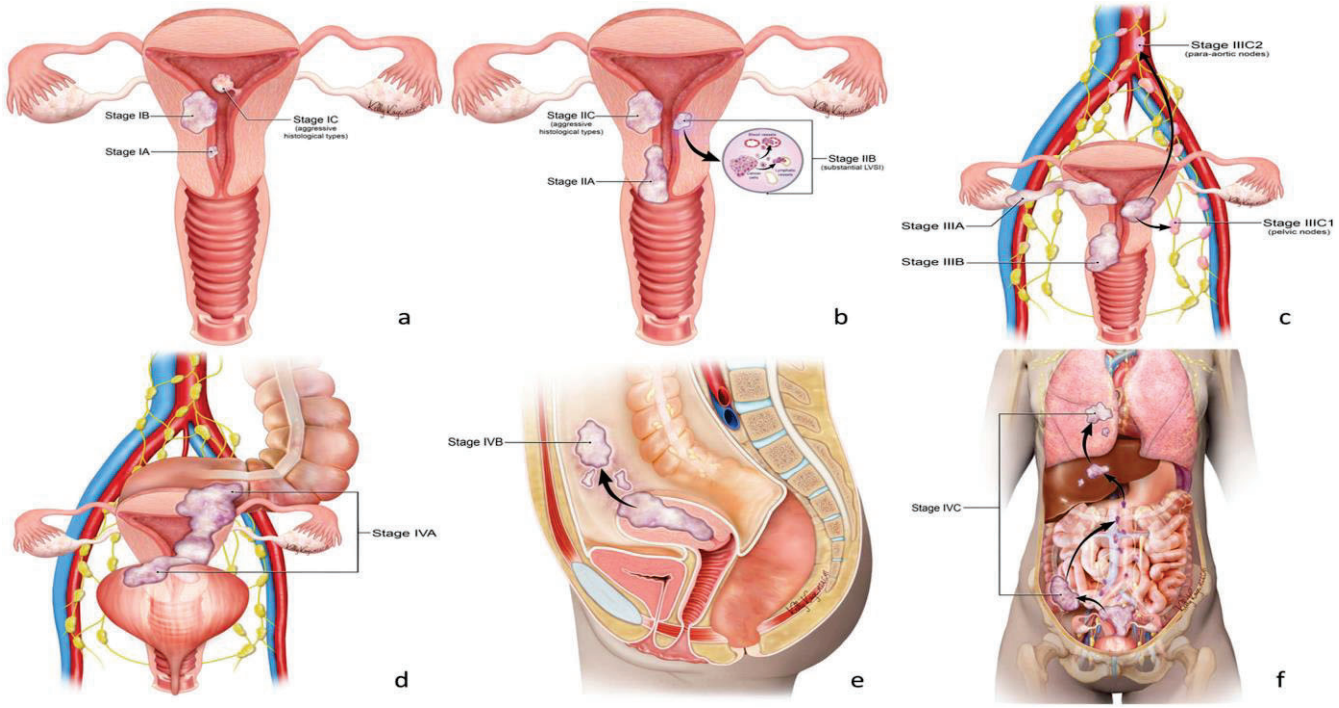


Figure 12. 2023 FIGO staging of endometrium cancer (Table 7). Stage I (a). Confined to the uterine corpus and ovary. Stage II (b). Invasion of cervical stroma with extrauterine extension OR with substantial LVSI OR aggressive histological types with myometrial invasion. Stage III (c). Local and/or regional spread of the tumor of any histological subtype. Stage IV (d–f). Spread to the bladder and/or intestinal mucosa and/or distance metastasis.
Image from Menendez-Santos M et al. 2024 (318).

Table 7. 2023 FIGO staging of cancer of the endometrium

Stage	Description
Stage I	Confined to the uterine corpus and ovary[c]
IA	Disease limited to the endometrium OR non-aggressive histological type, i.e. low-grade endometroid, with invasion of less than half of myometrium with no or focal lymphovascular space involvement (LVSI) OR good prognosis disease
	IA1 Non-aggressive histological type limited to an endometrial polyp OR confined to the endometrium
	IA2 Non-aggressive histological types involving less than half of the myometrium with no or focal LVSI
	IA3 Low-grade endometrioid carcinomas limited to the uterus and ovary[c]
IB	Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSI[d]
IC	Aggressive histological types[e] limited to a polyp or confined to the endometrium
Stage II	Invasion of cervical stroma without extrauterine extension OR with substantial LVSI OR aggressive histological types with myometrial invasion
IIA	Invasion of the cervical stroma of non-aggressive histological types
IIB	Substantial LVSI[d] of non-aggressive histological types
IIC	Aggressive histological types[e] with any myometrial involvement
Stage III	Local and/or regional spread of the tumor of any histological subtype
IIIA	Invasion of uterine serosa, adnexa, or both by direct extension or metastasis
	IIIA1 Spread to ovary or fallopian tube (except when meeting stage IA3 criteria)[c] IIIA2 Involvement of uterine subserosa or spread through the uterine serosa
IIIB	Metastasis or direct spread to the vagina and/or to the parametria or pelvic peritoneum
	IIIB1 Metastasis or direct spread to the vagina and/or the parametria IIIB2 Metastasis to the pelvic peritoneum
IIIC	Metastasis to the pelvic or para-aortic lymph nodes or both[f]
	IIIC1 Metastasis to the pelvic lymph nodes IIIC1i Micrometastasis IIIC1ii Macrometastasis IIIC2 Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes IIIC2i Micrometastasis IIIC2ii Macrometastasis
Stage IV	Spread to the bladder mucosa and/or intestinal mucosa and/or distance metastasis
IVA	Invasion of the bladder mucosa and/or the intestinal/bowel mucosa
IVB	Abdominal peritoneal metastasis beyond the pelvis
IVC	Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain, or bone

Table 8. 2023 FIGO endometrial cancer stage with molecular classification

Stage designation	Molecular findings in patients with early endometrial cancer (Stages I and II after surgical staging)
Stage $IAm_{POLEmut}$	*POLEmut* endometrial carcinoma, confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histological type
Stage $IICm_{p53abn}$	p53abn endometrial carcinoma confined to the uterine corpus with any myometrial invasion, with or without cervical invasion, and regardless of the degree of LVSI or histological type

Tables from Berek JS et al. 2023 (317).

4.5. Treatment

4.5.1. Primary Treatment: Surgery

Surgery is the primary treatment for localized EC (79). Surgical staging determines prognosis and identifies patients needing additional therapy. The standard procedure is total hysterectomy with BSO, performed either laparoscopically or abdominally (79).

Nevertheless, it is noteworthy that approximately 14% of EC cases emerge in premenopausal women, including 5% under 40 years old, often in nulliparous as early-stage cancers (319). For women with low-grade EEC and lacking evidence of MMI on imaging, including MRI, who desire to preserve fertility, a non-surgical route could be considered. Moreover, in younger women with low-grade, early-stage EC, ovarian preservation might be contemplated to alleviate the menopausal symptoms linked with more extensive surgery. However, determining which low-risk candidates are suitable for this surgical strategy poses a challenge, necessitating meticulous expert deliberation and counseling.

4.5.2. Adjuvant Treatment

Adjuvant treatment encompasses non-surgical interventions administered alongside primary surgery with the goal of minimizing the risk of recurrence. In the context of EC, the primary modalities for adjuvant treatment include chemotherapy, radiotherapy, and hormonal therapy. The decision to utilize adjuvant treatment depends on the disease stage and the patient's risk of recurrence. The ESGO/ESTRO/ESP guideline for managing EC patients classify patients into five risk groups, with or without molecular classification (Table 9) (101). This guideline provides specific recommendations for adjuvant treatment options tailored to each risk group:

Table 9. Definition of prognostic risk groups for endometrial cancer

Risk group	Molecular classification unknown	Molecular classification known*†
Low	► Stage IA endometrioid + low-grade‡ + LVSI negative or focal	► Stage I–II ***POLEmut*** endometrial carcinoma, no residual disease ► Stage IA **MMRd/NSMP** endometrioid carcinoma + low-grade‡ + LVSI negative or focal
Intermediate	► Stage IB endometrioid + low-grade‡ + LVSI negative or focal ► Stage IA endometrioid + high-grade‡ + LVSI negative or focal ► Stage IA non-endometrioid (serous, clear cell, undifferentiared carcinoma, carcinosarcoma, mixed) without myometrial invasion	► Stage IB **MMRd/NSMP** endometrioid carcinoma + low-grade‡ + LVSI negative or focal ► Stage IA **MMRd/NSMP** endometrioid carcinoma + high-grade‡ + LVSI negative or focal ► Stage IA **p53abn** and/or non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion
High–intermediate	► Stage I endometrioid + substantial LVSI regardless of grade and depth of invasion ► Stage IB endometrioid high-grade‡ regardless of LVSI status ► Stage II	► Stage I **MMRd/NSMP** endometrioid carcinoma + substantial LVSI regardless of grade and depth of invasion ► Stage IB **MMRd/NSMP** endometrioid carcinoma high-grade‡ regardless of LVSI status ► Stage II **MMRd/NSMP** endometrioid carcinoma
High	► Stage III–IVA with no residual disease ► Stage I–IVA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) with myometrial invasion, and with no residual disease	► Stage III–IVA **MMRd/NSMP** endometrioid carcinoma with no residual disease ► Stage I–IVA **p53abn** endometrial carcinoma with myometrial invasion, with no residual disease ► Stage I–IVA **NSMP/MMRd** serous, undifferentiated carcinoma, carcinosarcoma with myometrial invasion, with no residual disease
Advanced metastatic	► Stage III–IVA with residual disease ► Stage IVB	► Stage III–IVA with residual disease of any molecular type ► Stage IVB of any molecular type

*For stage III–IVA *POLE*mut endometrial carcinoma and stage I–IVA MMRd or NSMP clear cell carcinoma with myometrial invasion, insufficient data are available to allocate these patients to a prognostic risk group in the molecular classification. Prospective registries are recommended.
†See text on how to assign double classifiers (eg, patients with both *POLE*mut and p53abn should be managed as *POLE*mut).
‡According to the binary FIGO grading, grade 1 and grade 2 carcinomas are considered as low-grade and grade 3 carcinomas are considered as high-grade.
LVSI, lymphovascular space invasion; MMRd, mismatch repair deficient; NSMP, non-specific molecular profile; p53abn, p53 abnormal; *POLE*mut, polymerase-mutated.

Table from Concin N et al. 2021 (101).

-Low-risk EC: Low-risk EC, typically defined as early-stage, well-differentiated disease with no MMI or LVSI, generally does not require adjuvant therapy. This approach is supported by evidence demonstrating low recurrence rates and limited survival benefit from adjuvant treatment. Local recurrence can usually be managed effectively with radiotherapy when necessary (320–322).

-Intermediate-risk EC: Adjuvant pelvic radiotherapy (PRT) significantly reduces locoregional recurrence rates in patients with intermediate-risk EC, especially those with high-intermediate-risk features such as deep MMI, LVSI, or high-grade tumors (320,321). Both external beam radiation therapy (EBRT) and vaginal brachytherapy effectively control vaginal recurrence, but EBRT offers superior protection against pelvic relapse (323–325). Omitting adjuvant brachytherapy can be considered in patients under 60 years old due to the lower risk of vaginal recurrence in this age group (101). For patients with low-intermediate-risk features, the role of adjuvant therapy is less clear and may be considered on a case-by-case basis (101).

-High intermediate-risk EC: Adjuvant PRT has been established as the standard of care for patients with high-intermediate-risk EC, based on trials such as PORTEC-1 and GOG-99 (97,325). These studies demonstrated a significant reduction in locoregional recurrence, particularly vaginal vault recurrences, with PRT. While both EBRT and vaginal brachytherapy are effective, EBRT offers superior protection against pelvic relapse. The role of adjuvant chemotherapy in this setting is less clear, with limited evidence of OS benefit (326). The omission of any adjuvant treatment may also be considered only when close follow-up is guaranteed to ensure detection and prompt treatment of recurrence at an early-stage (101).

-High-risk EC: High-risk EC encompasses advanced-stage disease (III-IVA) and early-stage tumors with aggressive features (e.g., p53 mutations, non-endometrioid histology). Adjuvant therapy with chemotherapy and radiotherapy is recommended for patients with high-risk EC to reduce recurrence risk (327). While both chemotherapy and radiotherapy contribute to improved outcomes, the optimal treatment sequence and specific regimens remain areas of ongoing investigation (101).

-Advanced metastatic EC: Advanced EC carries a poor prognosis with 5-year survival rates of approximately 20-25% (328). Initial management typically involves surgery to remove as much of the cancer as possible. For patients with unresectable disease, systemic therapy (chemotherapy, targeted therapy, or immunotherapy) is the primary treatment option (304). Adjuvant therapy is recommended for patients with high-risk early-stage disease or following surgical resection of advanced disease to reduce the risk of recurrence. The optimal regimen often involves a combination of chemotherapy and radiation therapy (101).

4.5.3. Molecular Subtyping and Adjuvant Treatment

Molecular subtyping has revolutionized EC management. The identification of distinct molecular subgroups, including *POLE*-mutated, MMRd, p53-abnormal, and NSMP tumors, provides crucial prognostic and therapeutic insights. This classification system is transforming treatment decisions and guiding the development of targeted therapies.

The *POLE*-mutated group, characterized by high mutational load and excellent prognosis, may not require adjuvant therapy due to its favorable outcomes. In contrast, the MMRd group, while demonstrating intermediate prognosis, may benefit from immunotherapy given its high mutational load and potential response to immune checkpoint inhibitors. The p53-abnormal group, associated with aggressive disease and poor prognosis, may benefit from chemo-radiotherapy combinations and potentially poly (ADP-ribose) polymerase (PARP) inhibitors. Finally, the NSMP group, exhibiting heterogeneous outcomes, may respond well to hormonal therapies due to frequent estrogen receptor (ER) and progesterone receptor (PR) positivity (Table 10) (329).

Ongoing clinical trials are evaluating the optimal EC adjuvant treatment strategies based on molecular subtypes (330). The incorporation of molecular profiling into routine clinical practice is essential for tailoring treatment decisions and improving patient outcomes.

Table 10. Prognostic and therapeutic implications of the molecular classification of endometrial cancers

Molecular Group	Identifying Features	Surrogate Marker	Predominant Endometrial Cancer Histology	Prognosis (Progression Free Survival at 5 years)	Therapeutic Implication
POLE-mutated	Very high mutational load	*POLE* exonuclease domain mutation	All histologies except for serous carcinomas	Excellent (92-100%)	Adjuvant treatment may not be required given excellent prognosis
MMRd	High mutational load	Loss of *MLH1, MSH2,MSH6* and/or *PMS2* expression	Predominately endometrioid carcinomas	Intermediate (80-90%)	Limited benefit from chemotherapy. Improved response to immunotherapy
p53-abnormal	Low mutational load, high copy-number variations	Abnormal p53 expression	Serous, high grade endometrioid	Poor (50%)	Benefit from concurrent chemo-radiotherapy. PARP inhibitor therapy may also be effective
NSMP	Low mutational load, low copy-number variations	Absence of the other markers	Low grade endometrioid	Heterogenous but overall considered intermediate (75-80%)	May benefit from hormonal treatment given frequent ER+ and PR+

MMRd, Mismatch Repair Deficient; NSMP, No Specific Molecular Profile; PARP, poly(ADP-ribose) polymerase; ER+, Estrogen receptor-positive; PR+, progesterone receptors-positive.
Table from Baker-Rand H et al. 2024 (329).

HYPOTHESES

HYPOTHESES

HYPOTHESIS 1. The incidence and mortality rates of endometrial cancer may increase in Catalonia by 2030.

Rationale: EC ranks as the second most common gynecological cancer globally and the most prevalent in developed countries. Its incidence has been steadily rising in recent years. This increase is primarily attributed to the aging population and the growing prevalence of obesity, both well-established risk factors for EC. Robust forecast analyses predicting changes in incidence and mortality over the coming years are fundamental for healthcare providers, allowing them to anticipate and implement appropriate measures to treat future patients effectively and improve their quality of life.

HYPOTHESIS 2. Endometrial cancer may be associated with circadian rhythm disruption.

Rationale: EC is an estrogen-dependent cancer. The circadian rhythm regulates sleep-wake cycles and hormone release, and its disruption has been linked to hormonally related cancers. Night shift work and sleep disorders can disturb these circadian rhythms, potentially causing imbalances in estrogen and melatonin levels. Epidemiological studies suggest that lower melatonin levels and high unopposed estrogen levels may elevate EC risk. Understanding the association between circadian disruption (including night shift work, sleep duration and chronotype) and EC is pivotal. Given that 20% of Europeans work in night shifts and around 25% of older European adults have sleep problems, addressing these issues becomes particularly important. This understanding can help to develop strategies to mitigate the expected increase in these cancers and improve the identification of high-risk individuals.

HYPOTHESIS 3. Cervicovaginal cytology could have a role in the detection of endometrial cancer.

Rationale: EC currently lacks established screening or early detection methods despite its high incidence. Therefore, there is an urgent need for new detection approaches. Researchers are exploring various alternatives, such as cervicovaginal cytology, which has proven effective in screening for cervical cancer. Cervicovaginal cytology, primarily utilized for cervical cancer screening, often collects cells from the cervix, which may include endometrial cells due to the anatomical continuity. Detection of abnormal endometrial cells in Pap test samples, especially in postmenopausal women, may indicate underlying endometrial pathology, including EC. Recent research has focused on the sensitivity of molecular analysis in cervicovaginal samples for EC detection. While preliminary results suggest this approach might be more sensitive than traditional morphological evaluation, the exact sensitivity of morphological evaluation in cervicovaginal cytology for EC diagnosis remains unknown. Consequently, its accuracy in detecting EC remains debatable. Therefore, determining the sensitivity of cervicovaginal cytology's morphological evaluation for EC is essential to assess its potential clinical utility. This information will serve as a valuable baseline when evaluating the promise of molecular strategies.

OBJECTIVES

OBJECTIVES

OBJECTIVE 1. To forecast and evaluate changes in the incidence and mortality rates of endometrial cancer in Catalonia by 2030.

Article 1: Frias-Gomez J, Peremiquel-Trillas P, Alemany L, Ameijide A, Marcos-Gragera R, Ponce J, Brunet J, Matias-Guiu X, Galceran J, Izquierdo Á, Borràs JM, Costas L, Clèries R. Predicting the rising incidence and mortality of endometrial cancers among women aged 65-74 years in Catalonia. Maturitas. 2021 Feb;144:11-15. doi: 10.1016/j.maturitas.2020.09.006. Epub 2020 Sep 30. PMID: 33358202.

OBJECTIVE 2. To assess whether occupational or sleep-related exposures related to circadian rhythm disruption are associated with endometrial cancer.

Article 2: Costas L, **Frias-Gomez J**, Benavente Moreno Y, Peremiquel-Trillas P, Carmona Á, de Francisco J, Caño V, Paytubi S, Pelegrina B, Martínez JM, Pineda M, Brunet J, Vidal A, Matias-Guiu X, Bosch X, Ponce J, Kogevinas M, De Sanjosé S, Alemany L. Night work, chronotype and risk of endometrial cancer in the Screenwide case-control study. Occup Environ Med. 2022 Feb 24:oemed-2021-108080. doi: 10.1136/oemed-2021-108080. Epub ahead of print. PMID: 35210289.

Article 3: Frias-Gomez J, Alemany L, Benavente Y, Clarke MA, de Francisco J, De Vivo I, Du M, Goodman MT, Lacey J, Liao LM, Lipworth L, Lu L, Merritt MA, Michels KA, O'Connell K, Paytubi S, Pelegrina B, Peremiquel-Trillas P, Petruzella S, Ponce J, Risch H, Setiawan VW, Schouten LJ, Shu XO, Trabert B, Van den Brandt PA, Wentzensen N, Wilkens LR, Yu H, Costas L. Night shift work, sleep duration and endometrial cancer risk: A pooled analysis from the Epidemiology of Endometrial Cancer Consortium (E2C2). Sleep Med Rev. 2023 Dec;72:101848. doi: 10.1016/j.smrv.2023.101848. Epub 2023 Sep 7. PMID: 37716022; PMCID: PMC10840870.

OBJETIVE 3. To assess the sensitivity of the morphological evaluation of cervicovaginal cytology in endometrial cancer detection.

Article 4: Frias-Gomez J, Tovar E, Vidal A, Murgui L, Ibáñez R, Peremiquel-Trillas P, Paytubi S, Baixeras N, Zanca A, Ponce J, Pineda M, Brunet J, de Sanjosé S, Bosch FX, Matias-Guiu X, Alemany L, Costas L; Screenwide Team. Sensitivity of cervical cytology in endometrial cancer detection in a tertiary hospital in Spain. Cancer Med. 2021 Oct;10(19):6762-6766. doi: 10.1002/cam4.4217. Epub 2021 Sep 4. PMID: 34480514; PMCID: PMC8495290.

Article 5: Frias-Gomez J, Benavente Y, Ponce J, Brunet J, Ibáñez R, Peremiquel-Trillas P, Baixeras N, Zanca A, Piulats JM, Aytés Á, Matias-Guiu X, Bosch FX, de Sanjosé S, Alemany L, Costas L; Screenwide Team. Sensitivity of cervico-vaginal cytology in endometrial carcinoma: A systematic review and meta-analysis. Cancer Cytopathol. 2020 Nov;128(11):792-802. doi: 10.1002/cncy.22266. Epub 2020 Mar 23. PMID: 32202704.

MATERIAL AND METHODS AND RESULTS

SUMMARY OF THE ARTICLES INCLUDED IN THE THESIS

	Article 1	Article 2	Article 3	Article 4	Article 5
Design	Population-based cohort	Case-control study	Pooled analysis of case-control and cohort studies	Retrospective study	Systematic review and meta-analyses
Objectives	Incidence and mortality forecast until 2030 in Catalonia	EC association with circadian disruption factors: sleep duration, night shift work and chronotype[3]		Cervicovaginal cytology sensitivity for EC detection	
Study	Population-based cancer registries of Girona and Tarragona, and Catalan Mortality Registry	Screenwide case-control study	11 studies from E2C2	Bellvitge University Hospital database and Screenwide case-control study's database	45 studies from systematic review
Participants	An average of 176 cases/year[1] and 171 deaths/year[2] between 2005-2015	180 EC & 218 Co	6,335 EC & 18,453 Co	371 EC	6,599 EC
Statistical Methods	Bayesian autoregressive age-period-cohort models	Multivariable unconditional logistic regression models	Two-stage methodology: Multivariable unconditional logistic regression models and random effects models meta-analyses	Descriptive statistics	Random effects models meta-analyses
Statistical software	R 4.2.1	Stata v.16	Stata v.16	Stata v.16	Stata v.15

NA, Not applicable. E2C2, Epidemiology of Endometrial Cancer Consortium. EC, Endometrial cancer. Co, Controls
[1]Based on population-based cancer registries of Girona and Tarragona
[2]Based on Catalan Mortality Registry
[3]Chronotype only in Article 4.

ARTICLE 1

Frias-Gomez J, Peremiquel-Trillas P, Alemany L, Ameijide A, Marcos-Gragera R, Ponce J, Brunet J, Matias-Guiu X, Galceran J, Izquierdo Á, Borràs JM, Costas L, Clèries R. Predicting the rising incidence and mortality of endometrial cancers among women aged 65-74 years in Catalonia. Maturitas. 2021 Feb;144:11-15. doi: 10.1016/j.maturitas.2020.09.006. Epub 2020 Sep 30. PMID: 33358202.

Maturitas 144 (2021) 11–15

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Predicting the rising incidence and mortality of endometrial cancers among women aged 65-74 years in Catalonia

Jon Frias-Gomez [a,b,c], Paula Peremiquel-Trillas [a,b,c], Laia Alemany [a,b,d], Alberto Ameijide [e,f], Rafael Marcos-Gragera [d,g,h,i], Jordi Ponce [j], Joan Brunet [i,k,l,m], Xavier Matias-Guiu [c,l,n,o], Jaume Galceran [e,f], Ángel Izquierdo [g,h,k,m], Josep M. Borràs [b,p,q], Laura Costas [a,b,*,1], Ramon Clèries [b,p,q,1,*]

[a] Cancer Epidemiology Research Programme, Catalan Institute of Oncology, Av Gran Vía 199-203, L'Hospitalet de Llobregat, Barcelona, 08908, Spain
[b] Bellvitge Biomedical Research Institute (IDIBELL), Av Gran Vía 199-203, L'Hospitalet de Llobregat, Barcelona, 08908, Spain
[c] Faculty of Medicine, University of Barcelona, Barcelona, Spain
[d] Consortium for Biomedical Research in Epidemiology & Public Health (CIBER Epidemiología y Salud Pública - CIBERESP), Carlos III Institute of Health, Avda. Monforte de Lemos 3-5, Madrid, Spain
[e] Tarragona Cancer Registry, Cancer Prevention and Epidemiology Service, Sant Joan de Reus University Hospital, Reus, Spain
[f] Pere Virgili Health Reserach Institute (IISPV), Reus, Spain
[g] Epidemiology Unit and Girona Cancer Registry, Oncology Coordination Plan, Department of Health, Autonomous Government of Catalonia, Catalan Institute of Oncology, Girona, 17007, Spain
[h] Descriptive Epidemiology, Genetics and Cancer Prevention Group, Girona Biomedical Research Institute (IDIBGI), Spain
[i] Medical Sciences Dpt, School of Medicine, University of Girona, Girona, Spain
[j] Department of Gynecology and Obstetrics, Bellvitge University Hospital, IDIBELL, Hospitalet de Llobregat, Barcelona, Spain
[k] Hereditary Cancer Program, IDIBELL, Catalan Institute of Oncology, Hospitalet de Llobregat, Barcelona, Spain
[l] Centro de Investigación Biomédica en Red en Cáncer (CIBERONC), Madrid, Spain
[m] Medical Oncology Department, Catalan Institute of Oncology, Doctor Josep Trueta, Girona University Hospital, Av. França s/n, Girona, 17007, Spain
[n] Department of Pathology, Bellvitge University Hospital, IDIBELL. Hospitalet de Llobregat, Barcelona, Spain
[o] Department of Pathology, Arnau de Vilanova University Hospital, University of Lleida, IRBLLEIDA
[p] Cancer Plan, Catalan Institute of Oncology, Av Gran Vía 199-203, L'Hospitalet de Llobregat, Barcelona, 08908, Spain
[q] Department of Clinical Sciences, Faculty of Medicine, University of Barcelona Feixa Llarga s/n, L'Hospitalet de Llobregat, Barcelona, 08907, Spain

ARTICLE INFO

Keywords:
Endometrial cancer
Incidence
Mortality
Survival
Time trends
Elderly women

ABSTRACT

Endometrial cancer is currently one of the most common gynecological cancers. Reported incidence rates vary in Spain depending on the region. We estimated what the incidence and mortality of endometrial cancers in Catalonia will be by 2030 and compared the predictions with data from 2010. Bayesian autoregressive age-period-cohort models were employed to predict incidence and mortality rates for 2015−2030. The incidence of endometrial cancer for women younger than 65 years was predicted to be lower in 2030 than in 2010, whereas it was predicted to be higher for women aged 65–74 years. Moreover, mortality rates for women aged ≥65 in 2030 are likely to exceed the rates in 2010. Five-year relative survival for all ages was slightly higher in the period 2005–2009 (79.3 %, 95 %CI: 75.8 %–82.9 %) compared with those in 1995–1999 (76.0 %, 95 %CI: 72.1 %–80.2 %). This plausible new scenario might be useful to plan new clinical and preventive strategies in the near future.

1. Introduction

Cancers of the endometrium rank as the fourth most frequently diagnosed cancers among European women [1]. Endometrial cancer is the most common type, representing 90 % of the cancers of the corpus uteri. Endometrial cancers are mostly diagnosed after menopause and hormones play a key role in their etiology [2]. Established risk factors include early menarche, late menopause, nulliparity, menopausal

* Corresponding authors at: Cancer Epidemiology Research Program, Catalan Institute of Oncology (ICO), IDIBELL, L'Hospitalet de Llobregat, Pla Director d'Oncología, IDIBELL, Av Gran Vía 199-203 08908 Hospitalet de Llobregat, Av. Gran Via de L'Hospitalet 199-203, L'Hospitalet de Llobregat Barcelona, 08908, Spain.
E-mail addresses: lcostas@iconcologia.net (L. Costas), r.cleries@concologia.net (R. Clèries).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.maturitas.2020.09.006
Received 27 March 2020; Received in revised form 19 June 2020; Accepted 25 September 2020
Available online 30 September 2020

hormone use, obesity, diabetes, hypertension and Lynch syndrome [2–5].

A recent study reported an increasing trend of incidence rates among postmenopausal women in several European countries contrasted with their stabilization in premenopausal women [6]. In Spain, a large variability of rates has been reported depending on the region, with a steady overall rise since 1993 up to 2007 [7]. In Catalonia region, northeastern Spain, endometrial cancers ranked 3rd since 2010 and incidence rates leveled off earlier than in the rest of Spain [8]. However, the projections of the number of cases up to 2025 were predicted to growth mainly in women aged 65 and older, and the authors suggested that these changes could be associated with predicted changes in population structure (ageing) in Catalonia [8]. In that study, a stable trend for mortality was predicted suggesting also a stable trend in survival, although survival data was not available [8].

Hence, our aim was to inquire more about this trend in order to predict changes and to discuss their biological plausibility. Incidence and mortality rates were compared between 2010 and 2030 in Catalonia by different age groups. Since mortality depends on incidence and survival, we also evaluated the time trends of endometrial cancer patients' survival in order to assess a potential change in mortality trends.

2. Methods

2.1. Data

Corpus uteri cancer incidence (ICD-10 C54) was obtained from the population-based cancer registries of Girona (Girona Cancer Registry, GCR) and Tarragona (Tarragona Cancer Registry, TCR) provinces for the period between 1994 and 2012. These cancer registries follow the quality requirements specified by the International Agency for Research on Cancer (IARC) to publish [9]. Corpus uteri cancer is a heterogeneous group of neoplasms, consisting mainly of endometrial cancers, which account for more than 90 % of the cases, and other less frequent tumours such as endometrial sarcomas [10]. We used this information to estimate endometrial cancer incidence in the whole region of Catalonia. We obtained cancer mortality data for the period between 1994 and 2013 from the Catalan Mortality Registry (CMR). Mortality data was extracted from the registry using the main cause of death reported in the death certificates. Therefore, cases with ICD-10 code C54 were considered as main cause of death. Incidence and mortality data (number of new cancer cases and deaths) were categorized in annual intervals for eighteen 5-year age groups from 0 to 4 years to 85 and older. The Catalan Institute of Statistics (https://www.idescat.cat/) provided data on the Catalan population demographics by 5-year age groups for the period 1995–2017 (observed) and from 2018 to 2030 (projected).

The Epidemiology Unit, GCR, TGC and CMR are statistical units part of the Pla Estadístic de Catalunya approved to produce official estimates of cancer incidence and mortality. The GCR and TCR studies have an exception for informed consent as they involve large datasets, which are retrospective and observational, characteristics that make consent impractical to collect. Nonetheless, security measures are taken to protect patient confidentiality.

2.2. Statistical modeling

We estimated cancer incidence in whole region of Catalonia from 1994 to 2012 by applying the age-specific cancer rates in Girona and Tarragona, which accounted for 20 % of the Catalan population [8]. Based on these estimates, Bayesian autoregressive age–period–cohort models were fitted to data from the period between 1994 and 2012, and these models were used to predict incidence and mortality for 2015–2030. Details of these statistical modeling are described elsewhere [8]. Age-standardized rates (ASR) were reported according to the European Standard Population of 2013 [11]. We also compared the age-specific rates of endometrial cancer incidence and mortality in the years 2010 and 2030. For rates presented beyond 2012, 95 % prediction intervals were provided.

Ederer II 5-year relative survival (RS) for endometrial cancer was calculated using the web-application WebSurvCa [12]. RS has been used as a measure of the temporal evolution of the excess risk of death of a cohort of patients diagnosed with cancer, taking into account the mortality rates of the reference population. Time trends of survival were presented by 5-year periods during 1995–1999, 2000–2004 and 2005–2009 according to age groups 15–64 and 65 and older.

3. Results

Table 1 presents the burden of incidence and mortality for selected years 2000 and 2010 (observed) and 2020 and 2030 (predicted) by age group. The predicted increase in the number of cases and deaths observed during 2000–2030 is due to the rise in the number of cases among women aged 65 and older. This growth in the number of cases has an effect in the burden of disease in terms of mortality.

Fig. 1 shows time trends of endometrial cancer incidence and mortality ASRs for the 1995–2030 time period. Incidence rates fluctuated during the period 1994–2012, while a stable trend was observed for mortality. The projections of these rates showed a decreasing incidence trend and a very slight rise in mortality. However, by age-specific groups (Fig. 2), incidence rates for women aged younger than 65 in 2030 might be below their counterpart rates in 2010, whereas for women aged 65–74 incidence rates in 2030 will be surpassing the rates from 2010. Moreover, we observed that mortality rates for women aged 65 and older in 2030 will clearly exceed the rates in 2010.

Finally, time trends of 5-year survival of endometrial cancer showed a slightly rise since 1995 (Fig. 3). In 1995–1999, the 5-year RS (all ages) was 76.0 % (95 % confidence interval (CI): 72.1 %–80.2 %), and it reached 79.3 % (95 %CI: 75.8 %–82.9 %) in 2005–2009. A similar growth was observed in the 65 and older age group in which 5-year RS reached a value of 70.2 % (95 %CI: 64.7 %–76.2 %). However, in the 15–64 years age group no increase was observed and 5-years RS reached a value of 88.7 % (95 %CI: 85.1 %–92.4 %) in 2005–2009.

Table 1
Time trends of the number of cases and deaths by age group, and incidence and mortality rates for endometrial cancer in Catalonia for selected years during the period 2000-2030.

Incidence cases Year	35−64	> = 65	All ages	ASR
2000†	381	421	818	27.1
2010†	378	387	770	21.6
*2020**	312	512	828	20.4
(95 %PI)	(247−377)	(438−586)	(685−981)	(17.4−23.4)
*2030**	290	555	850	19.9
(95 %PI)	(195−385)	(458−592)	(649−989)	(14.9−24.9)
Mortality cases Year	**35−64**	**> = 65**	**All ages**	**ASR**
2000†	24	117	141	4.4
2010†	29	121	150	4.0
2020*	29	158	187	5.1
(95%PI)	(23−35)	(128−186)	(150−222)	(2.1−7.1)
2030*	33	192	220	5.7
(95 %PI)	(22−41)	(159−221)	(179−263)	(2.7−9.2)

ASR: Age-Standardized Rate (European Standard Population) per 100,000 women-years.
†: for 2000 and 2010 incidence and mortality were estimated for the whole Catalonia from the population-based cancer registries of Girona and Tarragona and from the Catalonia mortality registry.
*: for 2020 and 2030 the median of the projected number of cases and rates and their 95 % prediction interval (95 % PI) were provided.

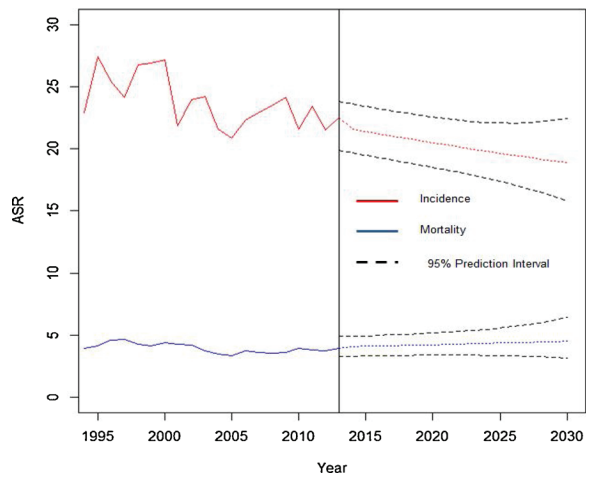


Fig. 1. Age-standardized incidence (red) and mortality (blue) rates (ASR, European Standard-2013) per 100,000 women-years of endometrial cancer in Catalonia from 1995 to 2030.

4. Discussion

Overall, our study showed a decrease in incidence and a slight increase in mortality of endometrial cancer up to 2030 in Catalonia. However, this reduction in incidence was not homogenous across age groups: a decrease was predicted for women 64 years old or younger, while a rise was expected among those aged 65–74. In parallel, a slight rise of mortality caused by endometrial cancers for the same period of time was also predicted for women aged 65–74. Moreover, 5-year relative survival remained high and did not present significant changes during this time period.

Since survival increased slightly during the study period, the increasing mortality in older ages could be due to the rise in incidence in these age groups, since the relationship between incidence-mortality-survival can be described as a multistate model [13]. The increment of incidence in women aged 65–74 might be explained by different factors: 1) overall growth of obesity and diabetes prevalence [14] which both are well-defined risk factors for endometrial cancer [3,4,15]; and 2) decreasing parity in most of developed countries [16], which is also a stablished risk factor [17]. On the other hand, the reduction of endometrial cancer cases for women younger than 65 years old might be due to other factors. Endometrial cancers in young women are mostly due to genetic predisposition, and genetic counseling improvements with subsequent prophylactic surgeries might decline them [18]. Also, hormonal contraception use, a well-known protective factor [17], is more frequent in young cohorts and it has also been described longer duration of consumption in Spain in those younger women [19]. Childbearing at an older age is becoming more frequent in developed countries, and it has been associated with a lower risk of endometrial cancer [20]. Therefore, late age at parity could contribute to the observed decreased risk in younger cohorts by cleaning accumulated premalignant and malignant cells from the mucosal lining of the uterine cavity during labor. Breast cancer burden is predicted to increase during the following years [21], and breast cancer patients have a higher risk of endometrial cancer due to tamoxifen treatment [22]. However, aromatase inhibitors, which are not associated with endometrial cancer risk, are currently used as an alternative to tamoxifen therapy, and we cannot therefore predict whether the increase of breast cancer cases over time will influence endometrial cancer incidence.

As the world population ages, a higher endometrial cancer burden among older women can be expected, which is in consonance with our results. Elderly patients are more likely to be diagnosed with high-grade disease, poor histology, and at advanced stages [23]. Standard-of-care treatment of most patients with endometrial cancer is surgical and usually consists in a hysterectomy; however, elderly patients are more likely to receive no surgery or less intensive surgery modalities because of the incremented morbidity and mortality related to this treatment

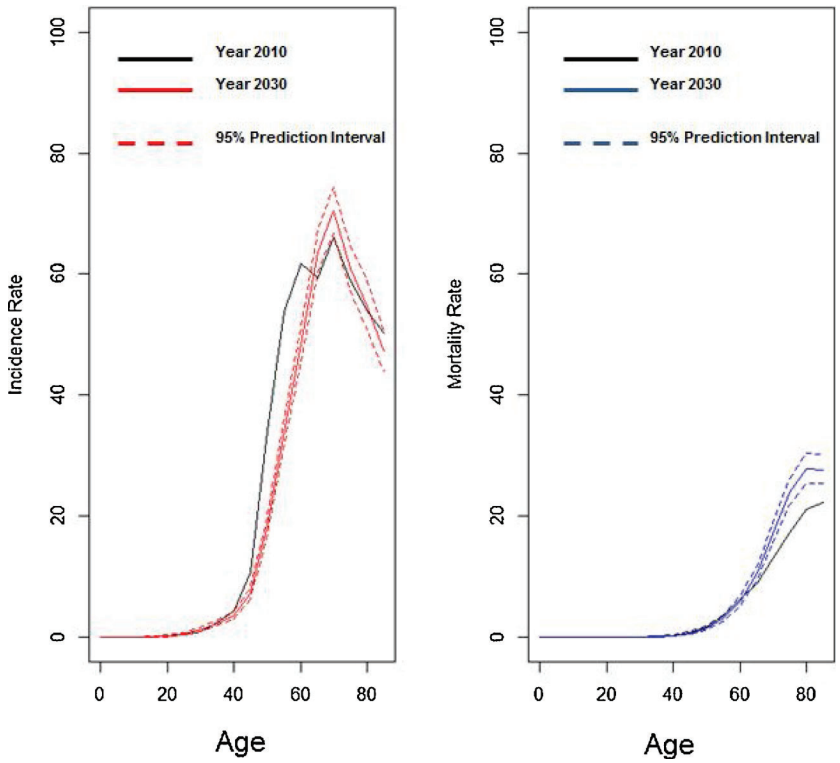


Fig. 2. Endometrial cancer incidence (red) and mortality (blue) age-specific rates (per 100,000 women-years): comparison between 2010 (observed rates) and 2030 (predicted rates).

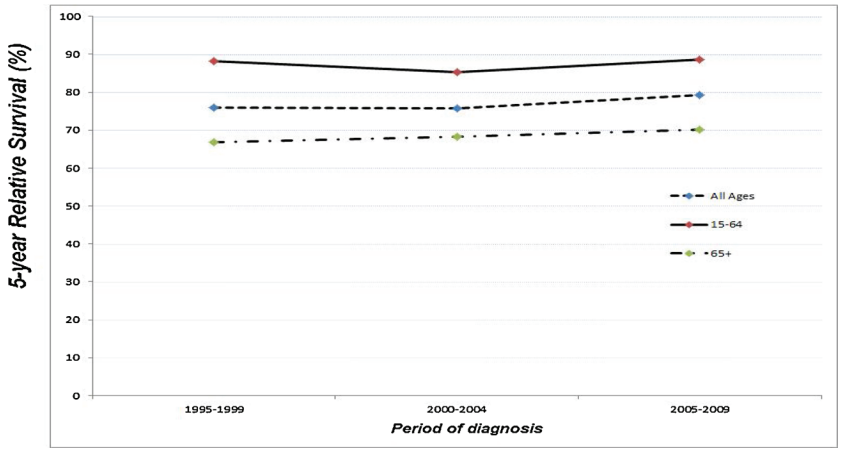


Fig. 3. Time trends of endometrial cancer 5-year relative survival by 5-years periods (from 1995-1999 to 2005-2009).

option [24]. This new scenario requires a better understanding of the burden of endometrial cancer to optimize the care of elderly endometrial cancer patients, which will require a multidisciplinary approach. This might be achieved by encouraging elderly patients to participate in new clinical trials specifically developed for oncogeriatric patients. Moreover, oncologists, gynecologists and geriatricians should work side by side to integrate the geriatric principles into endometrial cancer care. This collaborative work may generate new understanding which may allow offering surgery more often to elderly patients, increasing their survival by decreasing surgery and cancer-specific mortality.

The major strength of the present study is the Bayesian methodology employed to build predictive models, which provides robust estimates for endometrial cancer incidence and mortality in Catalonia until 2030. These predictions give the most plausible scenario for 2030 according to the current data. A limitation of our study is the availability of data: although mortality data was available for the whole region of Catalonia, incidence data was only provided from two cancer registries (GCR and TCR) covering 20 % of the region. However, differences in cancer incidence between these two registries were not found, and similarly we did not observe differences in mortality rates between the areas covered by the cancer registries versus those uncovered. The definition of endometrial cancer is another limitation of this study, given that cancer registries recorded information on corpus uteri cancer, which includes 10 % of other cancer types other than endometrial cancer, which may have other risk factors. The registries did not collect information about endometrial cancer types (type 1 and 2), and therefore we were not able to perform stratified analyses to assess if this trend was similar across cancer types.

In conclusion, the present analysis provides an overview on the most plausible scenario of endometrial cancers incidence and mortality predictions in Catalonia until 2030 by age group. It predicts a new scenario, where the incidence rates of endometrial cancer will decrease in younger women, and rise among women aged 65–74. Mortality is also expected to rise among women aged 65 years or older. Moreover, this elderly group will increase in absolute numbers due to a higher life expectancy in the next decades. Therefore, this information might be a useful warning for oncologists, gynecologists and geriatrics to develop new integrated clinical intervention strategies for elderly women in the near future.

Contributors

Jon Frias-Gomez contributed to the planning of the study and wrote the manuscript.

Laura Costas contributed to the planning of the study.

Ramon Clèriescontributed to the planning of the study, performed all statistical analyses, and prepared tables and figures.

All authors critically reviewed the manuscript and approved the final draft, tables and figures.

Declaration of Competing Interest

The authors declare that they have no conflict of interest regarding the publication of this article.

Funding

This work was conducted with the contribution of the Carlos III Health Institute through projects PIE16/0049, PI17/01179 and PI19/01835, as well as through CIBERESPCB06/02/0073 and CIBERONCCB16/12/00401, and CM19/00216, co-financed by the European Regional Development Fund ERDF, a way to build Europe. It also counts with the support of the Secretariat for Universities and Research of the Department of Business and Knowledge of the Generalitat de Catalunya, grants to support the activities of research groups 2017SGR01085, 2017SGR01718 and 2017SGR00735 and also with funding from the Health Department of the Generalitat de Catalunya (PERIS SLT006/17/76). We thank CERCA Programme / Generalitat de Catalunya for institutional support.

Ethical approval

The study used secondary data and so ethical approval was not applicable. The Epidemiology Unit, Girona Cancer Registry (GCR), Tarragona Cancer Registry (TGC) and Catalonia Mortality Registry (CMR) are statistical units part of the Pla estadístic de Catalunya approved to produce official estimates of cancer incidence and mortality. The GCR and TCR studies have an exception for informed consent as they involve large datasets, which are retrospective and observational, characteristics that make consent impractical to collect. Nonetheless, security measures are taken to protect patient confidentiality.

Research data (data sharing and collaboration)

The data set is anonymized. Data can be requested by contacting the corresponding authors. Authors will provide data once the consent of the two population-based Cancer Registries has been obtained.

Provenance and peer review

This article was not commissioned and was externally peer reviewed.

References

[1] J. Ferlay, M. Colombet, I. Soerjomataram, T. Dyba, G. Randi, M. Bettio, A. Gavin, O. Visser, F. Bray, Cancer incidence and mortality patterns in Europe: estimates for 40 countries and 25 major cancers in 2018, Eur. J. Cancer 103 (2018) 356–387, https://doi.org/10.1016/j.ejca.2018.07.005.

[2] P.M. Webb, D. Aune, L. Dossus, Endometrial cancer, in: B.W. Steward, C.P. Wild, B. W. Stewart (Eds.), World Cancer Report 2020, International Agency for Research on Cancer, Lyon, France, 2020, pp. 403–410.

[3] M.A. Onstad, R.E. Schmandt, K.H. Lu, Addressing the role of obesity in endometrial Cancer risk, prevention, and treatment, J. Clin. Oncol. 34 (2016) 4225–4230, https://doi.org/10.1200/JCO.2016.69.4638.

[4] O. Raglan, I. Kalliala, G. Markozannes, et al., Risk factors for endometrial cancer: an umbrella review of the literature, Int. J. Cancer 145 (7) (2019) 1719–1730, https://doi.org/10.1002/ijc.31961.

[5] P. Morice, A. Leary, C. Creutzberg, N. Abu-Rustum, E. Darai, Endometrial Cancer, Lancet 387 (2016) 1094–1108, https://doi.org/10.1016/S0140-6736(15)00130-0.

[6] J. Lortet-Tieulent, J. Ferlay, F. Bray, A. Jemal, International patterns and trends in endometrial Cancer incidence, 1978-2013, J. Natl. Cancer Inst. 110 (2018) 354–361, https://doi.org/10.1093/jnci/djx214.

[7] J. Galceran, A. Ameijide, M. Carulla, A. Mateos, J.R. Quirós, D. Rojas, A. Alemán, A. Torrella, M. Chico, M. Vicente, J.M. Díaz, N. Larrañaga, R. Marcos-Gragera, M. J. Sánchez, J. Perucha, P. Franch, C. Navarro, E. Ardanaz, J. Bigorra, P. Rodrigo, R. P. Bonet, REDECAN working group, Cancer incidence in Spain, 2015, Clin. Transl. Oncol. 19 (2017) 799–825, https://doi.org/10.1007/s12094-016-1607-9.

[8] R. Clèries, A. Ameijide, R. Marcos-Gragera, L. Pareja, M. Carulla, M.-L. Vilardell, L. Esteban, M. Buxó, J.-A. Espinàs, A. Puigdefàbregas, J. Ribes, A. Izquierdo, J. Galceran, J.M. Borrás, Predicting the cancer burden in Catalonia between 2015 and 2025: the challenge of cancer management in the elderly, Clin. Transl. Oncol. 20 (2018) 647–657, https://doi.org/10.1007/s12094-017-1764-5.

[9] F. Bray, M. Colombet, L. Mery, M. Piñeros, A. Znaor, R. Zanetti, J. Ferlay, Cancer Incidence in Five Continents, vol. XI, International Agency for Research on Cancer, Lyon, 2017 (electronic version), Available from: https://ci5.iarc.fr/Default.aspx (accessed 26/05/2020).

[10] S. Acharya, M.L. Hensley, A.C. Montag, G.F. Fleming, Rare uterine cancers, Lancet Oncol. 6 (12) (2005) 961–971, https://doi.org/10.1016/S1470-2045(05)70463-0.

[11] Revision of the European Standard Population - Report of Eurostat's Task Force, 2013 edition, (n.d.). https://ec.europa.eu/eurostat/web/products-manuals-and-guidelines/-/KS-RA-13-028 (accessed November 25, 2019).

[12] R. Clèries, A. Ameijide, M. Buxó, M. Vilardell, J.M. Martínez, F. Alarcón, D. Cordero, A. Díez-Villanueva, Y. Yasui, R. Marcos-Gragera, M.L. Vilardell, M. Carulla, J. Galceran, Á. Izquierdo, V. Moreno, J.M. Borràs, [WebSurvCa: web-based estimation of death and survival probabilities in a cohort], Gac. Sanit. 32 (2018) 492–495, https://doi.org/10.1016/j.gaceta.2017.10.015.

[13] L. Ellis, L.M. Woods, J. Estève, S. Eloranta, M.P. Coleman, B. Rachet, Cancer incidence, survival and mortality: explaining the concepts, Int. J. Cancer 135 (2014) 1774–1782, https://doi.org/10.1002/ijc.28990.

[14] T. Kelly, W. Yang, C.-S. Chen, K. Reynolds, J. He, Global burden of obesity in 2005 and projections to 2030, Int J Obes (Lond). 32 (2008) 1431–1437, https://doi.org/10.1038/ijo.2008.102.

[15] R.E. Schmandt, D.A. Iglesias, N.N. Co, K.H. Lu, Understanding obesity and endometrial cancer risk: opportunities for prevention, Am. J. Obstet. Gynecol. 205 (2011) 518–525, https://doi.org/10.1016/j.ajog.2011.05.042.

[16] G. Nargund, Declining birth rate in developed Countries: a radical policy re-think is required, Facts Views Vis. Obgyn 1 (2009) 191–193.

[17] L. Dossus, N. Allen, R. Kaaks, K. Bakken, E. Lund, A. Tjonneland, A. Olsen, K. Overvad, F. Clavel-Chapelon, A. Fournier, N. Chabbert-Buffet, H. Boeing, M. Schütze, A. Trichopoulou, D. Trichopoulos, P. Lagiou, D. Palli, V. Krogh, R. Tumino, P. Vineis, A. Mattiello, H.B. Bueno-de-Mesquita, N.C. Onland-Moret, P. H.M. Peeters, V. Dumeaux, M.-L. Redondo, E. Duell, E. Sanchez-Cantalejo, L. Arriola, M.-D. Chirlaque, E. Ardanaz, J. Manjer, S. Borgquist, A. Lukanova, E. Lundin, K.-T. Khaw, N. Wareham, T. Key, V. Chajes, S. Rinaldi, N. Slimani, T. Mouw, V. Gallo, E. Riboli, Reproductive risk factors and endometrial cancer: the European Prospective Investigation into Cancer and Nutrition, Int. J. Cancer 127 (2010) 442–451, https://doi.org/10.1002/ijc.25050.

[18] L. Chen, K.Y. Yang, S.E. Little, M.K. Cheung, A.B. Caughey, Gynecologic cancer prevention in Lynch syndrome/hereditary nonpolyposis colorectal cancer families, Obstet. Gynecol. 110 (2007) 18–25, https://doi.org/10.1097/01.AOG.0000267500.27329.85.

[19] L. Costas, V.G. Sequera, P. Quesada, J.M. Altzibar, V. Lope, B. Pérez-Gómez, Y. Benavente, V. Martín, D. Casabonne, C. Robles, J. Llorca, C. Moreno-Iribas, G. Fernandez-Tardón, V. Moreno, F.J. Caballero-Granado, D. Salas, J.J. Jiménez-Moleón, R. Marcos-Gragera, M.D. Chirlaque, P. Amiano, A.J. Molina, G. Castaño-Vinyals, N. Aragonés, M. Kogevinas, M. Pollán, S. de Sanjosé, Hormonal contraception and postmenopausal hormone therapy in Spain: time trends and patterns of use, Menopause 22 (10) (2015) 1138–1146, https://doi.org/10.1097/GME.0000000000000487.

[20] V.W. Setiawan, M.C. Pike, S. Karageorgi, S.L. Deming, K. Anderson, L. Bernstein, L. A. Brinton, H. Cai, J.R. Cerhan, W. Cozen, C. Chen, J. Doherty, J.L. Freudenheim, M.T. Goodman, S.E. Hankinson, J.V. Lacey, X. Liang, J. Lissowska, L. Lu, G. Lurie, T. Mack, R.K. Matsuno, S. McCann, K.B. Moysich, S.H. Olson, R. Rastogi, T. R. Rebbeck, H. Risch, K. Robien, C. Schairer, X.-O. Shu, A.B. Spurdle, B.L. Strom, P. J. Thompson, G. Ursin, P.M. Webb, N.S. Weiss, N. Wentzensen, Y.-B. Xiang, H. P. Yang, H. Yu, P.L. Horn-Ross, I. De Vivo, Australian National Endometrial Cancer study Group, Age at last birth in relation to risk of endometrial cancer: pooled analysis in the epidemiology of endometrial cancer consortium, Am. J. Epidemiol. 176 (2012) 269–278, https://doi.org/10.1093/aje/kws129.

[21] R. Clèries, A. Ameijide, R. Marcos-Gragera, L. Pareja, M. Carulla, M.L. Vilardell, L. Esteban, M. Buxó, J.A. Espinàs, A. Puigdefàbregas, J. Ribes, Predicting the cancer burden in Catalonia between 2015 and 2025: the challenge of cancer management in the elderly, Clin. Transl. Oncol. 20 (5) (2018) 647–657, https://doi.org/10.1007/s12094-017-1764-5.

[22] M.P. Barretina-Ginesta, J. Galceran, H. Pla, C. Meléndez, A.C. Bague, A. Ameijide, M. Carulla, J. Barretina, A. Izquierdo, R. Marcos-Gragera, Gynaecological malignancies after breast cancer diagnosis: a population-based study, Clin J Obstet Gynaecol. 2 (2019) 113–118, https://doi.org/10.29328/journal.cjog.1001031.

[23] L. Duska, A. Shahrokni, M. Powell, Treatment of older women with endometrial Cancer: improving outcomes with personalized care, Am. Soc. Clin. Oncol. Educ. Book 35 (2016) 164–174, https://doi.org/10.1200/EDBK_158668.

[24] A. Ahmed, G. Zamba, K. DeGeest, C.F. Lynch, The impact of surgery on survival of elderly women with endometrial cancer in the SEER program from 1992-2002, Gynecol. Oncol. 111 (2008) 35–40, https://doi.org/10.1016/j.ygyno.2008.06.026.

ARTICLE 2

Costas L, **Frias-Gomez J**, Benavente Moreno Y, Peremiquel-Trillas P, Carmona Á, de Francisco J, Caño V, Paytubi S, Pelegrina B, Martínez JM, Pineda M, Brunet J, Vidal A, Matias-Guiu X, Bosch X, Ponce J, Kogevinas M, De Sanjosé S, Alemany L. Night work, chronotype and risk of endometrial cancer in the Screenwide case-control study. Occup Environ Med. 2022 Feb 24:oemed-2021-108080. doi: 10.1136/oemed-2021-108080. Epub ahead of print. PMID: 35210289.