Endometrial Cancer - Improving Care and Driving Policy Change

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Foreword

Endometrial cancer is currently the most common gynecological cancer type in high-income countries. Despite its commonness, it has received far less attention than cervical cancer or ovarian cancer in the wider discourse on women's health. Contrary to many other cancer types, the incidence and mortality rates of endometrial cancer are increasing in several countries. This increase is partly attributed to the growing epidemic of overweight and obesity, which are significant risk factors for its development. Endometrial cancer has been shown to have the strongest association with obesity relative to any other malignancy.

Outcomes for women with endometrial cancer vary significantly across socioeconomic and ethnic groups. This report highlights some of these disparities. It also emphasizes the need for better awareness, equitable healthcare solutions, and increased research focus and funding to address challenges along the care pathway of women with endometrial cancer.

Global health policy initiatives for endometrial cancer do not exist. This report offers a comprehensive overview of endometrial cancer and common challenges that women face during the care process. It concludes with a set of high-level recommendations. This information is intended to help policymakers recognize the need to take and accelerate action for this neglected cancer type.

IHE is deeply grateful for the insights gathered from expert interviews and reviews conducted with patient advocates from the European Network of Gynaecological Cancer Advocacy Groups (ENGAGe) and their patient network, as well as the European Oncology Nursing Society (EONS), between February and March 2024. We extend our heartfelt thanks to all who shared their expertise, significantly enriching this analysis and furthering our understanding of endometrial cancer.

The responsibility for the analysis and conclusions in this report lies solely with the authors.

Lund, September 2024

Peter Lindgren
Managing Director, IHE

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Endorsements

This report is explicitly endorsed by the following organizations:

ENGAGe
ESGO | European Network of Gynaecological Cancer Advocacy Groups

EUROPEAN ONCOLOGY NURSING SOCIETY

Summary

Endometrial cancer accounts for around 90% of uterine cancer cases, which are cases originating in the body of the uterus. It stands as the most prevalent gynecological cancer type in the European Union, Northern America, and the United Kingdom, affecting around 154,000 women annually, more than the combined numbers of cervical cancer and ovarian cancer. Recent decades have seen a rise in both patient numbers and deaths in several countries within these geographic areas, not least because of the growing epidemic of overweight and obesity, which are major risk factors for the development of endometrial cancer. The rising patient numbers result in a considerable economic burden of the disease for our societies.

Unlike breast cancer and cervical cancer, endometrial cancer suffers from a lack of global policy initiatives and awareness. The World Health Organization's notable focus on other cancer types starkly contrasts with the neglect faced by endometrial cancer, leaving a gap in global women's health priorities despite its increasing burden. Endometrial cancer also receives less public research funding than both cervical cancer and ovarian cancer in the United States.

Key characteristics of endometrial cancer

- Endometrial cancer, while demonstrating relatively high survival rates among gynecological cancers, falls short when compared to breast cancer. In the US, the 5-year relative survival rate for uterine cancer was 81% in 2014-2020, and in the Nordic countries it was around 84% in 2017-2021. While survival rates increased over the last decades in the Nordic countries (up from 67% in 1972-1976), the 5-year survival rate in the US decreased from 87% in 1975-1977 to 81%, making uterine cancer one of the few cancer types to witness a reduction.
- The prognosis for endometrial cancer greatly depends on the stage at diagnosis. In the US, the 5-year survival rate soars to 95% for cases detected when the tumor is localized to the uterus but stands at 19% for advanced cases. The pattern is similar in England, where the survival rate is 92% for women diagnosed at stage I but only 15% for those diagnosed at stage IV.
- Most cases of endometrial cancer (around 60-66%) are diagnosed early at stage I. Approximately 18% of women experience a relapse within the first two years after their initial surgery. The recurrence significantly complicates the treatment, as options become more limited, and the risk of mortality increases sharply. The likelihood for the disease to recur is heavily influenced by the tumor's molecular profile. Studies have unveiled that high-risk endometrial cancer types exhibit recurrence rates up to four times higher than low-risk types.
- Disparities in the burden of endometrial cancer are evident across socioeconomic and ethnic lines, with variations in risk factors, detection, and survival. Examples of these inequities include:

Category	Socioeconomic status	Ethnicity
Risk factors	Women in the most deprived socioeconomic groups have a higher prevalence of risk factors. In England, 635 annual cases of endometrial cancer could be prevented if all women had the same incidence rate as the most advantageous group.	African American, Hispanic, and Caucasian women have a higher prevalence of obesity (40-57%) compared to Asian American women (17%) in the US. Incidence rates of endometrial cancer are lowest in Asian American women.
Stage at diagnosis	Lower education level is associated with later stage at diagnosis in Sweden.	African American women in the US are less often diagnosed at an early stage (53% of cases) compared to Caucasian women (69%).
Survival and recurrence	Survival rates of patients with private health insurance are higher in the US. In England, metastatic recurrences are more common among the most deprived groups.	African American women face a considerably lower 5-year survival rate (63%) compared to other ethnic groups (80-84%) in the US.

- Patients with endometrial cancer experience a negative impact on various aspects of their quality of life, including psychological distress, decline in physical functioning, worsening family dynamics and sexual health, infertility, and financial hardship.
- Endometrial cancer imposes a considerable financial strain on healthcare systems, intensifying with the disease's progression. Multiple studies highlight a sharp rise in healthcare costs associated with later stage at diagnosis. Specifically, data from England illustrate a pronounced cost differential, with stage III endometrial cancer patients incurring roughly 2.5 times the treatment expenses of those diagnosed at stage I, on a per patient-year basis.

Challenges in early detection of endometrial cancer

Early diagnosis of endometrial cancer largely depends on symptom awareness, particularly abnormal uterine bleeding, necessitating prompt medical consultation. Unlike for breast and cervical cancer, there are no screening programs for endometrial cancer. Current challenges for detecting endometrial cancer include:


Absence of effective screening methods for endometrial cancer.


Limited knowledge on factors that increase the risk of developing endometrial cancer.


Delay in seeking help due to underestimating symptom severity.


Misunderstanding that Pap smears can detect endometrial cancer.


Reluctance to seek medical advice due to obesity stigma.


Insufficient use of genetic screening for high-risk groups (e.g., Lynch syndrome).


Delayed diagnosis and treatment due to long wait times for healthcare services.


Limited use of nurses in promoting preventive measures and early detection.


Misattribution of symptoms in younger women leading to delayed diagnosis.

Challenges in diagnostics and treatment of endometrial cancer

Endometrial cancer is diagnosed through a detailed evaluation involving physical exams, imaging analyses, and biopsies. The treatment hinges on its stage and in recent years also increasingly on its molecular profile, guiding a personalized therapeutic approach. The treatment approach usually encompasses a combination of surgery, radiation therapy, and cancer medicines, ideally coordinated by a multidisciplinary team from a specialized center. The cornerstone of surgical intervention is the removal of the uterus (hysterectomy) including the removal of the fallopian tubes and ovaries. Radiation therapy typically serves to target residual tumor cells after surgery. Systemic therapies offer a diverse toolkit, including chemotherapy for aggressively dividing cells and hormonal therapy leveraging the cancer's hormone sensitivity. In recent years, immunotherapy to enhance immune response against cancer cells and targeted therapy to inhibit tumor growth have been added to the therapeutic arsenal for endometrial cancer.

Challenges in diagnostics

- Low accuracy (sensitivity/specificity) of available diagnostic tests.
- Accurate diagnosis often requires invasive procedures, such as biopsies.
- Guidelines derived from non-representative populations.
- Limited access to specialists can delay diagnosis and treatment initiation.
- Limited capabilities and resources for extensive molecular profiling, critical for personalized treatment.
- Unequal access to biomarker testing exacerbates health inequalities among ethnic groups.

Challenges in treatment

- Unequal access to high-quality treatment according to patients' socioeconomic status.
- Inadequate inclusion of diverse ethnic groups in clinical research trials.
- Insufficient number of specialists (gynecologic oncologists) limits patient access to expert care and treatment.
- Nurse shortages and insufficient details on their role in broader cancer care.
- Financial and bureaucratic hurdles delay access to the latest cancer medicines.
- Delayed reimbursement approval and slow adoption of new treatments into standard practice.

What to do?

Enhancing the management of endometrial cancer through early detection, accurate diagnostics, and effective treatment could improve survival rates and quality of life of patients, thereby reducing the overall disease burden. Furthermore, the variation in costs associated with different stages of the disease underlines the economic benefits of advancing early detection efforts for endometrial cancer.

In the absence of global health initiatives for endometrial cancer by the World Health Organization, this report highlights five key areas (listed in the table below) for improvement in the care of endometrial cancer patients. Notably, the recent establishment of the month of June as “Uterine Cancer Awareness Month” and the “World Gynecologic Oncology Day” on September 20 could help to increase the visibility of endometrial cancer. The ESGO quality indicators for the surgical treatment of endometrial cancer from 2021 could serve as a reference for national quality metrics in endometrial cancer care.

Raise awareness	Increase the visibility of endometrial cancer, educate women on symptoms and risk factors, and dispel stigma associated with its main risk factor, overweight/obesity.
Provide patient-centered support and information	Facilitate access to support groups and provide clear and comprehensive information to patients, including discussions on fertility-sparing treatments. Train and utilize nurses to provide patient education, symptom management, emotional support, and lead support groups.
Ensure optimal care delivery	Make treatment decisions by multidisciplinary teams, reduce waiting times until treatment initiation, and ensure access to comprehensive biomarker testing and effective cancer medicines.
Foster research	Boost public research funding and implement quality indicators in clinical practice to monitor and elevate the standard of care and improve survival.
Reduce health disparities	Enhance health coverage for disadvantaged groups and address language barriers to achieve more equitable health outcomes.

List of abbreviations

ADC	Antibody-drug conjugate
AJCC	American Joint Committee on Cancer
CT	Computed tomography
D/C	Dilation curettage
dMMR	Deficient mismatch repair
EMA	European Medicines Agency
ESGE	European Society for Gynaecological Endoscopy
ESGO	European Society of Gynaecological Oncology
ESHRE	European Society of Human Reproduction and Embryology
ESMO	European Society for Medical Oncology
ESP	European Society of Pathology
ESTRO	European Society for Radiotherapy and Oncology
EUR	Euro
FIGO	International Federation of Gynecology and Obstetrics
FDA	Food and Drug Administration
GP	General practitioner
HRQoL	Health-related quality of life
ICD-10	International Classification of Diseases, Tenth Revision
IGCS	International Gynecologic Cancer Society
IUD	Intrauterine device
KPI	Key performance indicator
LVSI	Lymphovascular space involvement
MDT	Multidisciplinary team
MMR	Mismatch repair
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
MSI-H	Microsatellite instability high
MSS	Microsatellite stable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGS	Next-generation sequencing
NHANES	National Health and Nutrition Examination Survey
NHS	National Health Service
NIH	National Institutes of Health
OPTEC	Ohio Prevention and Treatment of Endometrial Cancer
OS	Overall survival
PAF	Population attributable fractions
PET	Positron emission tomography
pMMR	Proficient mismatch repair
SEER	Surveillance, Epidemiology, and End Results program
SEK	Swedish krona
SES	Socioeconomic status
TCGA	The Cancer Genome Atlas
TKI	Tyrosine kinase inhibitor
WHO	World Health Organization

Country abbreviations

CA	Canada	DK	Denmark	LT	Lithuania
UK	United Kingdom	EE	Estonia	LU	Luxembourg
US	United States	FI	Finland	MT	Malta
EU-27	European Union’s 27 member states	FR	France	NL	Netherlands
AT	Austria	DE	Germany	PL	Poland
BE	Belgium	GR	Greece	PT	Portugal
BG	Bulgaria	HU	Hungary	RO	Romania
HR	Croatia	IE	Ireland	SK	Slovakia
CY	Cyprus	IT	Italy	SI	Slovenia
CZ	Czechia	LV	Latvia	ES	Spain
				SE	Sweden

1. Introduction

Endometrial cancer is a cancer type that originates in the uterus (womb). It accounts for around 90% of cases of uterine cancer (also called corpus uteri cancer), which comprises all cancers originating in the body of the uterus (1). Uterine cancer ranks as the fourth most commonly diagnosed cancer among women, and it is the leading gynecological cancer in the European Union (EU), Northern America (Canada and the United States) and the United Kingdom (UK). In these regions combined, it was responsible for an estimated 153,623 new cases and 33,550 deaths in 2022 (2). This represented 6% of all new cancer diagnoses in women and accounted for 3% of all cancer-related deaths in women; see Figure 1. There has been a concerning increasing trend not only in the incidence (the number of new cases) but also in the mortality (the number of deaths) associated with uterine cancer. Specifically, the United States (US) has witnessed an escalation in mortality, with the number of deaths nearly doubling over the past two decades. This increase has been especially pronounced in recent years, reflecting a significant and growing public health concern (3). Notably, endometrial cancer is the cancer type most strongly linked to obesity among the top 20 most common cancer types (4, 5).

Despite these statistics, uterine/endometrial cancer does not receive the same level of global attention as other women's cancers. The World Health Organization (WHO), in its global health initiatives, primarily focuses on breast cancer and cervical cancer. The Global Breast Cancer Initiative aims to reduce the mortality of breast cancer (6), and the Cervical Cancer Elimination Initiative aims to eradicate cervical cancer through a combination of vaccination, screening, and treatment (7). In stark contrast, at the time of writing this report, there are no global initiatives by the WHO for uterine/endometrial cancer that match the scale and intensity of the initiatives for breast and cervical cancer. This disparity underscores a striking gap in global women's health priorities, where uterine/endometrial cancer, despite its growing impact, remains under-addressed.

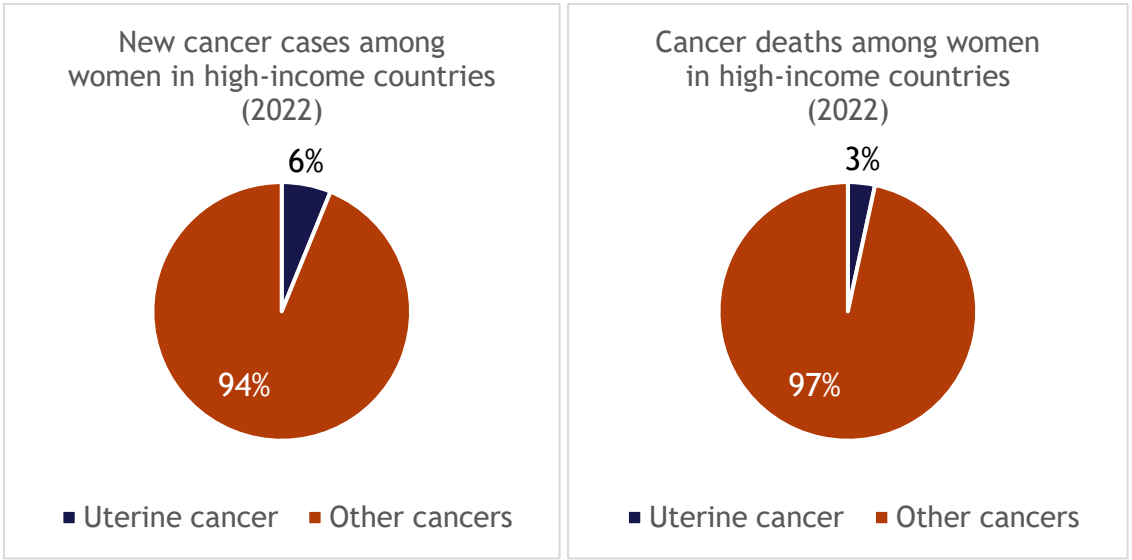

Figure 1: Estimated proportion of new uterine cancer cases and deaths among women in Europe and Northern America in 2022.

Notes: Cancer was defined as all types excluding non-melanoma skin cancer. High-income countries include the 27 member states of the EU, the UK, Canada, and the United States. Source: Globocan (2).

1.1 Purpose and outline of the report

The purpose of this report is to bring together evidence about the key characteristics of endometrial cancer (chapter 2), the disease and economic burden of endometrial cancer (chapter 3), health metrics for the care process, the detection, diagnosis, and treatment of endometrial cancer and associated challenges (chapter 4), and policy initiatives and recommendations for improved care (chapter 5).

The gathered evidence is supposed to give various stakeholders within the healthcare arena a better understanding of endometrial cancer. It should help to reflect on current unmet needs of patients and pain points in the care process, including disparities faced by patients within countries. The report recommendations can serve as a basis to set future priorities for improvements in endometrial cancer care and the mitigation of the societal impact of the disease.

1.2 Methods

This report employs a pragmatic review of publicly available literature to bring together evidence on the landscape of endometrial cancer. In carrying out this research, two distinct approaches were utilized, because of the different nature of information requirements and data availability:

1) Data and information were extracted from publicly available databases (e.g., from WHO, OECD) and official information provided by public authorities (e.g., National Cancer Institute in the US, NHS in the UK), international organizations (e.g., WHO, OECD), international professional societies (e.g., ESGO), or national organizations.
2) Data and information were collected in a targeted literature review via a search in PubMed and Google Scholar.

In addition, the information gathered through desk research was enriched through interviews with various stakeholders. The interviews were conducted not only to supplement the findings, but to enhance their credibility and depth. The interviews aimed at capturing nuances and perspectives not fully explored and captured in the literature review. The primary interview method involved hosting virtual workshop-style discussions with endometrial cancer patients affiliated with the European Network of Gynaecological Cancer Advocacy Groups (ENGAGe), alongside offering a written questionnaire option for those patients preferring to contribute in this manner. Similar workshop-style discussions were conducted with patient advocates and representatives from ENGAGe and representatives from the European Oncology Nursing Society (EONS), ensuring a diverse range of insights. The report content was further strengthened with input from leading practicing physicians, each with extensive experience in the clinical management of endometrial cancer, who reviewed and validated the findings.

Geographic scope

The geographic focus of the report is global, with a focus on “high-income countries” in Europe (the 27 member states of the EU and the UK) and Northern America (Canada and the US); see country abbreviations before the Introduction section for a complete list of countries.

Terminology

This report is centered on endometrial cancer; however, in instances where specific statistics for endometrial cancer were unavailable, information for uterine cancer (corpus uteri cancer) was utilized instead. Figure 2 provides a visual distinction between these classifications.

1) The uterus is divided into three main parts. The section of the uterus that makes up the upper two-thirds of its structure is called the body (corpus) (8). The cervix is the lower part and connects the body of the uterus to the vagina. The fundus is the uppermost part, situated above the openings of the fallopian tubes into the uterus (8). Cancers originating in the corpus uteri are usually referred to as uterine cancer (8), whereas cancers originating in the cervix are referred to as cervical cancer (9). Cervical cancer is not part of this report.
2) Uterine cancer can be of two types depending on their site of origin: endometrial cancer and uterine sarcoma (10). The body of the uterus has two main layers[1], the myometrium (muscular outer layer) and the endometrium (inner layer) (9, 11). Endometrial cancer begins in the endometrium, whereas uterine sarcoma begins in the myometrium (9). Endometrial cancer accounts for around 90% of all uterine cancers and uterine sarcoma for the other 10%; see in section 2.1.

Cancer registries and databases commonly record cancers based on their initial site of origin. Since endometrial cancer falls within the classification of corpus uteri cancers (ICD-10 codes: C54 and C55), these broader classifications are utilized in instances where available data does not allow for a more granular distinction of endometrial cancer.

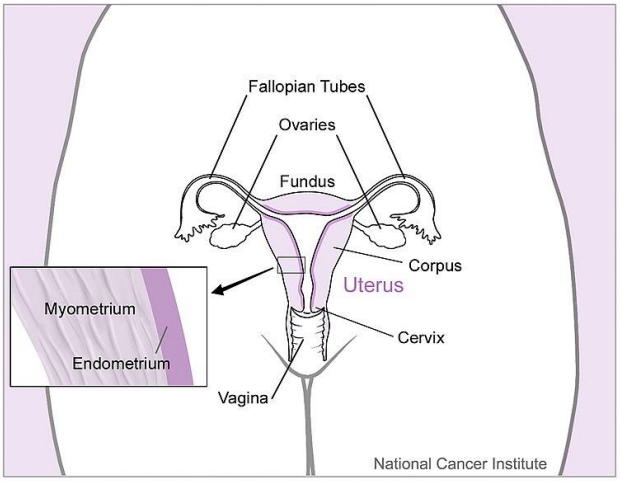

Figure 2: Illustration of female reproductive organs and the endometrium in the uterus.

Notes: The image is public domain and was released by NIH Medical Arts, an agency part of the National Institutes of Health, with the ID 4369. Source: (12).

[1] There is also a layer of tissue called serosa that covers the outside of the uterus.

2. Characteristics of endometrial cancer

Endometrial cancer is a type of uterine cancer that starts in the inner lining of the uterus (womb) (13). Endometrial cancer represents around 90% of uterine cancer cases (14); see Figure 3. Endometrial cancer is sometimes just referred to as uterine cancer, although uterine cancer can also refer to other rarer forms such as uterine sarcomas, that develop in the muscle of the uterus or other supportive tissues and that account for the remaining 10% of uterine cancer cases (15).

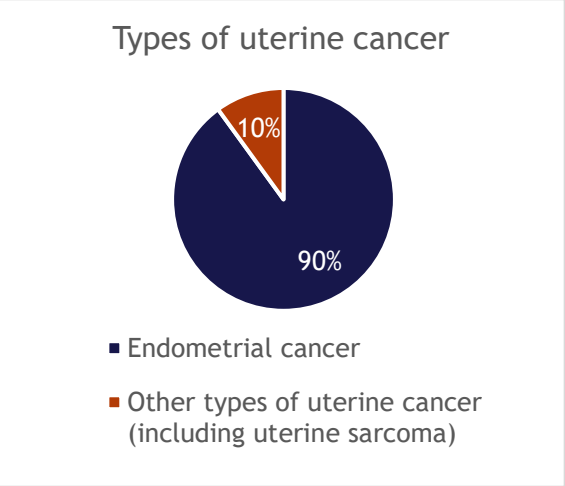

Figure 3: Types of uterine cancer.

Sources: (1, 14).

Uterine cancer is the most common gynecological cancer in the EU, Northern America, and the UK (3). In 2022, uterine cancer encompassed 45% of all new diagnosis of gynecological cancers in the EU. During the same period, it stood as the second leading cause of death among gynecological cancers, surpassed only by ovarian cancer, and represented 27% of all fatalities attributed to gynecological cancers; see Figure 4.

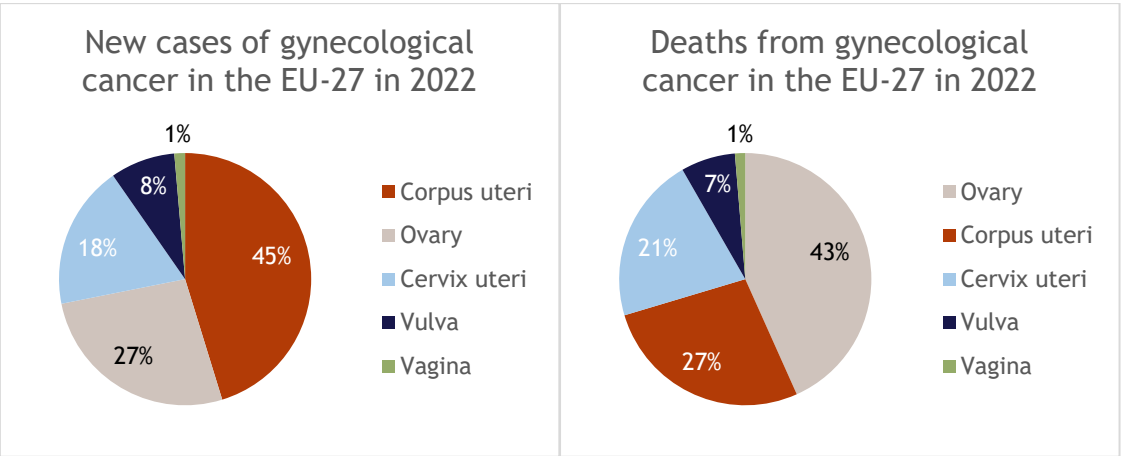

Figure 4: Proportion of newly diagnosed gynecological cancer cases and related deaths among women in the EU-27, 2022.

Source: ECIS (16).

2.1 Subtypes

The traditional way of classifying endometrial cancer by histological types (based on microscopic anatomy) involves dividing them into the following two groups (13):

- **Type I**, which is associated with estrogen exposure[2], typically exhibits slow growth (3, 13). It is the most prevalent type, and generally has a better prognosis with a 5-year overall survival (OS) rate of 85% (3, 13, 18). It includes endometrioid carcinomas (19).
- **Type II**, which is not linked to estrogen, tends to progress more rapidly, has higher recurrence rates, is rarer, and has a less favorable outcome (13, 20). It includes serous and clear cell carcinomas and carcinosarcomas (19). Although it constitutes only about 10% of all endometrial cancer cases, it is responsible for 40% of the deaths associated with the disease (3). The OS rate is close to 55% (13). TP53 mutations, HER2 overexpression, and loss of E-cadherin are more frequent in type II than type I (21). Serous carcinoma has a high recurrence rate of around 31% to 80%, even in the early stages (22). Carcinosarcomas exhibit characteristics of both endometrial carcinomas and sarcomas, yet they are classified under the umbrella of uterine cancers and treated based on guidelines for endometrial carcinomas (23).

Molecular subtypes

The traditional histological classification is transitioning to a novel system based on molecular profiling, originating from insights from the landmark cancer genomics program The Cancer Genome Atlas (TCGA) (24, 25). TCGA collected tumor samples and matched normal tissue samples from 11,000 patients across 33 cancer types to analyze genetic mutations, copy number variations, and other alterations (26). TCGA went beyond looking at the tissue characteristics of the tumor and examined the genetic and molecular alterations within the cancer cells. It identified four distinct groups of endometrial cancer, each with different prognostic implications, based on genetic mutations and variations in the number of copies of certain genes in the cancer cells.

Following this discovery, further research indicated that simpler and less expensive tests, like immunohistochemical and molecular tests, could be used instead of the more complex and costly TCGA analyses (27). By employing three immunohistochemical markers (p53, MSH-6, PMS-2 - the latter two being used to determine dMMR status) and one molecular indicator (POLE mutation), the four molecular prognostic groups can be accurately classified (28). This approach streamlines and economizes the stratification process (27, 29). Emerging rapid and cost-effective tests are also broadening access to testing for POLE status (30). Current international clinical guidelines, such as those from the European Society for Medical Oncology (ESMO) and the European Society of Gynaecological Oncology (ESGO), incorporate the four main molecular phenotypes; see Table 1.

[2] The excess estrogen promotes the growth of the endometrial lining, that could lead to hyperplasia and increase the risk of developing cancerous cells (17), among other risk factors mentioned in section 2.2.

Table 1: Molecular phenotypes of endometrial cancer

Molecular phenotype	Prevalence	Features	Prognosis	Source
POLE-ultra mutated	5 to 15%	Characterized by a specific change in the POLE gene causing a high number of mutations	Excellent (>96% 5-year survival rate)	(25, 31)
Mismatch repair deficiency (dMMR)	25 to 30%	Mismatch repair deficiencies are marked by genetic changes in any of the mismatch repair genes, which can lead to Microsatellite Instability (MSI). Tumors displaying MSI are typically associated with a deficient mismatch repair (dMMR) profile; overall concordance between dMMR and MSI in endometrial cancer is around 98%. Around 3-5% of these cases are hereditary (result from Lynch syndrome).	Intermediate	(25, 32-34)
p53-aberrant (mutations in TP53)	5 to 15%	Characterized by abnormal patterns of p53 most frequently overexpression, but in some cases complete absence of p53	Poor (<50% 5-year survival)	(25, 31, 35)
No specific molecular subtype (NSMP)	30 to 40%	Characterized by the lack of POLE, dMMR, and p53 mutations	Intermediate	(25, 29)

Notes: A study involving 1,029 patients revealed notable differences in recurrence rates among the four groups (36). Approximately 3% of patients with the POLE-ultra mutated subtype experienced recurrence, compared to 23-24% from the dMMR and NSMP subtypes. The p53-aberrant subtype had the highest recurrence rate, with nearly half (45%) of the patients experiencing a recurrence.

The combination of molecular and clinicopathological data has led to a system that classifies patients according to the risk of disease recurrence (how likely it is that the disease will come back after treatment); see Table A1 in the Appendix for a detailed description. ESMO divides endometrial cancer cases based on the risk of disease recurrence into four groups (25), as shown in Table 2.

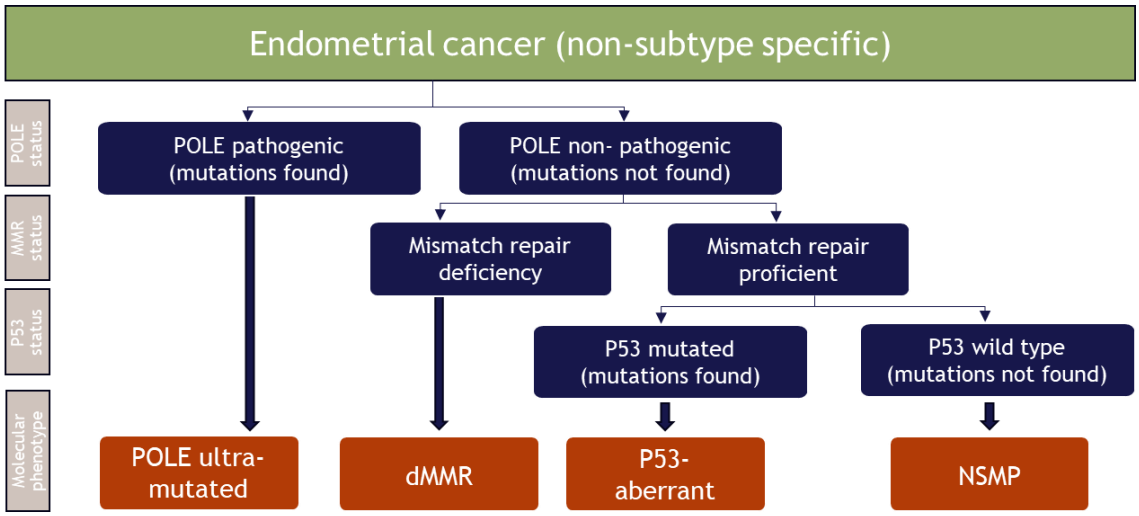

Figure 5: Diagnostic algorithm for molecular phenotype classification.

Notes: Adapted from ESMO guidelines (25). POLE-ultra mutated (high mutation burden due to errors in DNA replication), dMMR (deficient in DNA mismatch repair), p53 aberrant (abnormal p53 protein function due to TP53 mutations), and NSMP (lacks specific molecular alterations commonly seen in endometrial cancer). These classifications help in tailoring treatment approaches and prognostic assessments.

Table 2: Risk groups of endometrial cancer by risk of disease recurrence

Risk group	Prevalence	Recurrence rates
Low risk	49%	10%
Intermediate risk	14%	17%
High-intermediate risk	10%	17%
High risk	27%	39%

Notes: See Table A1 in the Appendix for a more detailed description of the risk groups. Source: Vizza et al. (2020) (37).

2.2 Risk factors

Numerous potential risk factors for developing endometrial cancer have been identified, each substantiated by varying degrees of evidence. Broadly, these risk factors are categorized into two types: non-modifiable (see Table 3) and modifiable (see Table 4).

Table 3: Non-modifiable risk factors in endometrial cancer

Risk factor	Description
Age	Endometrial cancer only occurs in women after the onset of puberty, and the diagnosis is more common in postmenopausal women than in premenopausal women (15). The average age at diagnosis is around 60-62 years in the US (15, 38).
Lynch syndrome	Women with a hereditary genetic disorder called Lynch syndrome (also known as hereditary non-polyposis colorectal cancer) face an elevated risk of endometrial cancer (15). The prevalence of Lynch syndrome in the general population was estimated to be 1 in 279 individuals (0.36%) in the US (39). About 2-5% of women with endometrial cancer have Lynch syndrome (40).
Ethnicity	Caucasian women have a greater propensity for being diagnosed with uterine cancer compared with women of other ethnic backgrounds in the US (41). African American and Hispanic women are at an elevated risk for the formation of more aggressive uterine tumors (40).
Late menopause and early menstruation	Early menstruation and late menopause lead to longer exposure of estrogen during a woman's lifetime, which may increase the risk of developing endometrial cancer (15).
Infertility	Infertility is associated with an increased risk for endometrial cancer, particularly in women with ovulatory disorders (42). Additionally, treatments for infertility could potentially alter the hormonal environment and be linked with the development of endometrial cancer (42).
Polycystic ovary syndrome	Women with polycystic ovarian syndrome have abnormal hormone levels. The increase of estrogen relative to progesterone can increase the risk of developing endometrial cancer (43).

Endometrial hyperplasia *	Endometrial hyperplasia is a condition where there is an excessive proliferation of cells that make up the endometrium. This causes the lining to become thicker than normal and may increase the risk of endometrial cancer (15).
Type 2 diabetes *	Endometrial cancer appears to be twice as prevalent in women who have type 2 diabetes (43). Since type 2 diabetes is associated with additional risk factors such as overweight/obesity and lack of physical activity, the causal link remains somewhat ambiguous (43).

Notes: * Endometrial hyperplasia is often treatable with progestin, which can be administered orally or through an intrauterine device (44). Due to this treatability, endometrial hyperplasia may also be considered a modifiable risk factor. Similarly, because type 2 diabetes involves modifiable lifestyle factors such as diet, exercise, and body weight, it represents a risk factor that can potentially be altered through lifestyle changes and medical management.

Studies indicate that a significant number of uterine cancer cases could theoretically be prevented, owing to their link to modifiable risk factors. Figure 6 illustrates the range of preventable cases across various countries, revealing a variation from 27% to 71% depending on each country's demographics and the specific risk factors included in the analysis. For instance, Cancer Research UK suggests that around 34% of uterine cancer instances may be avoidable, given their association with being overweight and obese (45, 46). Uterine cancer has been shown to have the strongest association with obesity relative to any other cancer type (47). Table 4 provides a detailed breakdown of these modifiable risk factors.

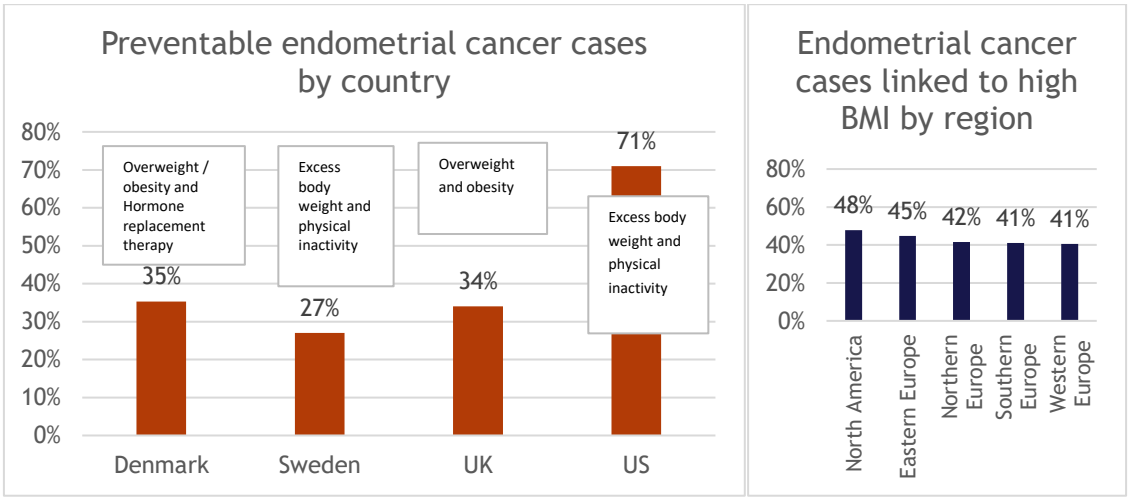

Figure 6: Preventable endometrial cancer cases by country and endometrial cancer cases due to excess body weight by region in 2012.

Notes: Data in both graphs are population attributable fractions (PAF) that estimate the proportion of cases of a disease that are attributed to a specific risk factor. The graph on the left presents estimates derived from a range of country-specific studies, utilizing diverse methodologies and spanning different years, making the country data non-comparable. The estimates refer to the year 2018 for Denmark and Sweden, 2015 for the UK, and 2014 for the US. In the left graph, high BMI is defined as ≥ 25 kg/m^2. Sources: (45, 47-51).

Table 4: Modifiable risk factors in endometrial cancer

Risk factor	Description
Obesity and overweight	Endometrial cancer has been shown to have the strongest link with obesity among the 20 most common malignancies (4, 5). The risk of developing endometrial cancer increases with higher levels of body mass index (BMI), for both premenopausal and postmenopausal women (52). Endometrial cancer occurs twice as frequently in women who are overweight and more than three times as frequently in obese women compared to those with normal weight (43). The effect of BMI on endometrial cancer risk is stronger in postmenopausal women than in premenopausal women (52). In total, it is estimated that around 30-50% of all endometrial cancer cases are linked to excess body weight as shown in Figure 6 (50, 51). Obesity increases the risk for both type I and type II endometrial cancer, with a particularly strong association with type I (53).
Use of tamoxifen	Tamoxifen may be prescribed to women at elevated risk of breast cancer as a preventive measure (or as a post-surgery treatment for up to 10 years for women with breast cancer). Yet, taking tamoxifen for over two years can heighten the likelihood of developing endometrial cancer, especially in postmenopausal women (15, 54).
No childbirths	Women who never have been pregnant are at a higher risk of endometrial cancer, because estrogen levels are lower during pregnancy (15).
Hormone replacement therapy with only estrogen	Using hormone therapy that contains estrogen without progestin elevates the risk of endometrial cancer (15). This risk increases with prolonged use (15).
Hair straightening products	Women who use hair relaxers might face a heightened risk of uterine cancer. In a prospective cohort study, women who at baseline reported the use of hair straightening products at least once in the past 12 months had an 80% higher risk of developing uterine cancer compared to those who never used them after a 11-year follow up (55). Frequent use (more than four times in the past 12 months) further increased the risk (155% higher than never users).

Table 5 presents a compendium of factors that offer protection against endometrial cancer (15). A “protective effect” is defined as any element that diminishes the risk of a disease within a given population.

Table 5: Protective factors against endometrial cancer

Protective factors[3]	Description
Hysterectomy	Women who have their uterus removed are no longer at risk of endometrial cancer (58).
Hormone replacement therapy with estrogen-progestin	Recent research presented in 2024 highlighted that combined estrogen-progestin hormone replacement therapy may reduce the incidence of endometrial cancer (59).
Pregnancy and breast-feeding	Women who have given birth and have breastfed typically exhibit lower estrogen levels during both pregnancy and breastfeeding periods (15). Research has demonstrated that these conditions can reduce the risk of endometrial cancer (15).
Birth control pills (oral contraceptives)	The use of birth control pills that contain estrogen and progestin can reduce the risk of endometrial cancer (15, 40). It has been observed that this protective benefit persists for up to 35 years after discontinuing the pills (60). Newer studies suggest that birth control devices inserted into the uterus (intrauterine devices, IUDs) may have the same protective effect (15).
Physical activity	There is suggestive evidence of a protective effect of physical activity against endometrial cancer (61). Studies have found a risk reduction of about 20–30% for those with the highest levels of physical activity compared to the least physically active (62).
Bariatric (weight loss) surgery	Undergoing bariatric surgery — a surgical procedure designed to help with weight loss by altering the digestive system — is associated with a decreased risk of endometrial cancer (15).

2.3 Signs and symptoms

Signs and symptoms of endometrial cancer typically arise early, which helps to diagnose the cancer at an early stage when the tumor is still small and localized. Figure 7 shows signs and symptoms associated with endometrial cancer. The most commonly present symptom is having abnormal uterine bleeding, particularly in postmenopausal women (3, 13). However, it is important to note that even though abnormal uterine bleeding is the most prevalent symptom, only a small percentage of women, approximately 1.2% of premenopausal and 9% of postmenopausal individuals with this symptom, receive a diagnosis of endometrial cancer (63).

[3] Cigarette smoking has also been found to be associated with a reduced risk of endometrial cancer (56). However, from a public health standpoint and in alignment with WHO recommendations, tobacco smoking is strongly discouraged due to the significant risks it poses for developing a wide range of diseases (57).

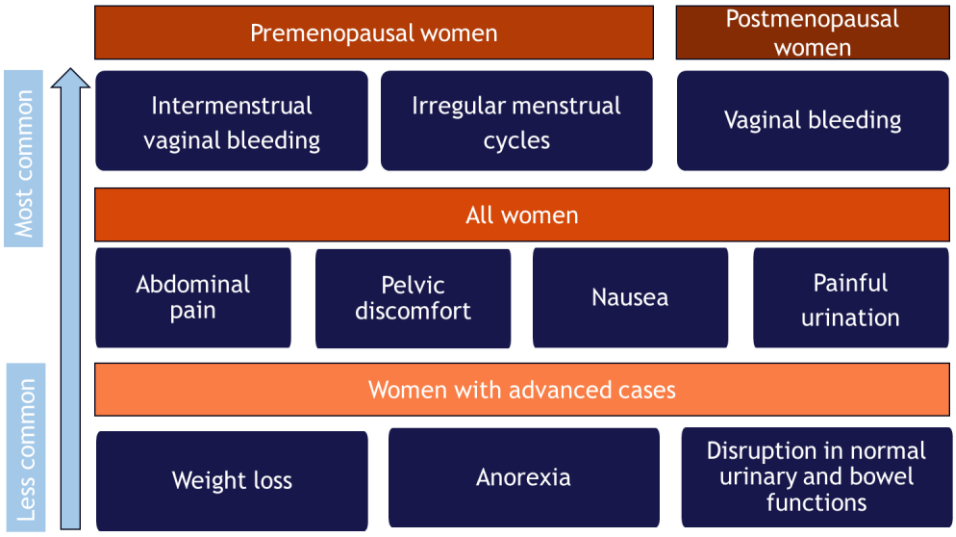

Figure 7: Signs and symptoms endometrial cancer.

Source: (64).

2.4 Age at diagnosis

Endometrial cancer and total cancer cases in women exhibit distinct age distribution patterns, reflective of the varying risk factors and biology associated with each type of cancer. Women with endometrial cancer tend to be younger than women with other cancer types; see Figure 8. When compared to the overall occurrence of cancer in women, endometrial cancer shows a higher relative prevalence within the age range of 45 to 74 years in the EU and the US, especially in the age group 55-74 years (65-67). In the US, the median age at diagnosis for endometrial cancer varies by ethnicity: it is 65 years for Caucasian women, 64 years for African Americans, and 59 years for Hispanics, Asian Americans, and Native Americans (66).

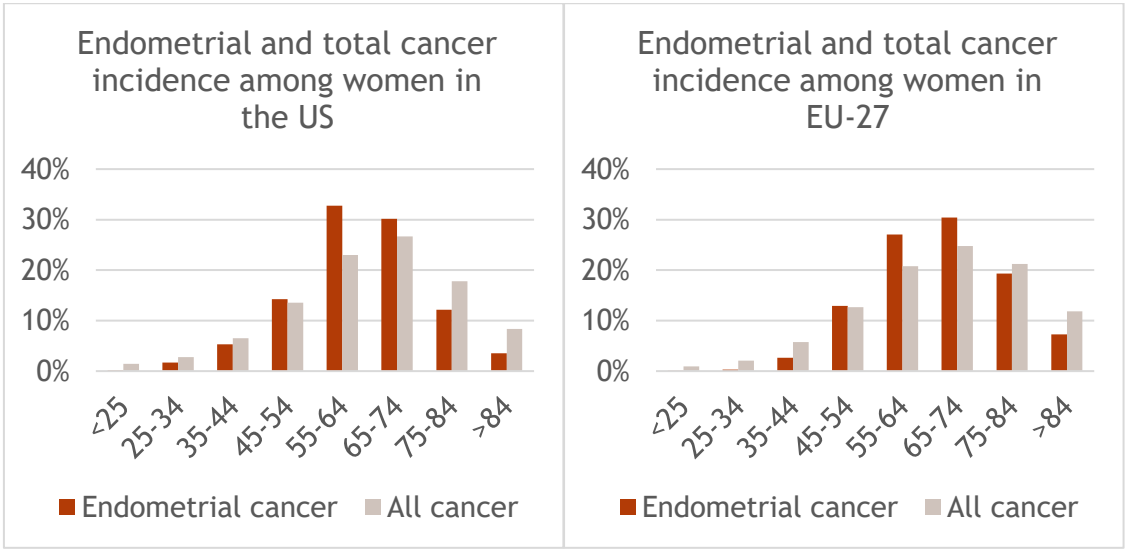

Figure 8: Endometrial cancer and total cancer cases by age group in the US and EU-27.

Notes: The bars sum up to 100%. The US cases are from 2016-2020 and EU-27 from 2022. All cancer cases correspond to all sites but non-melanoma skin. Source: EU-27 (65) US (66).

2.5 Stage at diagnosis

The staging of endometrial cancer describes the extent and spread of the tumor. Staging according to AJCC (American Joint Committee on Cancer) 2018 is shown below. For a comprehensive explanation, including substages and updates to the staging, see section 4.3.5.

Table 6: Staging of endometrial cancer

Stage	Description
Stage I	The cancer is confined to the uterus. It has not spread beyond the uterine body or the endometrium.
Stage II	The cancer has extended to the connective tissues of the cervix, but it remains within the uterine structure. It has not spread to other pelvic or abdominal organs.
Stage III	The cancer has spread beyond the uterus. The spread can be local, meaning it involves direct extension to areas immediately adjacent to the uterus, such as the vagina or ovaries and fallopian tubes. It can also be regional, involving the pelvic and/or para-aortic lymph nodes, but not distant body sites.
Stage IV	The cancer has invaded deeper structures such as the inner lining of the rectum or urinary bladder, or it has metastasized to distant organs. This may include the peritoneal cavity, upper abdomen, lungs, liver, or bones.

Source: American Cancer Society (68).

Most women diagnosed with endometrial cancer are identified in the early stages of the disease. For instance, data from the US, Austria, Czechia, and England show that 60-66% of cases are localized or in stage I; see Figure 9. The primary and most noticeable symptom of endometrial cancer is abnormal uterine bleeding, particularly postmenopausal bleeding, as highlighted in section 2.3 (1). This symptom, being hard to overlook and distinct, often leads women to seek medical attention promptly. Around 6–10% of cases are diagnosed with metastatic disease; see Figure 9. However, it is noteworthy that women over 70 years are twice as likely to receive a diagnosis at more advanced stages compared to their younger counterparts (69).

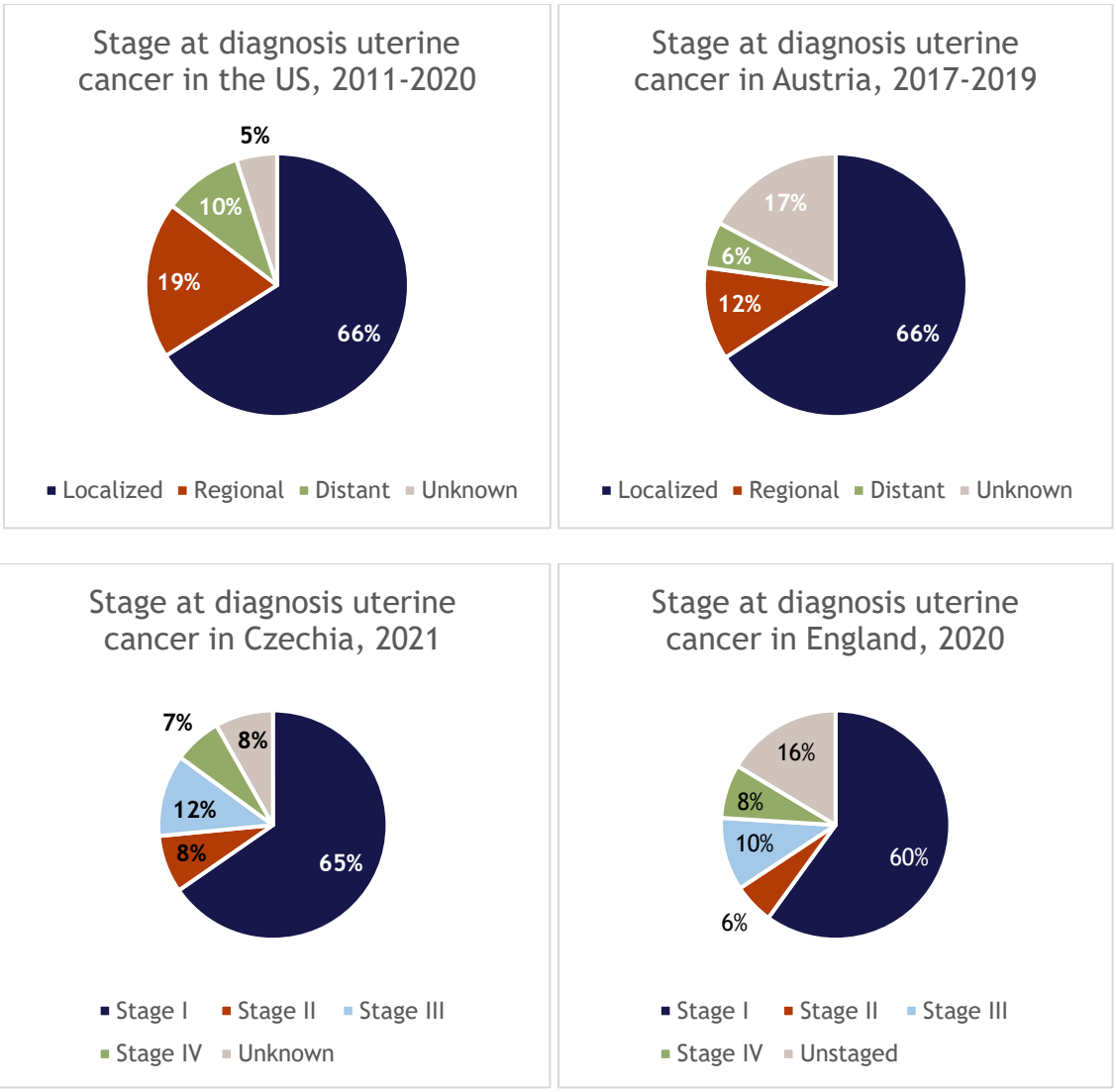

Figure 9: Stage at diagnosis of uterine cancer in the US, Austria, Czechia, and England.

Notes: Data for Austria, Czechia, and England come from nationwide cancer registries. For Austria, unknown includes unknown cases and death-certificate-only cases. In the graph, "localized" cases for the US and Austria represent endometrial cancer diagnoses confined to the uterus, without any spread, "regional" cases indicate the cancer has spread to nearby structures, while "distant" cases denote cancer that has spread to distant parts of the body (70). Sources: (66, 71-73).

2.6 Survival

Survival rates for endometrial cancer are high compared to other gynecological cancers but lower than those for breast cancer; see Figure 10. In the US, the 5-year relative survival rate for uterine cancer was 81% in the diagnosis period 2014-2020 compared to 91% for breast cancer.

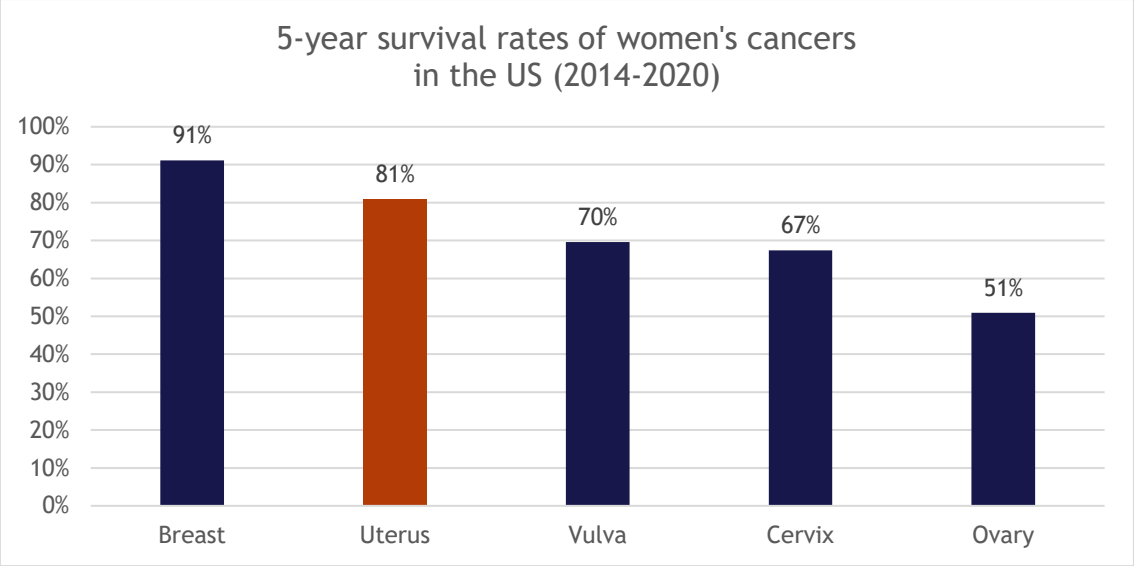

Figure 10: 5-year relative survival for various types of cancer among women in the US (2014-2020).

Source: National Cancer Institute (74).

The development of the survival rates of endometrial cancer shows a mixed pattern across geographies. In the Nordic countries, there was a clear upward trend in survival rates from 1972 to 2021; see Figure 11. During the period of 1972-1976, the 5-year survival rate stood at approximately 67% in these countries. This rate significantly increased to about 84% in 2017-2021, according to NORDCAN data (75). However, little progress has been achieved since the period 1997-2001, with survival rates stabilizing at around 80-86% in all countries.

Several factors have been found to explain the increasing survival rates in Sweden in a study examining the years 1960 to 2014 (76):

- **Shift in the stage distribution towards earlier stages**: There was a decline in stage II cases and a rise in stage I cases, indicating improved early diagnosis. This increases the total survival rate because the survival rates in stage I are higher than in stage II; see Figure 13.
- **Advancements in treatment**: This includes the development of more effective chemotherapies, refined surgical techniques, a deeper understanding of prognostic factors, and more tailored treatment choices (76).

However, the enhanced survival rates in Sweden in the past decades were not uniform across all demographics. The youngest cohort of women (18-44 years) did not exhibit a discernible increase in survival rates between 1960 and 2014 (76).

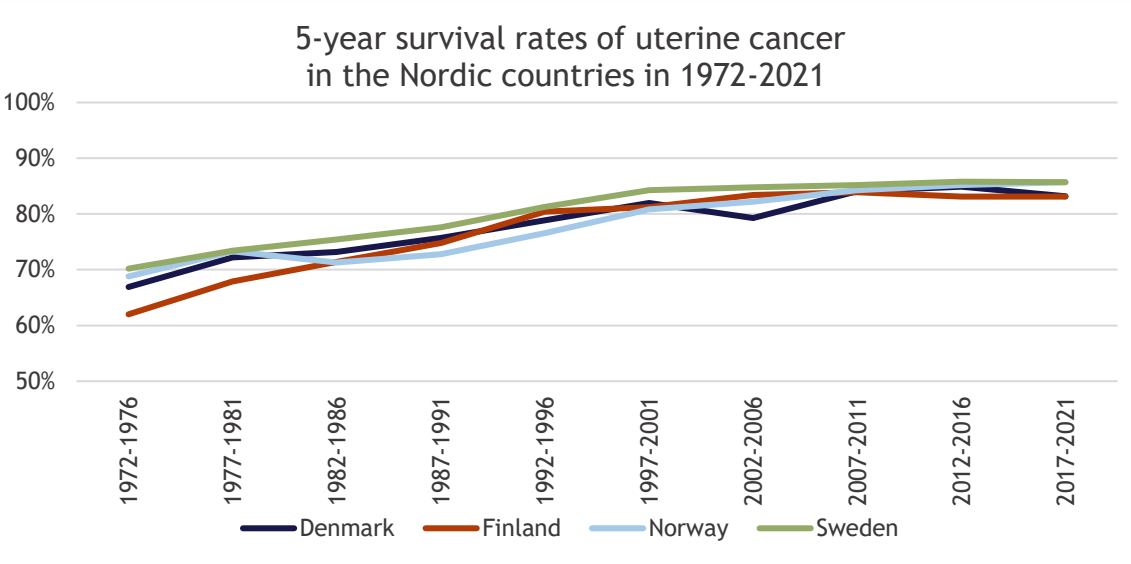

Figure 11: Evolution of 5-year relative survival rates of uterine cancer in the Nordic countries between 1972 and 2021.

Source: NORDCAN (75).

In the US, survival rates of uterine cancer have followed a negative trajectory over the past decades. As shown in Figure 12, there was a decrease in the 5-year survival rate for all women, dropping from 87% to 81% between 1975 and 2019 (77). Within the spectrum of 23 cancer types studied, uterine cancer stood out as one of three malignancies to register a dip in survival rates since 1975 besides laryngeal cancer and cervical cancer (77). Figure 12 also reveals a pronounced disparity in survival rates between Caucasian and African American women, both in the absolute numbers (higher for Caucasians and lower for African Americans) and the development over time (slight decrease in Caucasians and slight increase in African Americans). Health disparities are further described in section 2.8.

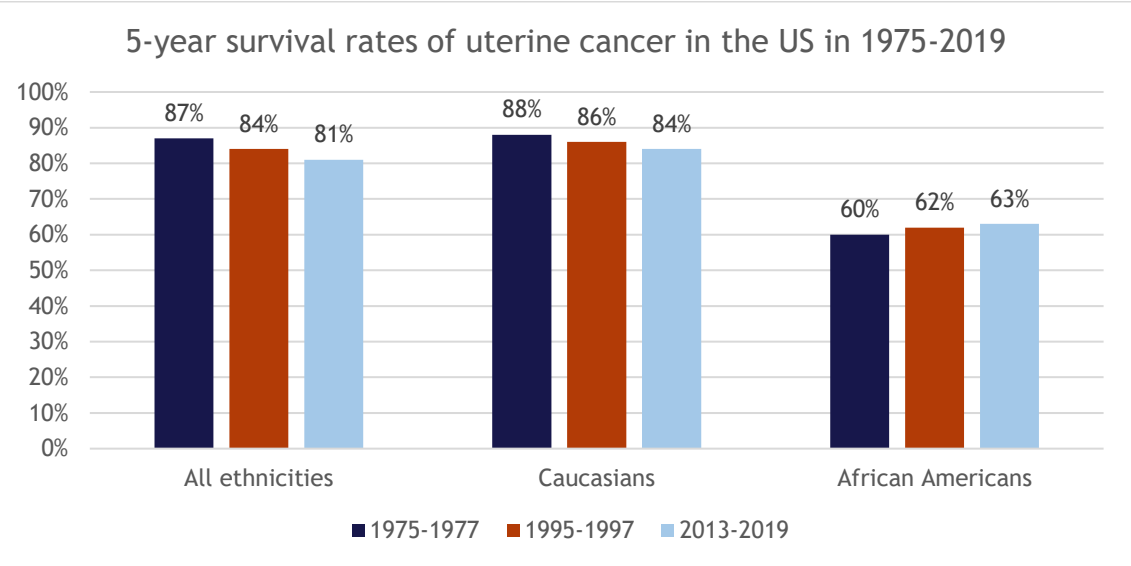

Figure 12: 5-year relative survival rates of uterine cancer in the US from 1975 to 2019.

Notes: The figure presents relative survival rates based on data from SEER 9 areas for the years 1975-1977, which encompassed 8% of the population, and from SEER 22 areas for the years 2013-2019, covering 42% of the population. Source: (77).

The primary determinant of survival in endometrial cancer is the stage at which the cancer is diagnosed; see Figure 13. In the US, the 5-year survival rate is 95% for cases when the cancer is localized, but it drops to 19% in instances when the cancer has already metastasized at the time of diagnosis. In England, the survival rates follow a similar pattern, with a 5-year survival rate of 92% for women diagnosed in stage I and dropping to 15% for stage IV. However, survival rates vary among different patient demographics, as described in section 2.8.

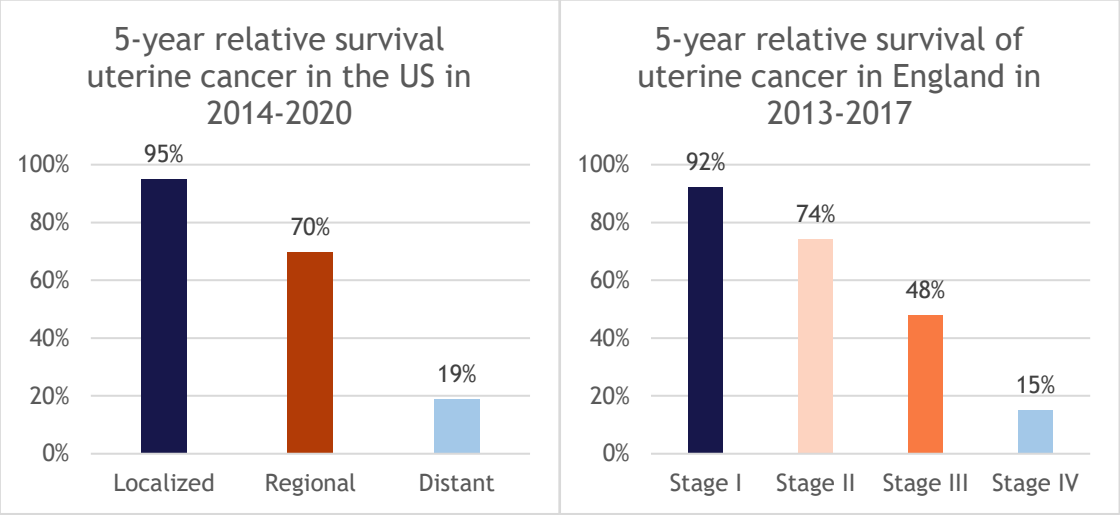

Figure 13: 5-year relative survival rates of uterine cancer by stage at diagnosis in the US and England.

Source: (66, 78).

Approximately 18% of women diagnosed with endometrial cancer face a relapse of the disease, primarily within the first two years following their initial surgery (79). For these patients, the available treatment choices are often restricted, and the risk of death is significantly elevated (79). The likelihood of recurrence, whether at local or distant sites, is influenced by the molecular characteristics of the tumors. Recent research indicates that high-risk types of endometrial cancer have recurrence rates that are four times higher than the low-risk types and twice as high as of the total endometrial cancer patient population (37); see Figure 14.

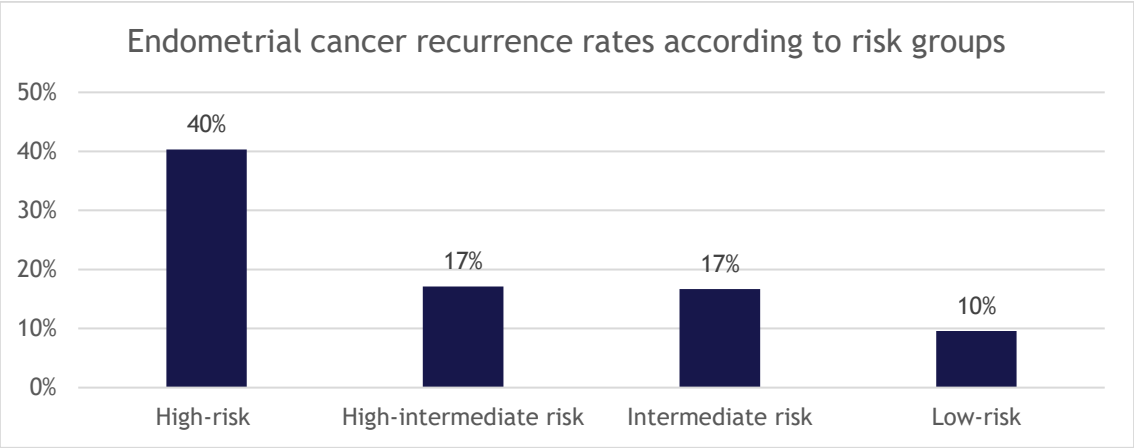

Figure 14: Endometrial cancer recurrence rates according to risk groups.

Notes: The study included 758 women diagnosed with stage I to III endometrial cancer who were followed for 5 years. In this study, the high-risk account for 27% of the cases, high-intermediate for 10%, intermediate for 14%, and low risk for 49%. For a complete description of each risk group see Table A1 in the Appendix. Source: (37).

2.7 Quality of life

Endometrial cancer significantly affects various aspects of life, not only for the patients but also for their families, impacting their overall quality of life. As the incidence of endometrial cancer increases and more women become survivors, the focus on quality of life during and after treatment is gaining a higher priority (80). Multiple factors contribute to a decline in well-being during and after treatment, as detailed in Table 7.

Table 7: Aspects of quality of life affected with endometrial cancer

Aspect	Description
Physical health	One year after being diagnosed with endometrial cancer, many patients report a noticeable decrease in both their physical and role functioning (81). The reduction in physical functioning expresses in the form of struggle with basic bodily activities and daily tasks, likely as a result of enduring side effects from their cancer treatment. In terms of role functioning, patients may find it more challenging to fulfill their usual responsibilities and roles, whether in work, family life, or social settings. The primary cause of this overall decline is typically the long-term effects of treatments like radiation therapy (81). Such treatments can result in persistent health issues, notably chronic diarrhea, as well as bowel and urinary incontinence, which significantly affect the patients' quality of life (81). Among other challenging physical symptoms for women with gynecological cancers are the loss of fertility (for younger women), treatments leading to early menopause and problems with sexual function (82). Indeed, studies report that a vast majority of women, between 81% and 89%, experience some form of sexual dysfunction after treatment (simple hysterectomy and radiation therapy), which may manifest as reduced satisfaction, difficulty achieving orgasm, diminished desire, dryness, and pain, among other symptoms (83).
Mental health	Women diagnosed with endometrial cancer frequently encounter various psychosocial challenges, encompassing, anxiety, emotional distress, and depression. This decline is sharper at the beginning (from diagnosis until 3 months thereafter) but rebounds somewhat after one year (82). Nonetheless, the effects can last for a long time. Studies show that even 6 to 12 years after early-stage endometrial cancer treatment, women often feel more anxious and depressed than other people of their age (84). For instance, in survivors aged 55-64 and 65-74, about 30% experience anxiety and depression, which is twice the usual rate of 15% seen in these age groups (84).
Informal care	The partners of women with endometrial cancer often find themselves adapting to the role of informal caregivers. Their new duties extend to providing practical help around the house, like handling extra chores, and caring for children or elderly relatives in households that span multiple generations. In the US, the average time spent on family caregiving for patients with uterine cancer, bladder cancer, and skin cancer was about 6.8 hours per day (85). This time included accompanying patients to treatments, managing symptoms, providing emotional support, helping them with household chores, helping with grocery shopping, dressing, bathing, providing financial support, transportation, among others.
Family life	Gynecological cancers can affect the relationship with one's partner in terms of closeness, sexual relations, and intimacy (86). Uterine cancer most often requires a hysterectomy (the removal of the uterus) as the primary form of treatment, leading to infertility in women of reproductive age (87).
Work life	The average age of diagnosis for endometrial cancer is around 60–62 years (38). Many newly diagnosed women are still of working age. For women within this age group, receiving a cancer diagnosis frequently gives rise to significant concerns about their employment status and ability to continue working. Patients may fear losing their jobs during or after undergoing treatment, and additionally, there can be apprehensions about facing discrimination or instability at the workplace. A study of employment challenges found that 22% of women with endometrial cancer in the US experienced a change in their employment status following their diagnosis (88). Most of these women shifted from full-time employment to another status. Specifically, 8% took early retirement, while 5% were classified as being on long-term disability (88).
Household finances	The financial situation of households with endometrial cancer patients can be affected in various ways. Women of working age, who are often burdened with severe symptoms, may find themselves needing to take prolonged sick leave or even

	permanently leaving their jobs, resulting in a loss of household income. There is a notable lack of studies specifically researching the economic impact of endometrial cancer on patients' household finances. However, insights from breast cancer research reveal that the probability of returning to work within a year of diagnosis ranges from 43% to 93% in high-income countries (89). Furthermore, research on caregivers of cancer patients indicates a productivity loss of 21–27% due to absenteeism or presenteeism (90). Additionally, families face the challenge of covering out-of-pocket expenses for transportation to healthcare facilities and medical services, which can include either co-payments or full payments for these services depending on one's health insurance coverage.

Women with endometrial cancer often have comorbid conditions, such as diabetes or hypertension, which may further deteriorate physical health, making everyday activities more challenging and intensify the side effects of cancer treatment. These additional health problems complicate the treatment process and negatively influence overall health outcomes. Studies have consistently shown that comorbidities are linked to a reduced quality of life in endometrial cancer survivors (80). For instance, one study noted a decrease of about 9 to 13.4 points on a health-related quality of life (HRQoL) scale (on a scale from 0 to 100 points) (81).

Socioeconomic status also has a strong influence on HRQoL of endometrial cancer patients (91). Socioeconomic disparities described in section 2.8 add another layer of difficulties to challenges outlined in Table 7. For instance, women from lower socioeconomic backgrounds may face barriers to accessing quality health care due to inadequate health coverage, resulting in delayed diagnosis and access to less effective treatment options.

2.8 Health disparities

This subsection analyzes disparities in endometrial cancer, focusing on differences based on socioeconomic status (SES) and ethnicity. It reviews studies from Sweden, the US, and England, showing how factors like education, health insurance coverage, community wealth, ethnicity, and income affect endometrial cancer staging, recurrence, and survival.

Risk factors and incidence

SES

More risk factors among the most deprived: In England, it is estimated that annually 635 cases of uterine cancer could be prevented if women from various income groups experienced the same age-incidence rate as those in the most advantageous group (Quintile 1) (92). Women from the most deprived groups are more likely to develop cancer, as they are often exposed to a range of risk factors. Being overweight or obese, which is more common in these groups, is a notable example of such risk factors. As illustrated in Figure 15, the number of preventable cases escalates with an increasing level of deprivation.

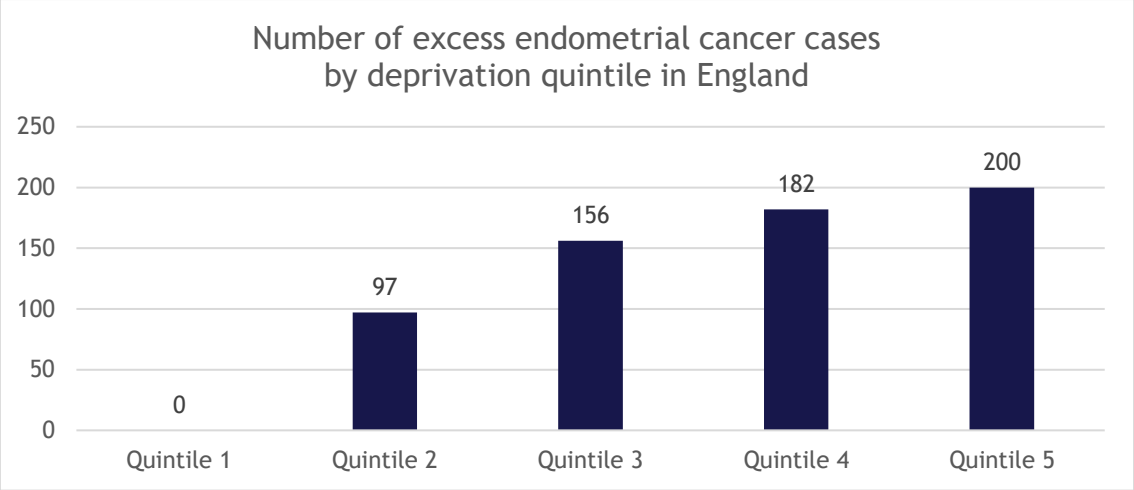

Figure 15: Average annual number of excess cases of endometrial cancer by deprivation quintile in England.

Notes: The estimation used cases for 2013-2017 and included the ICD-10 codes C54 and C55. Source (92).

Ethnicity

Higher levels of obesity: In the US, African American, Hispanic, and Caucasian women have a much higher prevalence of obesity (BMI≥30 kg/m^2) than Asian American women; see Figure 16.

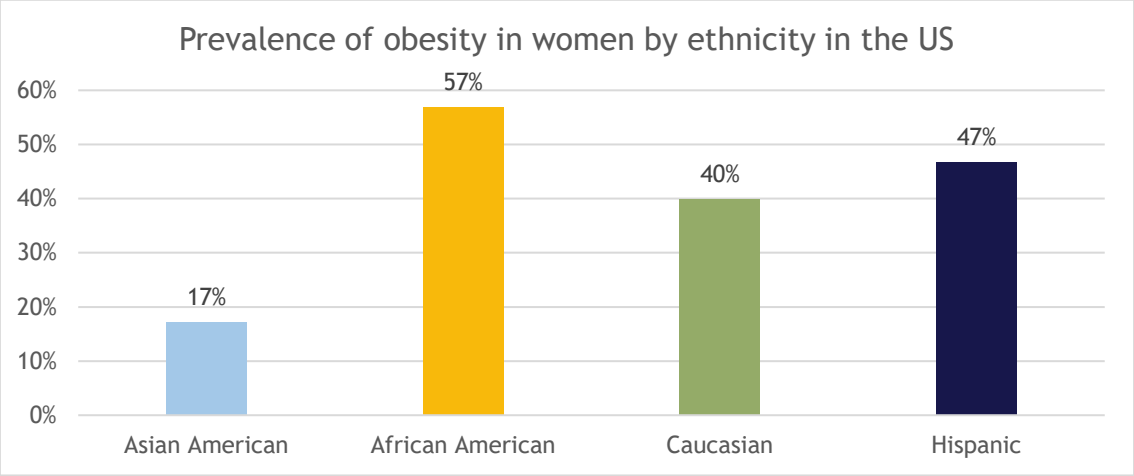

Figure 16: Age-adjusted prevalence of adult obesity in women by ethnicity in the US.

Notes: The graph presents data from the 2017-2018 National Health and Nutrition Examination Survey (NHANES), defining obesity as BMI ≥30 kg/m^2. The category labeled "Hispanic" represents an average of two subgroups, "Hispanics" at 44% and "Mexican Americans" at 50%. Source: (93).

Higher prevalence of comorbidities: In the US, African American endometrial cancer patients are more likely to have comorbidities such as obesity, hypertension, and heart disease that lead to shorter survival rates (94). However, the evidence regarding the impact of comorbidities on survival is mixed, with some studies suggesting that comorbid conditions do not account for the survival differences observed between Caucasian and African American patients (95).

Subtypes

Ethnicity

Higher prevalence of aggressive subtypes: African American women are more frequently diagnosed with endometrial cancer subtypes that carry a poorer prognosis, specifically type II endometrial cancer (96). A US study focusing on women under the age of 50 found that African Americans had a higher likelihood of presenting with non-endometrioid histology (45%) than Caucasians (31%), which is more aggressive and had a less favorable prognosis than endometrioid histology (41). Another study utilizing molecular, clinical, and progression-free survival data from TCGA analyzed information from 337 patients, finding a similar pattern of a higher prevalence of aggressive molecular subtypes in African Americans compared to Caucasians (97). Similarly, a more recent study found that endometrial carcinomas in African Americans and Caucasians showed significant differences in their molecular and histologic profiles, genetic alterations, and potential therapeutic targets (98). The study revealed that microsatellite instability, which can enhance responsiveness to immunotherapy (see section 4.4), occurred less frequently in tumors of African American patients compared to those of Caucasian patients. Mutations in the POLE gene, which are linked to a favorable prognosis, were more commonly found in Caucasians.

Age at diagnosis

Ethnicity

Foreign-born women in Sweden get gynecological cancer earlier in life: In Sweden, a study found that the mean age of diagnosis of gynecological cancers (including uterine cancer) was significantly lower for non-Europeans at 57.9 years compared to Sweden-born women at 65.8 years (99). As can be seen in Figure 17 among women born outside of Europe and in other European countries a majority of cases was found in women younger than 65 years, whereas only 36% of native-born women and 28% of women born in other Nordic countries were younger than 65 years at diagnosis.

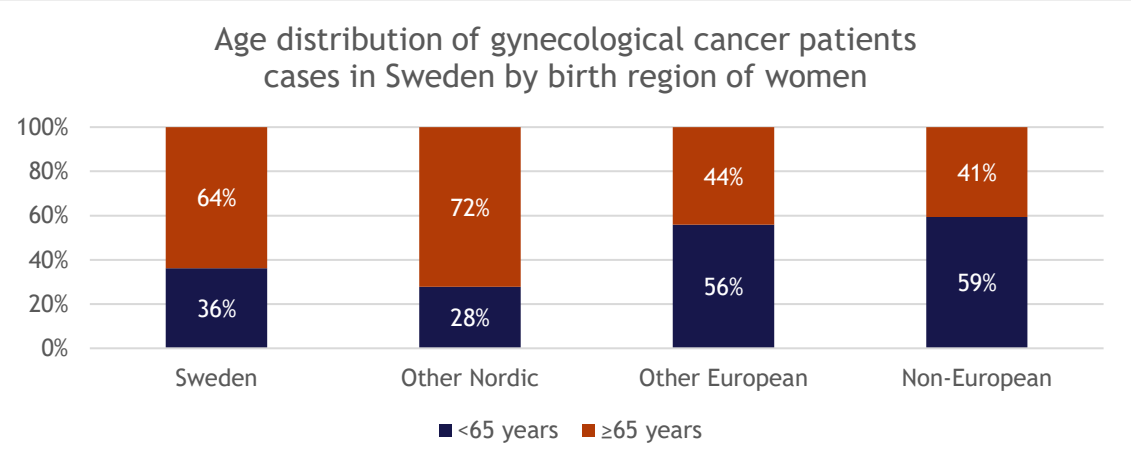

Figure 17: Age distribution of gynecological cancer cases in Sweden by birth region of women.

Notes: The study included 684 women aged ≥ 18 years old, diagnosed in 2014, 2016, or 2018 with gynecological cancers (vulvar, vaginal, cervical, uterine, ovarian, or fallopian tube cancer) in the Stockholm-Gotland healthcare region. Source: (99).

Stage at diagnosis

SES

Lower education is related with increased stage at diagnosis: A study conducted in Sweden with data from 1995 to 2016 demonstrated a correlation between lower education level and an increased stage of endometrial cancer at diagnosis (100). Women with a low education level had a 65% higher risk being diagnosed with stage II and an 82% higher risk of being diagnosed with stage III-IV than women with a high education level. This trend was especially pronounced in women aged between 50 and 74 years.

Ethnicity

Delayed diagnosis for African Americans: In the US, African American women are often diagnosed at a more advanced stage of the disease (13, 101). For instance, in the period 2011-2020, 69% of Caucasian women were diagnosed at a localized stage of EC, compared to only 53% African American women. In contrast, while 8% of Caucasian women were diagnosed at an advanced stage, this figure rose to 18% among the African American population; see Figure 18.

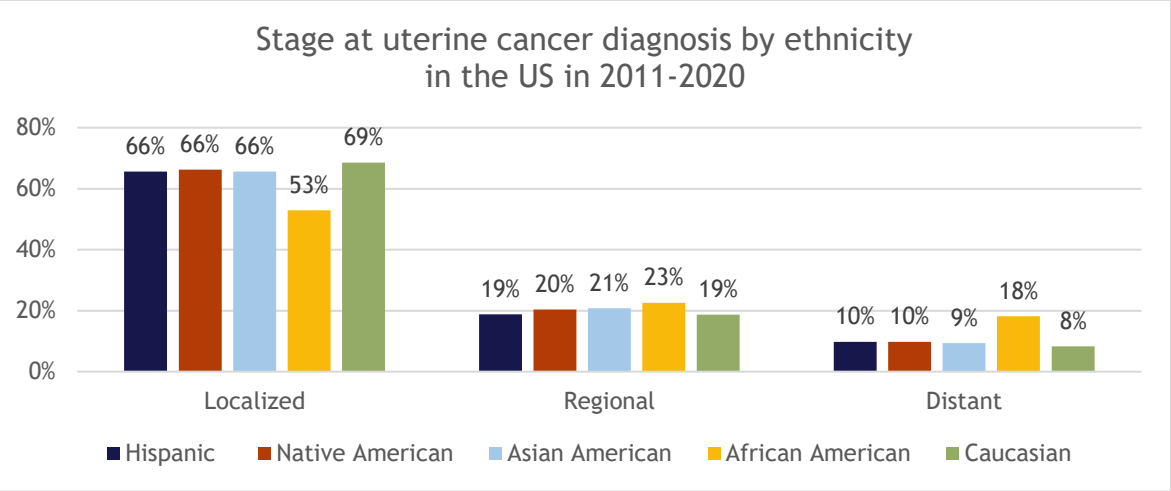

Figure 18: Stage at uterine cancer diagnosis by ethnicity in the US in 2011-2020.

Source: National Cancer Institute (66).

Survival and recurrence

SES

Private health insurance related with better survival rates: In the US, a study with data from 39,510 patients diagnosed between 2000 and 2001 found that endometrial cancer patients with private health insurance had better overall survival compared to uninsured patients and patients with Medicaid (102). However, Medicaid expansion has been linked to reductions in uninsured diagnoses, more early-stage diagnoses, increased treatments at academic facilities, and timely treatment and surgery within 30 days for women with a gynecological cancer (103).

Another study in the US, involving data from 9,367 Hispanic and 5,878 Asian American women, revealed that Hispanic women residing in the lowest SES communities experienced a 36% higher mortality rate from endometrial cancer compared to their Hispanic counterparts in the highest SES communities (104).

Metastatic recurrences more common in the most deprived groups: A study conducted in England with data from 2010 and 2015 found that the overall rates at which cancer came back (recurrence rates) were the same across women from different socioeconomic groups (91). However, women in the middle-deprived and most deprived groups were much more likely to have their cancer come back in a distant or metastatic form compared to women in the least deprived group. In the middle-deprived and most deprived group about 79-80% of women had a distant recurrence compared to 43% in the least deprived group (91).

Social deprivation is linked to poorer survival rates: A study in Northwest England revealed that socioeconomically deprived women face a significantly higher risk of cancer mortality. Specifically, women from the middle deprivation group were twice as likely to die from cancer as those from the least deprived group, who generally have higher income and education levels) (105).

Ethnicity

African Americans have much lower survival rates: There are great disparities in survival rates of endometrial cancer between African American women and other ethnicities in the US. African American patients have by far the lowest 5-year survival rate, standing at 63%, whereas women of all other groups have survival rates of 80% or higher; see Figure 19.

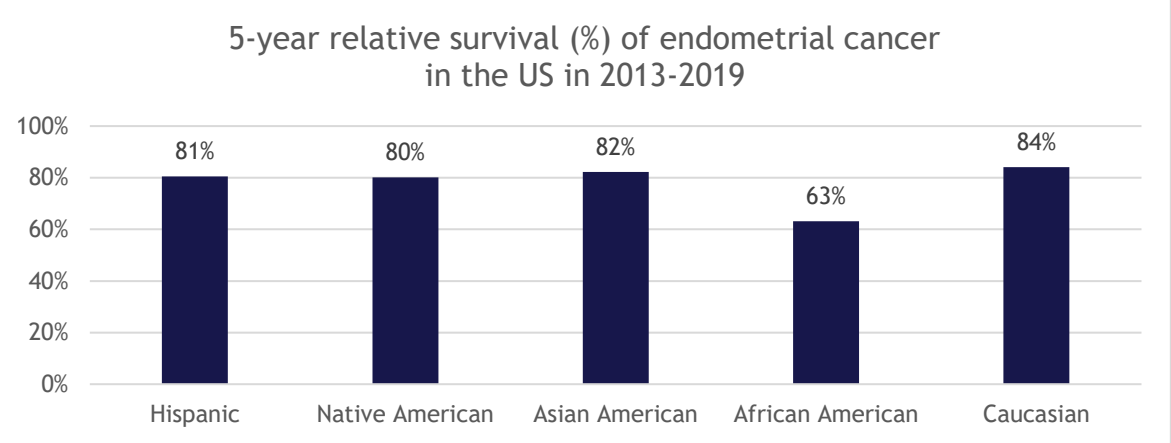

Figure 19: 5-year relative survival rates of endometrial cancer by ethnicity in the US in 2013-2019.

Source: National Cancer Institute (66).

Divergent treatment approaches: A US study found that Caucasian women receive surgery and lymph node examinations more frequently than their African American and Hispanic counterparts (106). Although the primary reasons for these differences were not specifically investigated, they are likely multifaceted. One notable factor is health insurance status; 41% of Caucasians in the study had private insurance, compared to 34% of Hispanics and 31% of African Americans. Additionally, only 3% of Caucasians reported being uninsured, in contrast to 5% of African Americans and 11% of Hispanics.

Quality of life

Ethnicity

Segregation impacts quality of life in women with gynecological cancers: A research study conducted in Sweden examined disparities in the quality of life between women born in Sweden and those born abroad who have been diagnosed with gynecological cancers in 2014-2018 (99). The primary finding indicates that the greater the distance from a woman's country of birth to Sweden, the lower her HRQoL tends to be. Residential segregation was pointed out as playing a big role (99). Health behaviors, influenced by social, economic, and cultural factors, can vary significantly across segregated communities. Moreover, the stress associated with living in segregated, often marginalized communities can have a direct impact on women's quality of life.

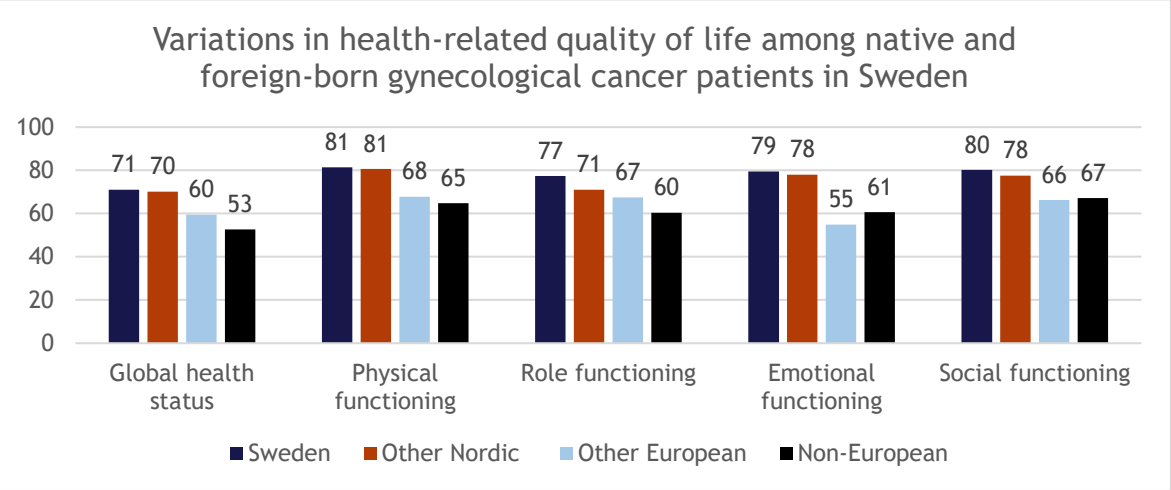

Figure 20: Variations in health-related quality of life among native and foreign-born gynecological cancer patients in Sweden.

Notes: The analysis involved 415 women aged 60 to 69 years diagnosed in 2014, 2016, or 2018 with gynecological cancers (vulvar, vaginal, cervical, uterine, ovarian, or fallopian tube cancer) in the Stockholm-Gotland healthcare region. It revealed statistically significant differences in the experiences of women born in Sweden compared to those born in non-European countries, and in many cases, between women from other European countries and those born in Sweden. Source: (99).

3. Disease and economic burden

3.1 Incidence and mortality

In the EU, UK, and Northern America, an estimated 153,623 new cases and 33,550 deaths of uterine cancer occurred in 2022 (2). Over time, several countries in Europe and Northern America have seen increases in endometrial cancer incidence, as shown in Figure 21. However, there are exceptions, such as Germany, where the crude incidence rate of 27 cases per 100,000 women remained virtually unchanged from 1999 to 2019. From 1990 to 2021, the growth in crude incidence rates varied significantly across different countries, increasing by as much as 114% in Slovenia and by only 8% in both Sweden and Denmark. The US had the highest crude rate of 29 cases per 100,000 women in 1990 and in 2020 it was still at the top with 39 cases per 100,000 women. This trend may reflect the high prevalence of obesity in the US, which was among the highest in the selected countries (alongside Czechia) in recent decades and has exhibited the most dramatic increase in recent years, as shown in Figure 22. Conversely, Sweden recorded the lowest incidence rate in 2020 in the sample, with 26 cases per 100,000 women, and it was also the country (jointly with Denmark) that had the lowest obesity rate in recent decades.

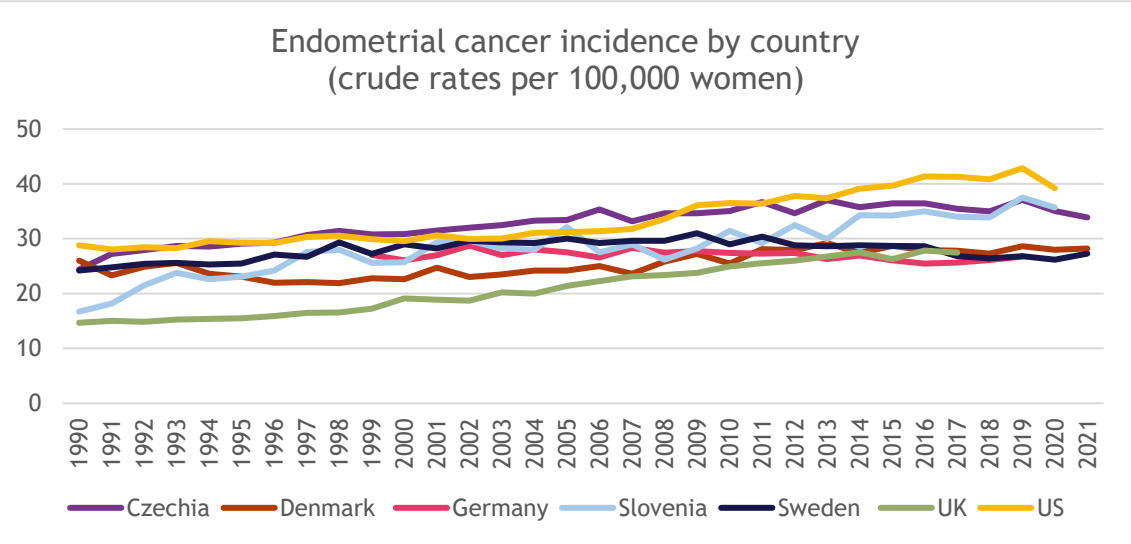

Figure 21: Incidence crude rates of endometrial cancer per 100,000 women, 1990-2021.

Notes: The estimation for US crude rates utilized the long-term trends SEER database, covering the years 1975-2020, based on case counts. The data encompasses SEER 8 registries, which include Connecticut, Atlanta, San Francisco-Oakland, Hawaii, Iowa, New Mexico, Seattle-Puget Sound, and Utah. Population estimates were derived from historical female population data at the state level, with specific considerations for San Francisco County in estimating the San Francisco-Oakland rates, and Fulton County for Atlanta rates. Sources: (66, 107-112).

Trends in the prevalence of several risk factors and protective factors (see section 2.2) have been identified as contributing to the rising number of endometrial cancer cases over the past decades:

- **Rising overweight and obesity rates**: The prevalence of overweight (affecting now more than half of all adult women) and obesity (affecting now between 18% of women in Sweden and 37% of women in the US) has been steeply increasing from 1975 to 2016

in most geographies as shown in Figure 22. Higher prevalence of excess body weight is closely linked to an increased risk of developing endometrial cancer (76, 113).

- **Decline in childbirths**: Declining childbirth rates are associated with a higher incidence of endometrial cancer, as pregnancy is known to offer some protective effects (76, 113).
- **Reduction in hysterectomy rates**: Undergoing a hysterectomy, which involves the removal of the uterus, effectively eliminates the risk of developing endometrial cancer. Recent research in Finland and Sweden observed a continuous decrease in the rate of hysterectomies from 1986 to 2017 and from 1999 to 2019, respectively (76, 114). In the US, hysterectomies decreased by 39% between 2000 and 2014 (115). One of the reasons for decreasing rates of hysterectomies has been treatment advances for other uterine conditions such as fibroids, endometriosis, prolonged menstrual bleeding, which decreased the need for removal of the uterus (58).
- **Reduced use of hormone replacement therapy (estrogen plus progestin)**: A supposed landmark randomized trial of using hormone replacement therapy was stopped early in 2002, due to an increased risk of breast cancer and other adverse events (116). Following extensive media coverage, there was a subsequent steep decline in the use of hormone replacement therapy in the US. The increase in endometrial cancer incidence rates after 2002 may be related to this decline (116, 117).
- **Improved diagnostic methods**: Enhanced medical diagnostics, such as transvaginal ultrasound and immunohistochemistry have led to more frequent and accurate identification of endometrial cancer cases, contributing to the registered increase in incidence (76).

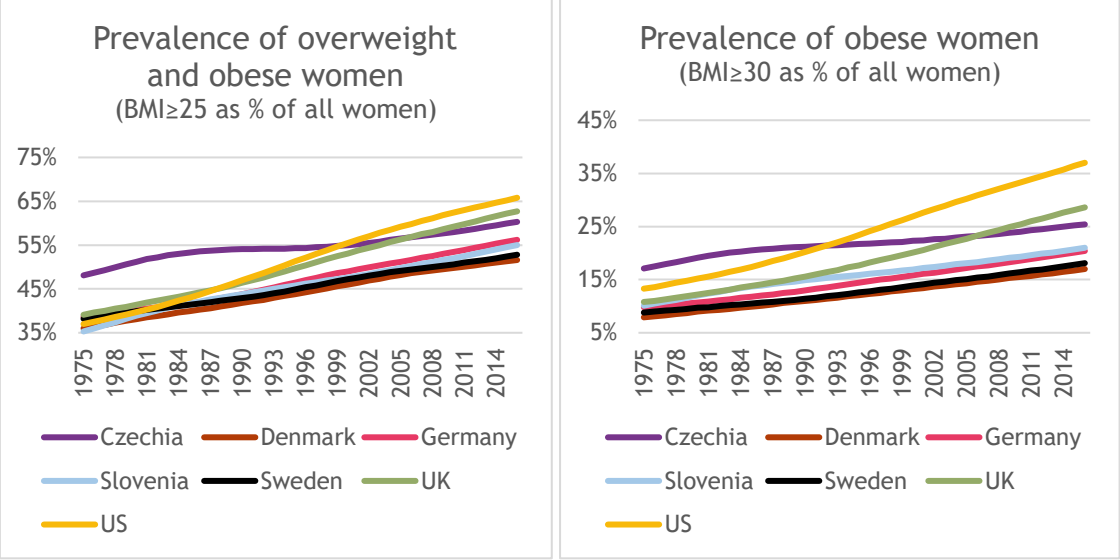

Figure 22: Prevalence of overweight and obesity in women between 1975 to 2016.

Notes: Overweight is defined as BMI ≥25 and obesity as BMI ≥30. Source: (118, 119).

The growth in the number of endometrial cancer cases varies by age group and geographies. In the US, the overall age-adjusted (not crude) incidence rate of endometrial cancer increased by 6% from 24.8 to 26.4 cases per 100,000 women between 1990 and 2021 (SEER) (66). As depicted in Figure 23, the growth in cases has been more pronounced in women under 50 years of age, with a rise of nearly 50% from 4.3 to 6.1 cases per 100,000 women. The observed trend for younger women is partially attributed to rising levels of excess body weight and a decline in childbirth rates (113). In contrast, the incidence rate for women aged 50-64 years showed a

smaller increase of 13%. The only age group to experience a decline in incidence rates was women aged 65 and over with a 9% decrease.

In Sweden, however, the pattern has been different; endometrial cancer cases decreased among women under 55 years between 1960 and 2014, whereas there was a significant rise in cases among women over 60 years (76). Additionally, data from Sweden indicate an increase in high-risk endometrial cancer cases (76). Similar trends of decreasing incidence in women under 50 years have been observed in France, the Netherlands, Denmark, Norway, and Czechia with data from 1978 to 2013 (120).

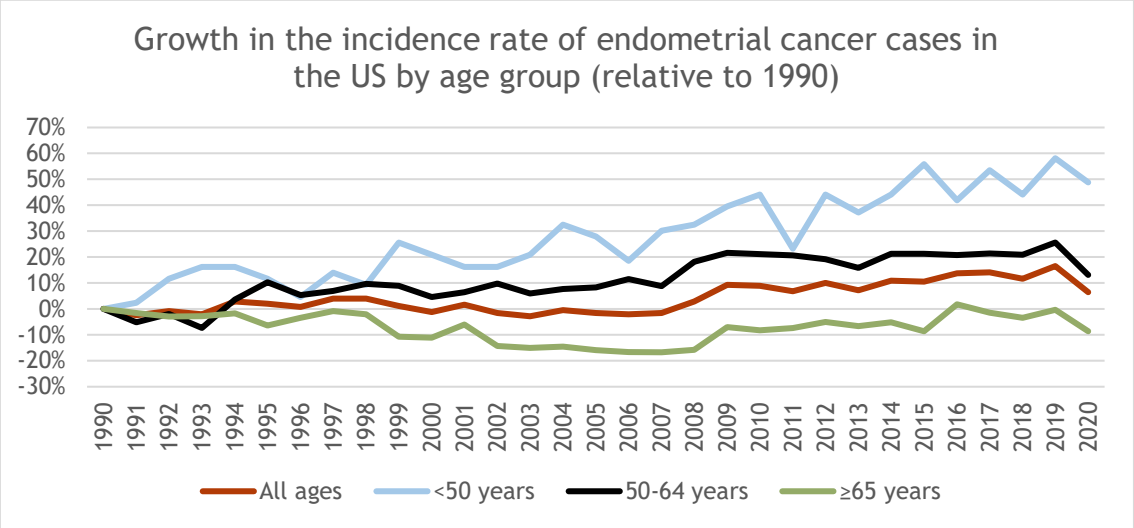

Figure 23: Growth in endometrial cancer incidence rate (age-adjusted rates per 100,000 women) by age group in the US between 1990 and 2020.

Source: National Cancer Institute (66).

Across the globe, the trajectory of endometrial cancer mortality crude rates presents a diverse picture; see Figure 24. In Czechia and Denmark, the trend is encouraging, with clear reductions in mortality rates since 1990, a decrease of 20% in Czechia, from 9.8 to 7.9 deaths per 100,000 women, and an even more pronounced 44% drop in Denmark, from 5.0 to 2.2 deaths. In contrast, Sweden and Germany have maintained steady mortality rates, with approximately 4 deaths per 100,000 women in Sweden and 6 deaths per 100,000 in Germany. The UK has experienced a 71% increase in mortality rates from 3.5 deaths per 100,000 women in 1990 to 5.9 deaths in 2020. Similarly, Slovenia and the US have seen gradual increases, with death rates climbing from 5.1 to 7.4 deaths in Slovenia and from 4.7 to 7.2 deaths in the US.

In the US, the age-adjusted mortality rates for endometrial cancer have shown an annual increase of 2% from 2008 to 2018 (77, 121). This trend makes endometrial cancer one of few cancer types with rising age-adjusted mortality rates (77). The uptick in mortality rates from endometrial cancer at the population level has been linked to a confluence of various health trends (58). This includes trends in risk factors (foremost obesity rates) and protective factors (such as hysterectomies and the use of combined hormone replacement therapy) which all influence trends incidence rates at the population level (58). The fact that trends in mortality rates mirror trends in incidence rates has been suggested to reflect limited progress in the treatment of endometrial cancer (122), which is also evidenced by the lack of improvements in survival rates in the US shown in section 2.6.

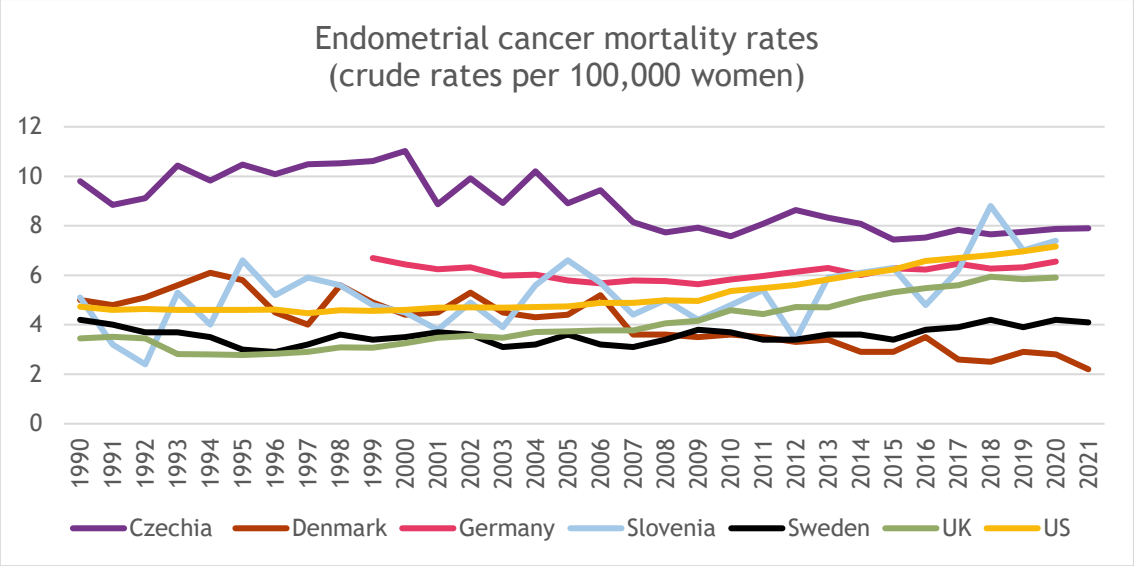

Figure 24: Mortality crude rates of endometrial cancer per 100,000 women, 1990-2021.

Source: (66, 107, 109, 112, 123, 124).

Incidence and mortality rates of endometrial cancer may vary considerably across population groups. Figure 25 presents the age-adjusted incidence and mortality rates of new endometrial cancer cases by ethnic groups in the US in the period 2016-2020. It reveals that Asian Americans exhibit the lowest incidence rate of 23 per 100,000 women, while other ethnic groups range between 26 and 29 cases per 100,000. This pattern may be explained by the much lower obesity rates in Asian Americans than in other ethnic groups; see Figure 16. The mortality rate for African Americans with 9 deaths per 100,000 women is nearly twice as high compared to other ethnicities with 4-5 deaths per 100,000. This pattern may be explained by the low survival rates of African Americans compared to other ethnicities; see Figure 19.

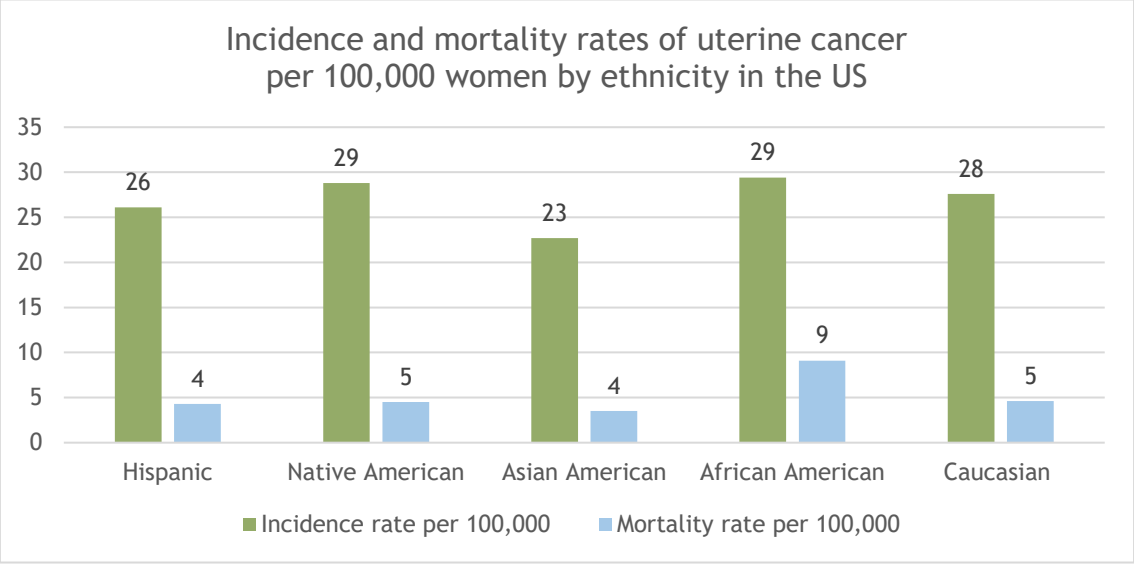

Figure 25: New cases and deaths of uterine cancer per 100,000 women (age-adjusted) by ethnicity in the US, 2016-2020.

Source: National Cancer Institute (66).

3.2 Economic burden

Endometrial cancer imposes an economic burden on society in addition to the costs arising for patients and their families (see also section 2.7). The economic burden is here defined more broadly than in an everyday meaning. Generally, three types of costs can be distinguished (125); see Table 8.

Table 8: Components of the economic burden of cancer

Direct costs	Indirect costs (productivity loss)	Informal care costs
These are costs of disease-related resource consumption. They include both public and private expenditure for services within the healthcare system, such as diagnostic procedures, surgeries, radiation therapy, and medicines. Transportation costs by patients for travelling to healthcare facilities are also direct costs. Expenditure for social support services outside of the healthcare system also belongs to direct costs.	These are costs of patients' productivity loss arising from the inability to work due to the disease. They consist of the temporary or permanent inability to work in the formal labor market (called morbidity) and from premature death (called mortality) of working-age patients.	These costs represent the value of the time spent by family members and friends to provide unpaid care, such as transportation to a healthcare facility and assistance with household chores.

There are few comprehensive estimates of the economic burden of endometrial cancer. A study from Sweden found the total costs to be SEK 375 million (around EUR 43 million) in 2013, or around SEK 39 (EUR 4.5) per capita (126). Figure 26 shows a comparison of the relative contribution of the different cost components to the economic burden of endometrial cancer compared to all cancers in Sweden. Direct costs of endometrial cancer account for 54% of the economic burden, which is more compared to all cancers. Indirect costs of endometrial cancer account for 34% of the economic burden, which is less compared to all cancers. This could be partly attributed to the higher average survival rate in endometrial cancer compared to all cancers as well as the generally lower salaries and employment rates of working-age women than men, resulting in comparatively less productivity loss to the economy.

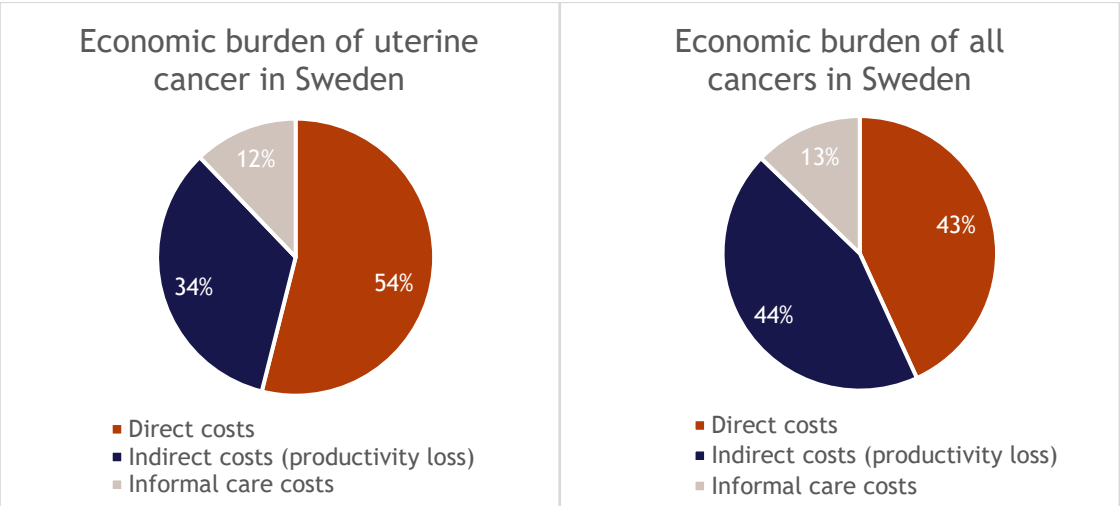

Figure 26: Economic burden of uterine cancer and all cancers by cost component in Sweden in 2013.

Source: (126).

In terms of healthcare expenditure (direct medical costs), uterine cancer accounts for a smaller proportion compared to more common cancers such as lung, prostate, colorectal and breast cancer (127). However, it still represents a significant portion of the total cancer care expenditure, exceeding the costs associated with many rare cancers. In the US, an estimated US$ 5.8 billion were allocated to uterine cancer care in 2020, accounting for approximately 3% of the total cancer care expenditure that year (128); see Figure 27. For comparison, breast cancer expenditure accounted for 14%, ovarian cancer for 3%, and cervical cancer for 1% of the total cancer care expenditure (128). A study from Canada for 2021 estimated that uterine cancer accounted for 2% of all direct health system costs (approximately CA$ 353 million) (127). In contrast, data from Sweden for 2013 indicated that about 1% of the total cancer care expenditure were dedicated to uterine cancer. These data points on expenditure can also be compared to the disease burden of uterine cancer (2). Overall, uterine cancer comprises 3% of all new cancer diagnoses and 2% of all cancer deaths among women and men in Europe and Northern America. The expenditure pattern in the US mirrors the proportion of the relative incidence of uterine cancer (3% of all cancer care expenditure and 3% of all cancer cases). By contrast, in Canada and Sweden, the spending share (2% and 1%, respectively) is lower than the incidence share (3% and 2%, respectively).

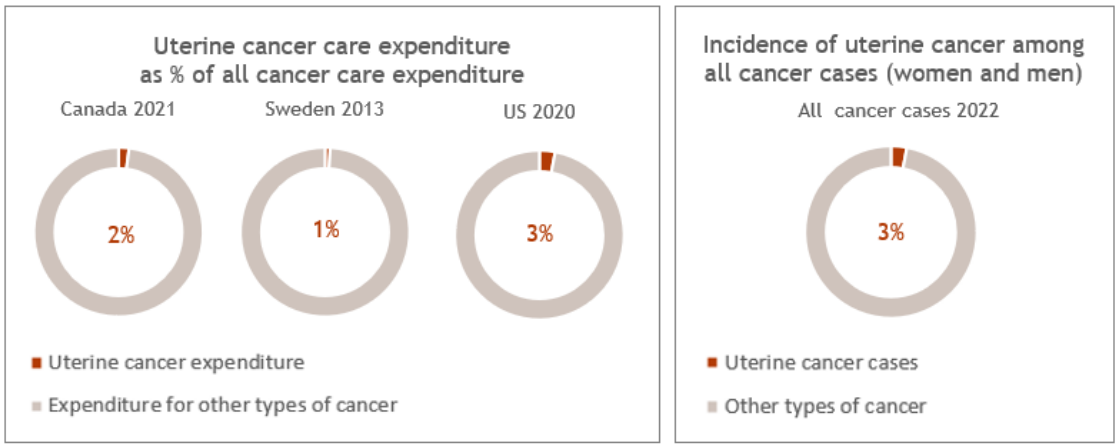

Figure 27: Uterine cancer care expenditure and uterine cancer cases in relation to all cancer care expenditure/cases.

Notes: The estimates for cancer care expenditure were derived using varied methodologies, sourced from different databases, and belong to different years. Therefore, a comparison of these figures between countries should be made with caution. Sources: (2, 126-128).

Multiple studies established a marked escalation in direct medical costs associated with the progression of cancer at the time of diagnosis. Data from England from the period 2001-2005 reveal a trend where stage III endometrial cancer patients incur approximately 2.5 times higher healthcare expenses compared to stage I patients (per patient-year) (129); see Figure 28. Patients with metastatic cancer also generate higher costs than those in stage I and II, although they incur less costs than stage III patients. Lower costs in stage IV than in stage III might relate to notable differences in surgical intervention rates, as only 20% of stage IV patients underwent a hysterectomy in contrast to 95-100% of patients in stages I to III in the example from England (129).

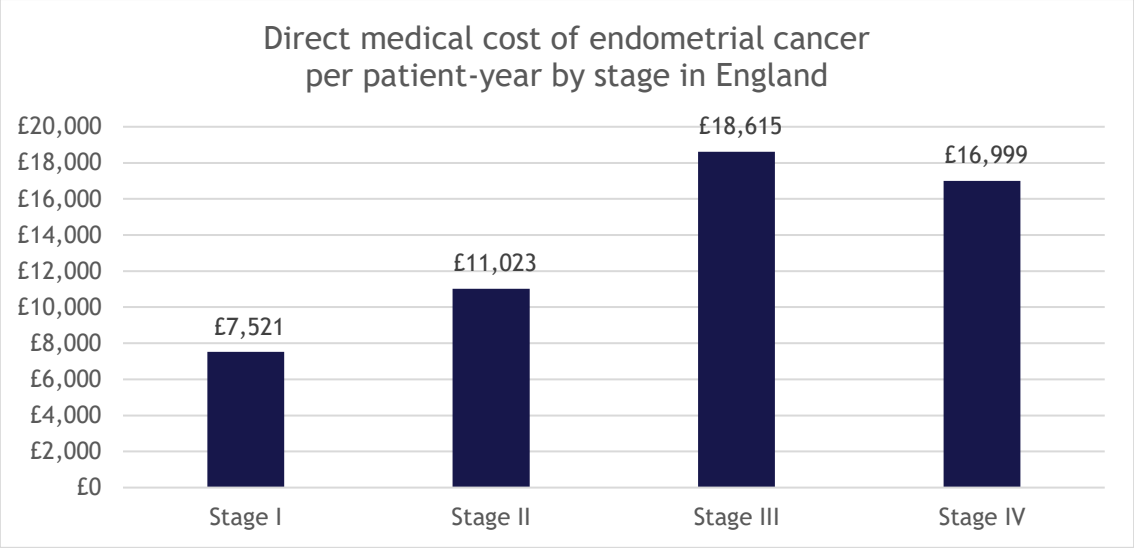

Figure 28: Direct medical cost of endometrial cancer per patient-year by stage in England.

Notes: The study used data from 491 patients from the Hospital Episode Statistics diagnosed from 2001 to 2005. Costs are in 2013 British pounds (£) Source: (129).

4. Care process and challenges

This chapter outlines the typical patient pathway for endometrial cancer from detection to treatment; see Figure 29. It highlights the services to be received and recent breakthroughs in the field, aligning with the global standard of care as per the latest international clinical guidelines. Health quality metrics defined in clinical guidelines are also described. An important part of this chapter is the description of challenges that patients face along the pathway.

The patient's journey usually begins with the onset of symptoms that prompt a visit to a healthcare provider. The most common symptom leading to the suspicion of endometrial cancer is abnormal uterine bleeding; see section 2.3. During the diagnostic process, healthcare providers perform a pelvic examination, imaging scans, and pathology tests to determine the characteristics of the tumor. Depending on these characteristics, the most suitable treatment modalities can be decided on. This may include surgery, and/or radiation therapy, and/or systemic therapy.

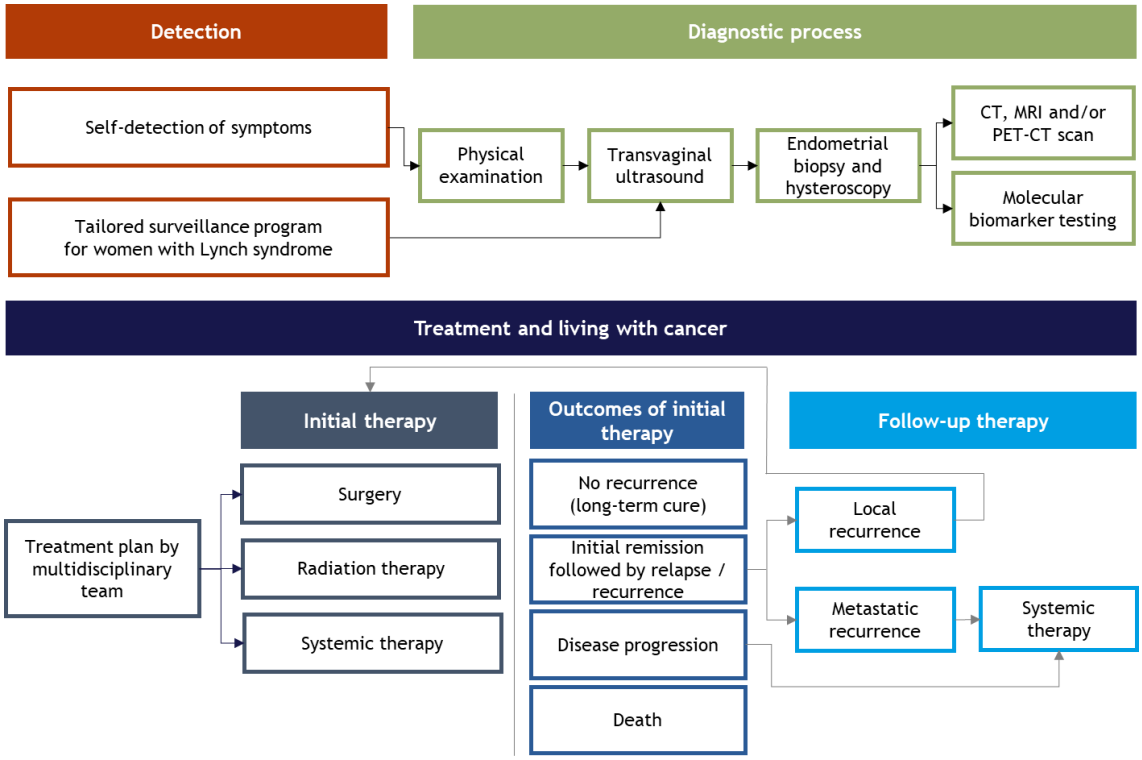

Figure 29: Stylized patient journey in endometrial cancer.

Notes: Based on ESGO/ESTRO/ESP guidelines and NHS optimal pathways. The patient journey may vary for women of childbearing age who seek fertility-sparing treatments. Source: (3, 28, 130).

4.1 Health quality metrics

The healthcare landscape features a diverse range of metrics and standards for cancer care, with notable disparities across different cancer types. Breast cancer, for instance, benefits from well-established and universally recognized standards and metrics. In contrast, endometrial cancer has historically lacked such standardized metrics. In 2021, ESGO introduced the first set of quality indicators for the surgical treatment of endometrial cancer, detailed in Table 9. Quality indicators are measurable elements of health care that are used by healthcare professionals and institutions to assess and compare their performance against ideal standards

(131). The main goal of using quality indicators is to improve patient outcomes, by reducing complications associated with medical interventions and increasing survival rates (131). For instance, research as part of the SUCCOR quality validation study has shown that adherence to the ESGO quality indicators for surgical treatment of cervical cancer is associated with better patient outcomes, including lower risks of relapse and potentially lower mortality rates (132).

Table 9: ESGO quality indicators for the surgical treatment of endometrial cancer

Pillar	Examples of indicators
Healthcare provider competency and institutional capacity indicators	• At least 95% of endometrial carcinoma surgeries at a clinic are performed or supervised by a gynecologic oncologist • At least 90% of initial treatment plans and 99% of relapse treatment plans for endometrial carcinoma are made by a multidisciplinary team (MDT)
Adequate pre-operative investigations	• At least 90% of patients undergo pre-operative work-up according to the ESGO/ESTRO/ESP guidelines • Less than 5% of patients have presence of peritoneal carcinomatosis and distant metastases in patients who have been considered early-stage disease (stage I and II)
Alignment of peri-operative practices with accepted care standards	• At least in 99% of early-stage cases undergoing a hysterectomy the uterus should be removed intact (i.e., no rupturing, fragmentation) • At least 80% of early-stage patients should undergone a minimally invasive surgery (laparoscopic or robotic hysterectomy)
Molecular markers for endometrial carcinoma diagnosis and as determinants for treatment decisions	• At least 90% of patients should undergo a complete molecular classification of their tumor (POLE mutation, mismatch repair deficiency, non-specific molecular profile, p53 abnormality)
Management of patients after primary surgical treatment	• At least 90% of patients with early-stage endometrial carcinoma should receive adjuvant treatment according to the ESGO/ESTRO/ESP guidelines
Standardized and comprehensive documentation	• At least 99% completeness in pathology reports according to ESGO/ESTRO/ESP guidelines • At least 99% completeness in surgical reports • Keep reoperation rate below 2% within 30 days for complications after primary minimally invasive surgery

Notes: ESGO: European Society of Gynecological Oncology, ESTRO: European Society for Radiotherapy and Oncology, ESP: European Society of Pathology. Source: (133).

Sweden and England have established their own key performance indicators (KPIs) to monitor and assess the quality of care for uterine and other gynecological cancers. Table 10 and Table 11 present some of the recognized metrics used in both countries.

Table 10: Quality indicators and time frames in uterine cancer care in Sweden

Type of indicator	Definition
Quality indicators *Motivation:* To monitor the quality of care according to the national care program	
Degree of coverage in the National Quality Registry	Over 95% of endometrial cancer cases are registered in the national system within two years. • High registration rates ensure that patient data is captured promptly and accurately, aiding in treatment planning and epidemiological studies.
Survival rate	A 5-year relative survival rate of more than 84% for endometrial cancer. • This is a measure of treatment effectiveness, with a higher percentage indicating better survival outcomes.

Pathological diagnosis	Over 50% of pathology reports are reviewed by a reference (expert) pathologist. • This measure ensures quality and accuracy in the diagnosis.
Proportion of patients operated on with the participation of an experienced tumor surgeon	For patients with high-risk endometrial cancer, 100% are operated on with the involvement of an experienced tumor surgeon. • This highlights the emphasis on specialized surgical expertise for complex or high-risk cases.
Proportion of patients with high-risk endometrial cancer undergoing pelvic or para-aortic lymph node dissection	Over 90% and 80% of patients with high-risk endometrial cancer have a pelvic or para-aortic lymph node dissection, respectively. • This demonstrates adherence to surgical protocols in treating high-risk patients.
Access to a named contact nurse	Every endometrial cancer patient in Sweden has access to a designated contact nurse. • This ensures continuity of care and provides a consistent point of contact for patients, which can improve patient experience and care coordination.
Lead times for national follow-up *Motivation:* To standardize the care process in the whole country	
Diagnosis to first surgery	For endometrial cancer, once there is a well-founded suspicion of endometrial cancer, the healthcare system aims to start the patient's primary surgical treatment within 32 days
Diagnosis to first radiation or cancer medicine	For endometrial cancer, once there is a well-founded suspicion of endometrial cancer, the healthcare system aims to start the patient's primary radiation or drug treatment within 39 days
Diagnosis to palliative care	For endometrial cancer patients with an advanced disease, there should be no more than 25 days from diagnosis to start of palliative symptom-relieving care

Notes: The standardized course of care of uterine cancer aims to create a patient-centered, efficient, and uniformly high standard of care for patients across Sweden, with a focus on reducing waiting times and ensuring that every procedure or step adds value to the patient's journey. Source: (134).

Both Sweden and England emphasize timely and effective cancer care, although they differ in their specific targets and areas of focus; see Table 10 and Table 11. One of the major differences is that Sweden has a set of specific indicators for uterine cancer, while England has a joint set of indicators for all gynecological cancers. Also, Sweden's approach leans more towards precision in diagnosis and treatment, especially for high-risk cases, and ensuring high survival rates. England's KPIs, on the other hand, highlight the importance of fertility sparing, multidisciplinary collaboration, and enhancing the overall patient care experience.

Table 11: Quality indicators and time frames in the National Health Service (NHS) England

Type of indicator	Definition
Quality indicators *Motivation:* To provide high-quality care that addresses not just the medical aspects of gynecological cancers but also the broader needs of the patients	
Maximize fertility preservation	Over 90% of appropriate cases are offered consultation regarding the possibility of fertility preservation. • To enhance the quality of life of women with long-term conditions
Proportion of cases discussed by MDTs	All cases should be discussed by MDTs. • Pertains to the domain to prevent women from prematurely dying
Clinical nurse specialist	All patients need to have access to a clinical nurse specialist. • To ensure that patients have a positive experience of care
Lead times for national follow-up *Motivation:* To standardize the care process	
From primary care to first treatment	When a general practitioner (GP) refers a gynecological patient urgently for suspected cancer, the patient should receive their first treatment within 62 days of that referral.

Diagnosis standard	Patients should get a gynecological cancer diagnosis within a maximum of 28 days of referral.
Decision to treat to first treatment	For gynecological cancer, once it has been decided to treat a patient (either for their initial cancer treatment or for a recurrence of cancer), the patient should start their first treatment within 31 days.
Subsequent treatment	For gynecological cancers, there should be no more than a 31-day delay between treatments.

Notes: These indicators are for all gynecological cancers. Source (135, 136).

4.1.1 Challenges in health quality metrics

Implementing and adhering to international quality standards

The recent introduction of the ESGO quality indicators for the surgical treatment of endometrial cancer in 2021 marks a significant advancement in setting standardized benchmarks for care (133). However, there are no insights yet on whether and how closely these quality metrics are being used to assess local quality of care in different countries. A validation study of ESGO quality indicators similar to the SUCCOR quality validation study for ESGO cervical cancer care guidelines might increase the credibility of ESGO guidelines and expedite their application in national contexts.

4.2 Detection

Endometrial cancer is typically identified through the patient's recognition of symptoms such as abnormal uterine bleeding; see section 2.3. The early detection of endometrial cancer is thus primarily reliant on symptom awareness and prompt medical evaluation. This means that education and awareness about the symptoms of endometrial cancer together with accessible healthcare services are crucial factors to facilitate earlier diagnosis. Early detection of endometrial cancer significantly enhances the likelihood of successful treatment and survival as well as results in lower treatment costs; see sections 2.6 and 3.2 for further details.

Unlike breast cancer and cervical cancer, where population-based screening programs play a significant role in early detection, endometrial cancer lacks screening initiatives. Screening with currently available methods in women with no symptoms is not appropriate for detecting endometrial cancer (137). Tailored surveillance programs are only recommended for women with Lynch syndrome (around 0.36% of the population in the US; see section 2.2) (28). Women with Lynch syndrome are often advised to have annual or biannual endometrial cancer screening starting at around 35 years (28). This screening might include pelvic examinations, transvaginal ultrasound, and endometrial biopsy.

4.2.1 Self-detection process

Upon experiencing symptoms related to gynecological health, women typically first consult a primary care provider (a GP) and then are referred to a gynecologist or they directly consult a gynecologist depending on the structure of the healthcare system in a country. Abnormal uterine bleeding is the most common symptom triggering a visit to health care for eventual endometrial cancer patients; see section 2.3. Notably, in postmenopausal women, the likelihood of such bleeding being a sign of endometrial cancer is between 5-10%, but only 1.2% in premenopausal women (63, 138). These statistics imply that a significant majority of abnormal bleeding cases are due to causes other than cancer, such as vaginal atrophy, hormone imbalances, structural abnormalities such as polyps and fibroids, infections, side effects of medications, etc. (139, 140).

4.2.2 Challenges for early detection

Absence of effective screening methods

Unlike breast cancer (mammography) or cervical cancer (Pap smear / HPV test), there is not a universally accepted, effective screening tool for endometrial cancer that is suitable for use in the general population. Diagnostic methods such as transvaginal ultrasound and endometrial sampling (later described in section 4.3) while useful, are not considered practical or cost-effective for screening asymptomatic women on a large scale (141). Thus, the current approach focuses on individualized risk assessment. Women with known risk factors (see section 2.2), need to be more aware and vigilant of signs and symptoms.

Unawareness of risk factors

A systematic review exploring disparities in the stage of cancer diagnosis revealed that there was a high level of unawareness in the general population about various risk factors for endometrial cancer (142). For example, public awareness of obesity as a risk factor varied between 21% and 48% across studies, and the recognition that age and menopause are risk factors was noted in a range from 7% to 54%. Studies have highlighted several overlapping vulnerabilities that contribute to delayed endometrial cancer detection in African Americans, including a lack of knowledge about menopause and the menopausal transition (143). A qualitative study in the US, aimed at understanding the reasons behind delayed diagnoses among African American patients, discovered that some women interpreted bleeding as a normal extension of menopause or as an unrelated occurrence, rather than a potential symptom of cancer (144). A study in the UK observed that older women, those with less education, and women from lower socioeconomic backgrounds—especially non-Caucasian women—tended to have lower health literacy levels (145). Groups with low health literacy were less likely to benefit from educational interventions, such as leaflets intended to increase awareness of gynecological cancer symptoms.

De-prioritization of seeking medical advice for symptoms

Studies have shown that the decision to seek medical consultation for symptoms outlined in section 2.3 is heavily influenced by various factors, including socioeconomic and cultural backgrounds (146, 147). For instance, lower income can limit access to healthcare services due to the cost of care, lack of insurance, or high copayments. In the US, a study identified a link between income levels and the likelihood of seeking medical attention for symptoms indicative of a gynecological cancer (148). Education background can affect health literacy, i.e., the ability to understand health information and make informed decisions. Cultural beliefs can shape women's perceptions of the severity of their symptoms and, consequently, influence the urgency with which they seek medical consultation. In a qualitative study in the US, it was reported that within some African American communities, there is often a general silence around the topic of menopausal bleeding, influencing perceptions and responses to potential symptoms (144).

Confusion about interpretation of Pap smear test results

Several studies observed that women often had difficulties in distinguishing between cervical cancer and endometrial cancer. This confusion can result in a scenario where women upon receiving clear Pap smear results from their screening are under the false impression that they are not at risk for endometrial cancer. Pap tests generally do not detect cells from the inside of the uterus (149). When endometrial cells are found in a Pap smear of a postmenopausal

woman, there is a 3-5% chance that it could be associated with endometrial cancer (138). As a result, a Pap smear is not reliably effective in identifying endometrial cancer, although in some instances, endometrial cells may appear in Pap test results (141). Interviewed experts noted that part of the confusion between cervical cancer and uterine/endometrial cancer arises because in many European languages (especially Germanic languages and also some Romance languages), the words for cervical cancer and uterine cancer are very similar.

Stigma around obesity

The stigma related to obesity, which is a recognized risk factor for endometrial cancer (see section 2.2), can affect patients in several ways. A qualitative study conducted in Canada found as a recurring theme that obese women diagnosed with endometrial cancer (with a BMI greater than 40 kg/m^2) often delayed seeking medical care (150). This hesitation was primarily due to fears of being judged or past negative encounters with healthcare professionals (150). Although there is limited research specifically examining the impact of obesity stigma on endometrial cancer, studies have consistently shown that obese women, in general, are less likely to participate in early detection programs such as cancer screening, including screening for cervical cancer (151).

Lack of genetic risk assessment for at-risk women

Women with Lynch syndrome have a lifetime risk of 60% to develop endometrial cancer (152). Testing for Lynch syndrome is recommended for individuals who have a personal or family history suggesting an increased risk of developing Lynch syndrome-associated cancers (colon, endometrial, stomach, etc.). Without proper genetic risk assessment, individuals at high risk of Lynch syndrome may remain unidentified, missing out on the opportunity for early detection and preventative measures. For example, in the US, the Medicare criteria for genetic testing for Lynch syndrome are quite stringent, requiring detailed family and medical histories (153). This requirement can pose a significant barrier for patients.

Barriers to seeking medical care

A study in the US found that African American women's prior negative experiences with reproductive health could contribute to delays in detecting endometrial cancer (144). These experiences often include racist microaggressions and race-based discrimination that ultimately discouraged women from seeking help promptly (144). In the US, there are numerous factors that create barriers to accessing medical care which have not been fully explored in research studies for endometrial cancer patients such as lack of health insurance, reliable transportation, living far from healthcare centers, immigration status, language barriers, etc. (142). Meanwhile, research in the UK identified barriers to seeking medical care, such as making appointments and communicating with healthcare professionals, for women with lower levels of health literacy (145).

Gaps in visibility of nursing practice

Nurses play a crucial role in promoting effective preventive measures against endometrial cancer, such as encouraging healthy lifestyles and breastfeeding (154). They advocate for maintaining a healthy body weight, adopting beneficial diets, and engaging in regular exercise. Despite their vital contributions, the research on nurses' roles in the prevention and early detection of endometrial cancer is sparse. This lack of research underscores the insufficient visibility of nurses' roles in this domain. As a result, the significant impact of nurses in cancer prevention is not adequately recognized or utilized. Enhanced visibility and deeper

investigation into their contributions are essential to fully leverage nurses' expertise in combating endometrial cancer effectively. Nurses are often deeply embedded within their communities and have firsthand knowledge of the specific health challenges, cultural norms, and resources available. This localized knowledge can be valuable in tailoring prevention and screening initiatives to be more culturally and contextually appropriate, thereby increasing their effectiveness.

Long waiting times for medical appointments

The time to get an appointment with a primary care provider and then be referred to a specialist gynecologist or gynecologic oncologist can be lengthy. In England, during 2018, the median timeline for uterine cancer patients from initial referral to first consultation by a specialist was 10 days, slightly higher than the median for ovarian and cervical cancer (7 and 8 days, respectively) (136). The waiting time may even be longer. Figure 30 illustrates that according to OECD statistics, between 25% and 61% of (any kind of) patients experienced a wait time of over one month to consult a specialist physician in 2016 (155). This delay reduces the chances of early detection in the case of cancer.

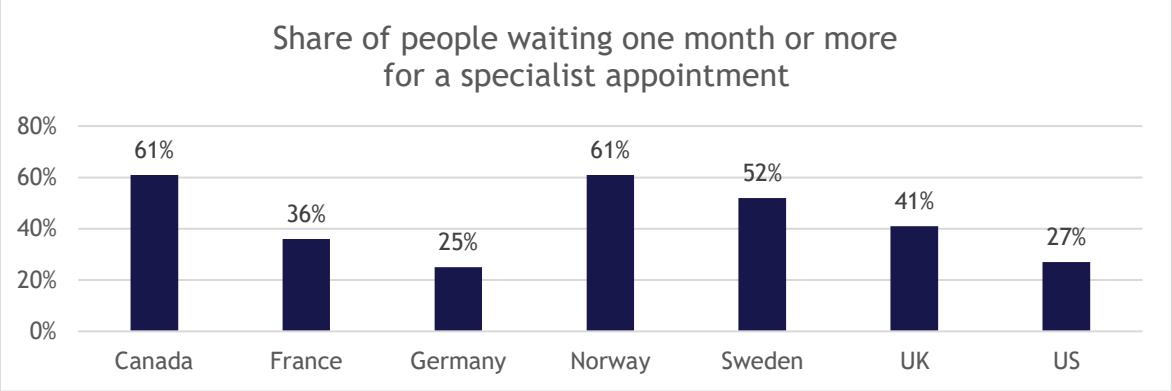

Figure 30: Share of people waiting for one month or more to have a specialist appointment, 2016.

Source: OECD (155).

Delayed referral of younger women

A study in England involving 24,431 women diagnosed with endometrial cancer in 2006–2010 revealed that age significantly influences primary care physicians' decisions to use the fast-track pathway, which ensures women suspected of having endometrial cancer are referred to specialist hospital services within two weeks (156). Women under the age of 55 were significantly less likely to receive prompt referrals compared to their counterparts over 55 when presenting with symptoms. While this trend was also observed for other cancer types (liver, rectal, colon, ovarian, among others), the disparity in referral rates between younger and older women was greater for endometrial cancer. The authors proposed that uterine bleeding, the most common sign of endometrial cancer in postmenopausal women, does not generate the same level of alarm in younger women. This discrepancy may lead primary care physicians to overlook the possibility of cancer in younger women.

4.3 Diagnostic tests

Endometrial cancer is diagnosed through a comprehensive assessment that includes physical examination, imaging tests such as ultrasound and/or MRI, and a biopsy to examine the

endometrial tissue. To further characterize the tumor and guide treatment decisions, additional tests assess relevant biomarkers. With the combined insights from the cancer's stage—determining how far it has spread—and its molecular profile, a tailored therapeutic strategy can be developed. For advanced or recurrent cases, novel treatment options may necessitate further biomarker testing to optimize treatment effectiveness.

4.3.1 Physical examination

The first step at the physician/gynecologist typically involves a detailed review of a woman's medical history and a physical examination, including a pelvic exam. The physician will inquire about symptoms (see section 2.3), risk factors (see section 2.2), coexisting medical conditions, among others. The clinical examination may encompass the following components:

- **Abdominal examination**: The abdomen is checked for any abnormalities such as masses, organ enlargement, or signs of fluid accumulation, which could indicate advanced disease or other gynecologic conditions (138).
- **Speculum examination**: A speculum is used to inspect the vagina and cervix for signs of lesions, polyps, unusual discharge, or other abnormalities (138).
- **Pelvic examination**: This involves a physical assessment of the pelvic area, including the uterus, cervix, ovaries, fallopian tubes, bladder, and rectum (28, 138). The examination focuses on detecting any abnormalities in size, shape, or tenderness that might suggest tumors, cysts, or other pathologies.

4.3.2 Imaging

If the physical examination indicates the presence of a tumor, an imaging test is performed to locate the tumor in the uterus. Endometrial cancer diagnosis and staging involve a series of imaging tests, each serving a distinct purpose in the overall assessment of the disease. Ultrasound is often the first test for women with suspicion of endometrial cancer. International clinical guidelines by ESGO/ESTRO/ESP, ESMO, and the National Comprehensive Cancer Network (NCCN) recommend transvaginal ultrasound, as it provides more detailed images of the pelvic organs than pelvic ultrasound (25, 28, 157). Typically, this procedure is carried out by gynecologists with training in conducting and interpreting ultrasound examinations. The transvaginal ultrasound helps to determine the thickness of the endometrium, which is indicative of the risk of endometrial cancer. A thicker endometrium increases the risk of having endometrial cancer (158, 159).

Table 12: Common imaging tests for endometrial cancer

For diagnosis	
Transvaginal ultrasound	In the initial investigation, a transvaginal ultrasound is a key diagnostic test. In a transvaginal ultrasound, the transducer is inserted into the vagina. This allows for closer proximity to the uterus, fallopian tubes, and ovaries, providing a clearer and more detailed image (160).
Pelvic ultrasound	A pelvic ultrasound is performed by applying a transducer externally to the abdomen (161). This method is less invasive and can be used for a general overview of the pelvic area.
Post-diagnosis	
Magnetic resonance imaging (MRI)	MRI is regarded as the most accurate method for imaging before surgery in the context of endometrial cancer (25). MRI is particularly effective at differentiating between different types of soft tissue structures (25). It can provide detailed images that clearly show the distinction between

	normal tissue, cancerous tissue, and the structures surrounding the uterus.
Computed tomography (CT)	CT is an additional test that is used for assessing the spread of the cancer in the pelvis, abdomen, and chest (28, 157).
Positron emission tomography and CT (PET/CT)	PET/CT diagnostic exams are increasingly valuable in managing endometrial cancer due to their superior reliability in identifying lymph node metastases, distant metastases, and disease recurrence (162).

4.3.3 Endometrial biopsy

An endometrial biopsy is performed if the ultrasound results indicate the presence of a tumor. The procedure is carried out by a gynecologist in a clinic or a healthcare office (163, 164). The two main methods for endometrial sampling are aspiration biopsy and dilation and curettage (D&C) (165). Aspiration biopsies are currently the preferred method as they are simpler, less expensive, and can be performed at a gynecologist's office without the need for anesthesia (165). The procedure entails the insertion of a thin, flexible tube through the cervix into the uterus to collect the tissue sample from the lining of the uterus. A small sample of the endometrium is removed through the tube using suction. The procedure itself takes less than 15 minutes (166). The D&C method requires general anesthesia and is comparatively more invasive and often necessitates a combination with hysteroscopy, a procedure that involves dilating the cervix and inserting a narrow camera for internal examination (167). The D&C method allows to remove a bigger piece of tissue to look for abnormal cells.

The collected tissue is sent to a laboratory where a pathologist performs a histology, an examination of the tissue under a microscope to detect and assess abnormalities such as endometrial cancer cells (166). The report of the pathology results should include the following parameters according to the ESGO/ESTRO/ESP guidelines (28):

- Histological type of the tumor (e.g., endometrioid carcinoma, serous carcinoma, clear cell carcinoma, etc.)
- Size of the tumor (added after surgery)
- Grade of cancer cells (how fast the cancer cells are likely to grow and spread)
- Extent of tumor invasion and metastasis
- Status of specific proteins (e.g., p53, MLH1, MSH2, MSH6, PMS2)
- Provisional staging pre-MDT meeting

4.3.4 Molecular testing

Historically, the classification of endometrial cancer was primarily based on histological types, such as endometrioid, carcinosarcoma, squamous cell carcinoma, among others. Recent advancements have led to a paradigm shift. Current guidelines from ESGO/ESTRO/ESP, ESMO, and NCCN recommend categorizing endometrial cancer across all specimens based on a molecular classification. This approach is crucial for providing detailed prognostic and predictive information (25, 28, 157). The molecular classification system, a relatively new development, was integrated into the ESGO/ESTRO/ESP guidelines in 2021 and into the ESMO guidelines in 2022 (168). According to these guidelines, molecular tests should classify endometrial cancer at diagnosis into four groups: 1) POLE-ultra mutated, 2) dMMR, 3) p53 aberrant, and 4) no specific molecular subtype (see section 2.1 for more details).

Some molecular characteristics, such as mismatch repair deficiency (dMMR), high microsatellite instability (MSI-H), and high tumor mutational burden (TMB-H), are already crucial in guiding treatment decisions in advanced stages of the disease, as detailed in section 4.4. Meanwhile, other molecular features are anticipated to lay the groundwork for the development of more targeted therapies in the future. The NCCN guidelines recommend molecular testing, noting that the availability of testing capabilities (infrastructure and medical personnel) can influence this decision (169). These guidelines emphasize the importance of identifying women with dMMR, due to its clinical implications (169).

Table 13: Tests for molecular diagnostics

Tests
Immunohistochemistry (IHC) staining: This is a technique used to identify specific proteins in cancer cells. It helps in understanding the type and behavior of cancer. It can detect a protein called p53, that when abnormal can indicate a more aggressive cancer (25). It also helps to detect defects of mismatch repair proteins (MLH1, MSH2, MSH6, PMS2) in tumor tissue - if any of these four proteins is missing, it suggests that the tumor has dMMR.
Polymerase chain reaction (PCR): Another testing method for MSI-H/dMMR status involves PCR amplification of specific microsatellite regions followed by analysis of the length of these DNA segments. Variations in the length of microsatellite sequences between tumor DNA and normal DNA indicate MSI (170).
Next-generation sequencing (NGS) testing: This technology allows for the sequencing of a large portion of the tumor's genome. NGS can be targeted (focusing on specific areas known to have mutations) or more comprehensive (whole-exome sequencing, which covers all coding regions of genes). ESMO clinical guidelines recommend targeted tumor sequencing for a detailed genetic analysis focusing on specific areas (hotspots) of the POLE gene (25). More comprehensive genomic profiling tests, such as FoundationOne CDx, can be used to detect TMB-H status (171).

Info box 1.
What is Microsatellite Instability High/Deficient Mismatch Repair system (MSI-H/dMMR)?

When cells divide, they copy their DNA, so each new cell has the same genetic information. Sometimes, mistakes happen during this copying process. A common mistake is putting the wrong building block (nucleotide or base) into the DNA. Usually, cells have a system to find and fix these mistakes, known as the mismatch repair mechanism, or MMR.

- **dMMR: I**t refers to the loss of function in mismatch repair proteins, leading to errors during DNA replication.

Having mismatch repair deficiency (dMMR) is closely related to but not exactly the same as having microsatellite instability-high (MSI-H).

- **MSI-H:** In the case of a tumor that is MSI-H, the DNA in the cancer cells has many mutations within DNA's microsatellites.

On the contrary, when the mismatch repair mechanism works correctly, the following terms are used:

- **MSS (Microsatellite stable):** This term refers to tumors in which the DNA's microsatellites - short, repeated sequences of DNA - are stable. In MSS tumors, the usual DNA repair mechanisms are functioning properly, preventing the accumulation of errors in these microsatellite regions.
- **pMMR (proficient Mismatch Repair):** pMMR indicates that the tumor cells have a functioning mismatch repair system.

Source: (172, 173).

4.3.5 Staging

Endometrial cancer is staged using two primary systems: the FIGO (International Federation of Gynecology and Obstetrics) staging system and the AJCC (American Joint Committee on Cancer) TNM (Tumor, Nodes, Metastasis) staging system. Both systems categorize endometrial cancer based on the tumor's extent, lymph node involvement, and distant metastasis. The AJCC's latest staging guidelines went into effect in 2018 (68). The FIGO system, revised in 2023, incorporates modern insights into tumor's histological and molecular characteristics, aiming to refine treatment strategies and improve outcome data collection (174). It introduces significant improvements in granularity and prognostic accuracy over the previous FIGO 2009 version (175); see also Table A2 in the Appendix for a comparison of disease stages. A study comparing the 2023 and 2009 staging systems showed that the newer system offers a more accurate prediction of patient outcomes, evidenced by substantial shifts in staging observed in many patients, with 27.6% experiencing changes in their cancer stage (176). The study's statistical analyses verified that the 2023 FIGO staging system provides more precise predictions of progression-free survival and OS based on stage (176).

However, while the FIGO 2023 system enables more precise risk stratification and potentially greater personalization of treatment, its implementation introduces greater complexity, increasing the number of subcategories. This complexity and the use of subjective histopathologic variables (e.g., quantification of lymphovascular space invasion) may lead to significant interobserver variability, potentially impacting patient care due to differing treatment recommendations based on staging differences. These challenges could hinder universal adoption of the new system, especially in resource-poor settings where the gap in care might be further widened.

Table 14: FIGO 2023 staging system of endometrial cancer

Stage	Description
Stage I	Confined to the uterine corpus and ovary
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 local lymphovascular space involvement (LVSI) or good prognosis disease
$IAm_{POLEmut}$	POLEmut endometrial carcinoma, confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histological type
IB	Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSI
IC	Aggressive histological types 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 of non-aggressive histological types
IIC	Aggressive histological types with any myometrial involvement
$IICm_{p53abn}$	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
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
IIIB	Metastasis or direct spread to the vagina and/or to the parametria or pelvic peritoneum
IIIC	Metastasis to the pelvic or para-aortic lymph nodes or both

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

Notes: Please refer to Table A2 in the Appendix for a comparison of the FIGO 2023 and 2009 staging systems. Source: (174).

4.3.6 Challenges for diagnosis

Low accuracy of diagnostic tests

Different methods for measuring endometrial thickness with ultrasound show varied sensitivity and specificity, indicating a lack of accuracy in these tests. This variability affects the ability to precisely identify individuals with or without the disease. As a result, about half of the women who undergo ultrasound for abnormal uterine bleeding find themselves in need of further invasive testing to obtain a definitive diagnosis (63). The challenge highlights the critical need for more accurate and less variable diagnostic tools in the initial examination for endometrial abnormalities.

Need for invasive testing

Following inconclusive transvaginal ultrasound results, endometrial biopsy is a common follow-up test despite being uncomfortable and having a significant risk of false-negative results (where the test erroneously indicates the absence of cancer) (177, 178). Additionally, when combined with hysteroscopy (allowing the physician to visually inspect the inside of the uterus with a camara) this approach allows for targeted examination but introduces potential complications like pain, infection, bleeding, and vasovagal episodes (178). This challenge could potentially be mitigated by the development of new, minimally invasive tests that are under investigation. This includes tests that examine changes in DNA methylation (alterations in DNA that can affect how genes function) in samples collected from around the cervix and vagina, using methods for sample collection like tampons or cervical swabs (63). Early trials of these novel tests have shown promising results in comparison to traditional transvaginal ultrasound in clinical trials and could reduce the need for further invasive procedures in many women in the future (63). However, these findings are based on a limited number of cases and still require larger, confirmatory trials.

Guidelines based on non-representative populations

Current guidelines and endometrial thickness thresholds for diagnosing endometrial cancer are based on study populations that may not accurately represent the genetic, environmental, and health characteristics of all ethnic groups, particularly African American women. This discrepancy could render the guidelines less effective for these groups (179). Additionally, these studies often exclude women with uterine fibroids because fibroids can alter endometrial thickness measurements, complicating the diagnosis (179). Given that up to 80% of African American women may develop fibroids (180), this exclusion likely affects a significant portion of this population, indirectly omitting them from the data used to set these diagnostic standards. A simulation study involving a cohort of African American women applied the standard endometrial thickness threshold of 4mm to prompt a diagnostic biopsy (179). The results indicated that this threshold failed to detect over half of the cases in this cohort, with

the rate of false negatives being eight times higher than that observed in the general population.

Limited availability of gynecologists

A shortage of gynecologists can result in extended wait times for appointments, leading to delays in diagnosis. OECD data from 2021 indicates that the average number of gynecologists and obstetricians was 17 per 100,000 population; see Figure 31. Countries like Canada, Ireland, the Netherlands, France, UK, US, among others, are well below the average. In the US, for example, there have been projections of a minimal or modest shortage of obstetricians-gynecologists that is expected to worsen over time (181). The main factors contributing to shortages are a growing female population (that naturally increases the demand for reproductive health and maternity care services) combined with a limited growth in the number of residency graduates (181). An additional issue in the US is that obstetrician-gynecologists tend to retire at an earlier age compared to other specialists (182). The median retirement age was 64 years in 2013, with female gynecologists retiring on average 5 years earlier than male colleagues (182).

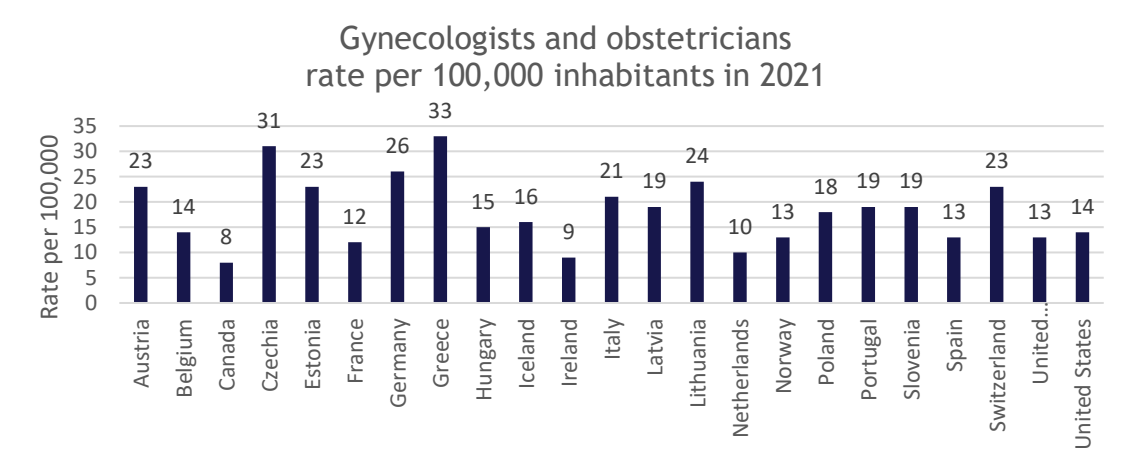

Figure 31: Number of gynecologists and obstetricians per 100,000 inhabitants in 2021.

Source: OECD (183).

Resource-dependent molecular profiling

Testing for immunohistochemical markers (p53, dMMR) and mutations of POLE depends on the availability of resources (capabilities of diagnostic laboratories and medical professionals) and the decision by the MDT of each treatment center (28). Molecular profiling is mostly recommended for settings where the classification is able to help make treatment decisions, i.e., predictive testing mostly for high-grade and advanced-stage patients (25).

Ethnic disparities in genomic testing access

Research from the US has highlighted concerns regarding the potential exacerbation of disparities in health outcomes among different ethnic/racial groups (77). This issue arises particularly if access to modern genomic testing (such as NGS) is not uniformly available across ethnic demographics due to differences in health insurance coverage. Such a scenario could result in women from certain vulnerable groups not receiving the most appropriate and effective therapy tailored to their specific cancer type.

4.4 Treatment

The recommended treatment of endometrial cancer differs by disease stage and tumor characteristics. In general, endometrial cancer patients may be treated with surgery, radiation therapy, systemic therapy (i.e., cancer medicines), or a combination of these treatment modalities; see Table 15. According to ESGO's quality indicators, the treatment requires a centralized approach, meaning it should ideally be coordinated from a single, specialized center (133). The treatment decision should be made by an MDT composed of at least a gynecologic oncologist (or trained surgeon dedicated to gynecological cancer), a radiologist, a radiation oncologist, a medical oncologist, and a pathologist (133).

Table 15: Treatment modalities in endometrial cancer

Surgery	**Hysterectomy:** This is the standard surgery for endometrial cancer. It involves the removal of the uterus and cervix (184). Historically, the uterus was removed either through a large abdominal incision or via the vagina. Nowadays, the preferred approach is through minimally invasive surgery, known as laparoscopic hysterectomy, which involves removing the uterus through small incisions made in the abdomen. **Bilateral salpingo-oophorectomy:** This surgery involves the removal of both ovaries and fallopian tubes (184). It is usually performed alongside a hysterectomy. However, it may be omitted under special circumstances to preserve hormonal function, particularly in premenopausal patients (25). Lymph node staging is an essential component of surgery, as it helps assess the extent of disease spread. This can be performed through sentinel lymph node biopsy, which involves removing and examining the first lymph node (or group) likely affected by cancer (185). Alternatively, a systematic lymphadenectomy may be performed, involving the removal of multiple lymph nodes to provide a comprehensive assessment of any spread, although it carries greater risk of complications (185).
Radiation therapy	Radiation therapy is a form of cancer treatment that uses high-energy rays or particles to eradicate cancer cells. In the treatment of endometrial cancer, it is often administered post-surgery to eliminate any residual cancer cells (186). In certain cases, radiation therapy can serve as the primary treatment, offering an alternative to surgery. Additionally, in very rare instances, it may be administered before surgery to shrink the tumor. There are two main types of radiation therapy: • **Internal radiation therapy (brachytherapy):** This involves placing a small device with radioactive material inside the vagina, allowing for direct radiation to the targeted area (186). • **External radiation (external beam radiation therapy)**: This method delivers radiation from outside the body, precisely targeting the affected area in a controlled manner (186).
Systemic therapy (cancer medicines)	There are four types of systemic therapy used in the treatment of endometrial cancer: • **Chemotherapy** employs potent chemicals to target and eliminate rapidly dividing cells in the body, a characteristic commonly found in tumors. While effective in attacking cancerous cells, chemotherapy can also inadvertently affect healthy cells that grow quickly. Chemotherapy is not a standard treatment in low-risk early stages of endometrial cancer (187). However, it is frequently used in high-risk types of early-stage disease and in advanced stages, where the benefits of targeting aggressive cancer cells outweigh the potential harm to normal, fast-growing cells.

- **Hormonal therapy** (also called endocrine therapy) can be an effective strategy in certain cases of endometrial cancer, because the cancer is often sensitive to hormonal changes in the body (188). This treatment modality revolves around manipulating levels of hormones, such as estrogen and progesterone, which can influence the growth of endometrial cancer cells. Hormonal therapy is used in selected patients with low-risk cases (less aggressive, typically growing more slowly) (28). Additionally, hormonal therapy can be used as a fertility-sparing option, as detailed in Info Box 2.
- **Immunotherapy** refers to the use of immune checkpoint inhibitors. To initiate an immune response against malignant cells, the immune system must be able to distinguish between cancer and healthy cells (189). Checkpoint inhibitors are proteins that cover cells and assist the body in differentiating between normal and malignant cells. Cancer cells are capable of "fooling" checkpoint proteins and use them as shields to avoid an immune response against them. Checkpoint inhibitors block these proteins, resulting in a better immune response to attack cancer cells. In the case of endometrial cancer-approved treatments, the checkpoint protein that gets "blocked" is the protein PD-1.
- **Targeted therapy** in endometrial cancer refers to the use of anti-angiogenic tyrosine kinase inhibitors (TKIs) and antibody-drug conjugates (ADCs). Anti-angiogenic TKIs prevent tumors from forming new blood vessels (angiogenesis) (190), a process crucial for tumor growth because blood vessels supply the tumor with oxygen and nutrients. By blocking angiogenesis, TKIs can starve the tumor of these necessary resources. ADCs targeting the HER2 protein on tumor cells may be used in endometrial cancers that express the HER2 protein at high levels[4] (192). ADCs combine the properties of targeted therapy that blocks tumor growth signals and chemotherapy.

4.4.1 Endometrial cancer in early stages

In the early stages of endometrial cancer, surgery is the gold standard for primary treatment (193); see Figure 32. During surgery, the uterus is removed usually along with the fallopian tubes and ovaries, a procedure known as hysterectomy with bilateral salpingo-oophorectomy. Since the ovaries produce hormones (estrogen) that promote the growth of endometrial cancer, and because they themselves can be affected, they are removed. Lymph nodes are also removed to understand the spread of the disease.

The medical community has yet to reach a consensus on the most effective additional treatments post-surgery (adjuvant), as the most appropriate approach can vary significantly depending on the specifics of each case (194). After surgery, some higher-risk patients may receive radiation therapy to eliminate any remaining cancer cells and reduce the risk of recurrence (186). Radiation therapy is initiated 4 to 6 weeks after surgery. Most often brachytherapy is given 3-6 times in weekly intervals. Another post-surgery treatment option is chemotherapy. While less common in the early stages, chemotherapy may be used in certain situations, such as if the cancer is more aggressive or there are certain unfavorable histologic subtypes (for a detailed description of risks and stages see Table A1 in the Appendix).

[4] Estimates of the prevalence of HER2 in endometrial cancer vary widely. A study reported HER2 overexpression in approximately 4% to 69% of cases and HER2 gene amplification in 18% to 80% of cases (191). HER2 positivity also varies according to histopathological subtypes; serous and clear cell carcinomas, in particular, show a higher prevalence of HER2 presence (191).

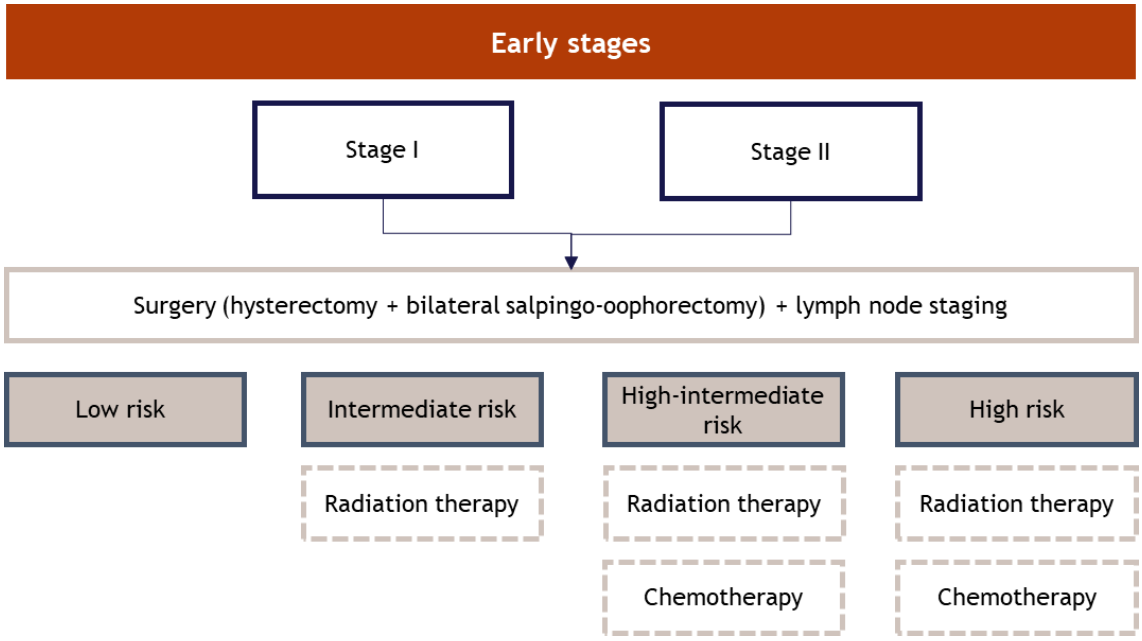

Figure 32: Treatment algorithm for early stages of endometrial cancer in 2022.

Notes and source: The algorithm is an adaptation of the 2022 ESMO guidelines (25). The use of dashed lines in the algorithm indicates that the choice of therapy should be tailored to individual patient factors. The risk classification is determined based on a combination of factors that include histological type (type and origin site), grade of the cancer (how much the cells look like normal or abnormal cells), stage (size and spread), invasion to lymphatic or blood vessels, and molecular characteristics (four groups described in section 2.1). A detailed description of each risk group by stage is provided in Table A1 in the Appendix.

Advances in adjuvant (post-surgery) treatment

No immunotherapies or targeted therapies for the adjuvant treatment of endometrial cancer have been approved by the European Medicines Agency (EMA) in Europe or the Food and Drug Administration (FDA) in the United States as of June 2024. However, several clinical trials are currently being conducted to evaluate the efficacy of newer treatment options. One example is the use of adjuvant immunotherapy in combination with either chemotherapy or chemoradiotherapy in patients with newly diagnosed, high-risk early endometrial cancer (195, 196). However, a recent phase III trial of adjuvant immunotherapy failed to demonstrate a statistically significant improvement in disease-free survival (197).

Info box 2.
Fertility-sparing treatment in early-stage endometrial cancer patients

For early-stage endometrial cancer, the typical course of treatment involves a hysterectomy. This surgical procedure, which entails the removal of the uterus, can present a significant concern for women of childbearing age, as it permanently eliminates the possibility of pregnancy.

The importance of fertility sparing for many women has been recognized in clinical guidelines. In 2023, ESGO/ESHRE/ESGE published guidelines that specifically address fertility-sparing treatment for women with endometrial cancer (198). These guidelines highlight that for young women seeking to maintain fertility, hysteroscopic tumor resection followed by continuous progestin-based therapy is the preferred approach. This therapy can be administered via intrauterine devices (IUDs) or oral medication. The primary objective of this therapy is to manage and potentially reverse the abnormal growth associated with both endometrial hyperplasia and early-stage endometrial cancer. This method provides an opportunity to preserve the uterus and the patient's fertility, offering hope for future pregnancy.

Notes: ESHRE = European Society of Human Reproduction and Embryology, ESGE = European Society for Gynecological Endoscopy.

4.4.2 Endometrial cancer in advanced stages

For newly diagnosed metastatic cases of endometrial cancer and recurrent cases from earlier stages, the primary line of treatment typically involves chemotherapy. However, treatment options can differ based on individual patient characteristics.

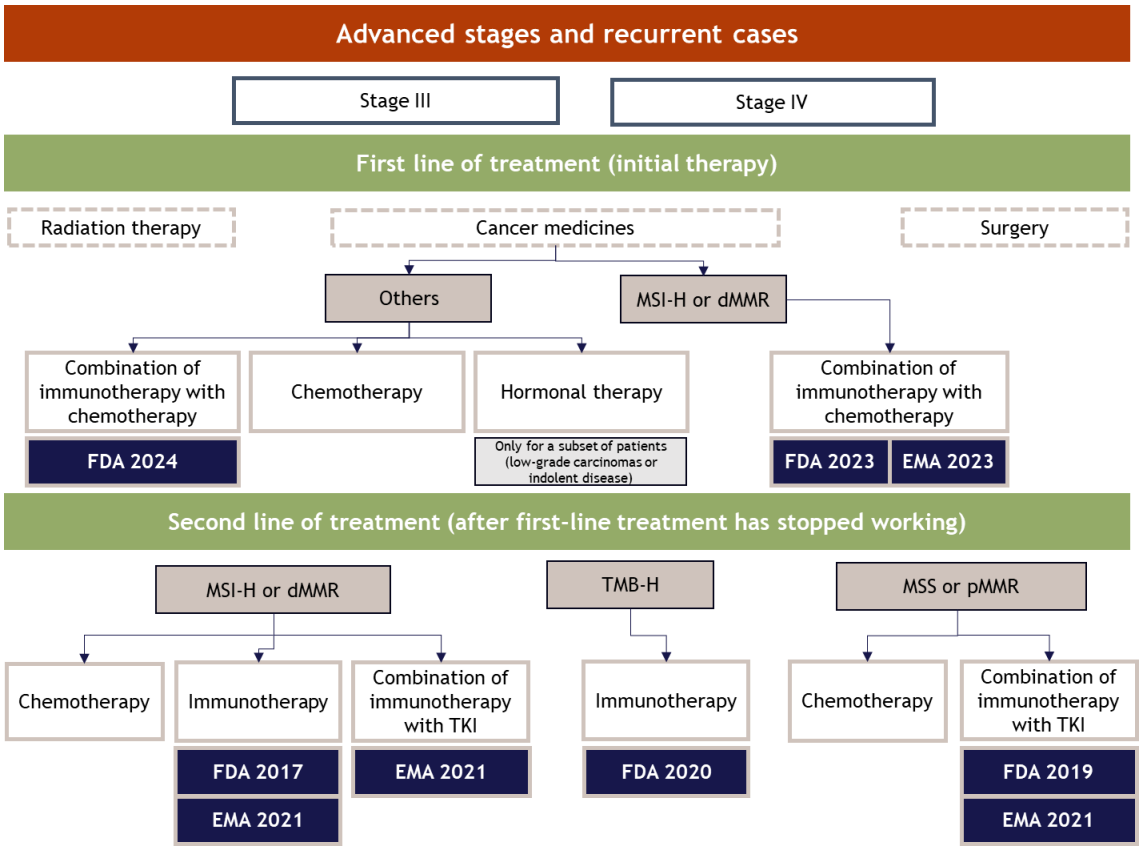

Figure 33: Treatment algorithm for advanced stages and recurrent cases of endometrial cancer in mid-2024.

Notes: The algorithm is based on the most recent recommendations from the 2022 ESMO and the 2024 NCCN guidelines. The use of dashed lines in the treatment algorithm indicates that the choice of therapy should be tailored to individual patient factors. These factors include the patient's overall health, the stage and spread of the disease, previous treatments received, and specific molecular characteristics of the tumor. For NTRK-positive solid tumors, the NCCN also recommends larotrectinib and entrectinib for patients who have no satisfactory alternative treatments or whose cancer has progressed following treatment, based on FDA approvals in 2018 and 2019, respectively (201, 202). An additional NTRK-targeted therapy, repotrectinib, was approved by the FDA in 2024 (203). Molecular terms are defined as follows: MSI-H = Microsatellite Instability-High; dMMR = Deficient Mismatch Repair; MSS = Microsatellite Stable; pMMR = Proficient Mismatch Repair; TMB-H = Tumor Mutational Burden-High. TKI = tyrosine kinase inhibitor. Note that hormonal therapy is only used for selected patients for newly diagnosed advanced frail patients or for very indolent disease as described in Table 15 or for recurrent disease. Source: FDA approvals (171, 199, 200, 204-206) and ESMO/NCCN guidelines (25, 157).

According to ESMO guidelines, the primary treatment for patients experiencing locoregional recurrence — defined as the resurgence of cancer in its original site or in nearby regional structures such as lymph nodes, the vagina, or pelvic tissues, after an initial remission — generally entails radiation therapy (25). Additionally, surgery may be considered in certain cases of locoregional recurrence where all visible disease can be surgically excised.

For newly diagnosed advanced cases and cases with distant recurrence, the main treatment option is chemotherapy (usually in the form of platinum-based agents in combination with taxanes, most often carboplatin plus paclitaxel) (187); see Figure 33. Hormonal therapy, mainly progestins such as megestrol acetate and medroxyprogesterone acetate, may be used in certain cases (188). NCCN guidelines also recommend certain non-FDA approved hormonal therapies such as the combinations of everolimus/letrozole and the combinations of abemaciclib/letrozole and ribociclib/letrozole for estrogen-receptor positive tumors (157). A new treatment option at this stage is the combination of immunotherapy with chemotherapy for patients with MSI-H or dMMR (since 2023) and for patients regardless of MMR status (since 2024) (199, 200).

When first-line therapies cease to be effective, indicated by the continued spread of cancer (disease progression), patients can continue on various second-line treatments. Significant progress in personalized therapy has been made in the realm of second-line treatment for endometrial cancer. Second-line therapies are nowadays tailored to distinct molecular characteristics of the tumor, such as MSI-H/dMMR and TMB-H; see Figure 33.

Advances in first-line treatment

In 2023, the combination of the immunotherapy agent dostarlimab with chemotherapy (carboplatin and paclitaxel) was approved by the FDA for use in the US and by the EMA for use in Europe [approval based on the RUBY trial] (199, 207). This combination is approved as initial therapy for patients with primary advanced or recurrent dMMR/MSI-H endometrial cancer. Patients are treated with six cycles of the combination every three weeks followed by dostarlimab as monotherapy every six weeks for up to three years. The 2024 NCCN guidelines have already incorporated this combination as a recommended first-line systemic therapy (157), whereas the latest versions of the ESMO guidelines from 2022, and ESGO/ESTRO/ESP guidelines from 2021 do not yet included it. In 2024, the FDA approved another immunotherapy agent, durvalumab, together with chemotherapy (carboplatin plus paclitaxel) in a similar indication for primary advanced or recurrent endometrial cancer that is dMMR based on the DUO-E trial (208). Also in 2024, the FDA approved the combination of the immunotherapy agent pembrolizumab with chemotherapy (carboplatin and paclitaxel) as a first-line treatment for advanced or recurrent endometrial cancer regardless of MMR status (i.e., dMMR and pMMR), based on the KEYNOTE-868/NRG-GY018 trial (200).

Advances in second-line treatment

There has been a notable development in treatment options for settings where first-line therapies (chemotherapy) have ceased stopping the growth of cancer. Second-line therapies now include immunotherapies and targeted treatments (tyrosine kinase inhibitors), specifically designed to target tumors with distinct molecular characteristics, as outlined below in three groups. These advancements are reflected in the updated 2024 NCCN, 2022 ESMO, and 2021 ESGO/ESTRO/ESP guidelines.

Advances for MSI-H/dMMR

The first landmark development was the FDA's accelerated approval in 2017 of the immunotherapy agent pembrolizumab for the treatment of advanced dMMR or MSI-H solid tumors without any satisfactory alternative treatment options after prior treatment (206). It was the first time a tumor-agnostic treatment was approved based on a tumor’s molecular characteristics rather than the site of the body where the tumor started. The decision was based on the treatment's efficacy across various solid tumors, including endometrial cancer, as

evidenced in the KEYNOTE-158 trial (25). In 2021, dostarlimab, another immunotherapy, received approval from both the FDA and the EMA for use as a monotherapy in treating patients with dMMR (FDA) or dMMR/MSI-H (EMA) recurrent or advanced endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen [approval based on the GARNET trial] (25). In 2022, both the FDA and the EMA approved pembrolizumab as a monotherapy for dMMR/MSI-H advanced or recurrent endometrial cancer cases that have disease progression on or following prior treatment with a platinum-containing regimen in any setting and that are not candidates for curative surgery or radiation [approval based on the KEYNOTE-158 trial] (209, 210). In 2021, the EMA approved the combination of the immunotherapy agent pembrolizumab with the TKI lenvatinib using a more general indication text that does not explicitly mention MSI-H or dMMR status [approval based on the KEYNOTE-775 trial] (211).

Advances for TMB-H

In 2020, the FDA approved pembrolizumab as a monotherapy for the treatment of unresectable or metastatic solid tumors (including endometrial cancer) that have a high tumor mutational burden (TMB-H), specifically ≥10 mutations per megabase (mut/Mb) of DNA, and that have progressed following prior treatment and who have no satisfactory alternative treatment options [approval based on the KEYNOTE-158 trial] (171). A high mutational burden can sometimes make the cancer more visible to the immune system, potentially making immunotherapy a more effective treatment option (212). TMB-H can be a result of MSI-H or dMMR, as well as due to exposure to carcinogens (212). The EMA has not approved this indication as of June 2024.

Advances for MSS/pMMR

In 2019, the FDA approved the combination of the immunotherapy agent pembrolizumab with the TKI lenvatinib for the treatment of advanced or recurrent endometrial cancer cases that are not MSI-H or dMMR and that have disease progression following prior systemic therapy and that are not candidates for curative surgery or radiation [approval based on the KEYNOTE-146 trial] (213). As stated above, the EMA approved this combination in 2021 using a general indication text that does not explicitly mention MSI-H or dMMR status [approval based on the KEYNOTE-775 trial] (211).

Advances in last-line treatment

In 2024, the FDA granted approval to the ADC agent trastuzumab deruxtecan for the treatment of patients with unresectable or metastatic HER2-positive (defined as IHC 3+ by gastric scoring criteria) solid tumors who have previously undergone systemic therapy and lack satisfactory alternative treatment options (214). This approval also applies to endometrial cancer cases and is based on the results from the DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02 trials.

4.4.3 Challenges for treatment

Socioeconomic disparities in medical treatment

A study utilizing data from the SEER database in the US, spanning from 2006 to 2015 with a sample size of 83,883 women, revealed that certain ethnic/racial groups and individuals from lower socioeconomic status groups were more likely to receive substandard care (215). Specifically, African American, and Hispanic women were found to have lower odds of receiving

endometrial cancer treatments that adhere to NCCN guidelines compared to Caucasian women. Additionally, the study indicated that women residing in neighborhoods with lower socioeconomic status were less likely to receive treatment in accordance with NCCN guidelines than those from higher-status neighborhoods. Parallel findings from other research indicated that African American, Hispanic, and Native American women were less likely to undergo minimally invasive hysterectomies in 2012 (216). Another study conducted in the US, analyzing data from 2011 to 2022 with a focus on cancer disparities related to socioeconomic status, found that the most significant treatment inequities were observed among patients with advanced endometrial cancer (217). The research revealed that patients from low socioeconomic neighborhoods initiated treatment on average 91 days after diagnosis, in contrast to 76 days for patients from the highest socioeconomic neighborhoods (217). Research from the US has cautioned that even though immunotherapies are a significant advancement in the treatment of endometrial cancer, these benefits might not be experienced equally by all ethnic/racial groups (77). If the medicines are not equally available to all groups due to factors like cost, insurance coverage, or geographic location, then the existing ethnic/racial disparities in cancer outcomes could worsen.

Underrepresentation of ethnic minority groups in clinical trials

A significant challenge in the treatment of endometrial cancer, as well as other gynecological cancers, is the underrepresentation of certain racial and ethnic groups in clinical trials. A systematic review revealed that Caucasian patients accounted for 73% of participants in endometrial cancer clinical trials (218). Moreover, representation was notably inadequate for East Asian and African descent women in gynecological cancer clinical trials (218). In the US, a retrospective cohort study utilizing data from the National Cancer Database revealed marked disparities in clinical trial enrollment (219). Analyzing data from over half a million women diagnosed with endometrial, ovarian, or cervical cancer between 2004 and 2019, the study found that Asian American, African American, and Hispanic women were less likely to be enrolled in clinical trials compared to their Caucasian counterparts. Specifically, in endometrial cancer clinical trials, while Caucasian and African American women were found to be adequately or overrepresented, Asian American and Hispanic women's participation did not proportionally reflect their prevalence in the overall US population.

Lack of gynecologic oncologists

Although the sub-specialization of gynecologic oncology[5] has been increasing in high-income countries, it is still common that general gynecologists treat gynecological cancers (220). Gynecologic oncologists have an important and distinct role as they have been found to be an important prognostic independent factor that leads to higher overall survival rates (220). For instance, there has been evidence that surgeries performed by gynecologic oncologists are associated with better survival outcomes for high-risk patients, as compared to surgeries done by other types of surgeons (221). In addition, patients treated by them were more likely to receive adjuvant therapies in advanced stages (221).

[5] In certain countries, formal certification for gynecologic oncologists may not be available (133). Despite this, international standards acknowledge that surgeons who have dedicated at least 80% of their practice to working with gynecological cancers, or those possessing an ESGO accreditation, are considered sufficiently experienced to be recognized as gynecologic oncologists (133).

Disparities in access to gynecologic oncologists

In 2020, the US had 1,178 gynecologic oncologists, a figure that is on the rise (222). However, 98% of these specialists were based in urban areas, resulting in a distribution of 1.09 physicians per 100,000 women in urban settings, compared to a sparse 0.1 physicians per 100,000 in rural areas (222). Additionally, access to these specialists was significantly lower for certain ethnic minorities. For example, 24% of Native American women and 9.5% of Hispanic women lacked adequate access to a gynecologic oncologist, as they lived more than 100 miles (160 km) away from the nearest one.

Nurse shortages and insufficient details on their role in broader cancer care

Nursing services play a crucial role in enhancing patient satisfaction and improving health outcomes for both noncommunicable diseases, such as cancer, and communicable diseases (223). Nurses significantly influence patient outcomes through their critical decision-making during direct patient care. Despite their importance, there is a global shortage of nurses, which adversely affects the capacity of health systems to provide effective services (223). To address this, existing nurses need comprehensive support, including adequate education and training, along with sustained workplace support. This support is essential for maintaining and enhancing their skills, and for managing the demands of their roles effectively. For example, the State of the World's Nursing 2020 report by the WHO underscores the role of nurses in cervical cancer prevention and cervical cancer screening (223). However, there is a lack of details about cancer care more broadly which could limit effective planning and implementation of nursing roles in oncology.

Insurance coverage disparities

In the US, insured individuals with Medicaid are less likely to receive comprehensive care for gynecological cancer. Notably, about 40% of Medicare Advantage plans do not include a gynecologic oncologist in their network of approved healthcare providers (224). This absence means that patients covered by these plans may lack direct access to a specialist in gynecologic cancer care, which could lead to higher out-of-pocket costs if they seek treatment outside their network or difficulties in accessing specialized care. Additionally, women diagnosed with gynecological cancer who are on Medicaid are 25% less likely to receive treatments that adhere to established guidelines (224).

Delayed and restricted reimbursement of new cancer treatments

The approval of new cancer medicines by regulatory bodies, such as the FDA in the US and the EMA in Europe, represents just the first step in ensuring patient access. In healthcare systems that are publicly funded, a decisive step for patient access is the reimbursement of these new medicines by public payers. The timeline from regulatory approval to reimbursement for new cancer medicines varies significantly across Europe. In countries like Germany and Denmark, the process takes fewer than 150 days, whereas in Estonia and Romania, it can extend to nearly 1000 days (225). Moreover, in many Western European countries, only about 50-80% of new cancer medicines receive full reimbursement in the initial years after being approved by the EMA. This figure drops to approximately 20-50% in Eastern European countries (225).

Slow adoption of newly reimbursed cancer treatment

The reimbursement of new cancer medicines in public healthcare systems does not automatically ensure access for all clinically eligible patients (125). Several factors can lead to the delayed adoption of these new medicines in clinical practice. These include diverse budget control strategies at national, regional, or hospital level, the absence of or inadequate use of essential biomarker testing (due to restrictions in human resources, infrastructure, reimbursement of the tests), outdated local clinical guidelines, and insufficient training of medical staff in the application of new treatments.

5. Policy initiatives and recommendations

This chapter sheds light on global health initiatives for endometrial cancer. There is a clear gap in prioritization compared to other women's cancers, specifically breast and cervical cancer. In order to fill this gap, this chapter provides a comprehensive list of recommendations. These recommendations can serve as a basis to set future priorities for improvements in endometrial cancer care and the mitigation of the societal impact of the disease.

5.1 Policy initiatives and research

The WHO prioritizes women's cancers in its global health initiatives, with a particular focus on breast cancer and cervical cancer. The Global Breast Cancer Initiative is dedicated to reducing the age-standardized mortality rate by 2.5% annually until 2040 (6). In parallel, the Cervical Cancer Elimination Initiative sets forth KPIs related to vaccination, screening, and treatment, with targets to be achieved by 2030 towards the goal of eradicating cervical cancer (7).

At the time of writing this report, there are no global initiatives for endometrial cancer paralleled to the scale and focus of the WHO's initiatives for breast and cervical cancer. However, some international and national organizations have embarked to put endometrial cancer on the map; see Table 16 for an overview. On the global level, this includes "Uterine Cancer Awareness Month" in the month of June (226), which was initiated by the International Gynecologic Cancer Society (IGCS) and its patient advocacy arm, the International Gynecologic Cancer Advocacy Network in 2023 and inspired by similar strategies for breast cancer (month of October) and cervical cancer (month of January). The "World Gynecologic Oncology Day (World GO Day)" on September 20, observed every year since 2019, was initiated by ENGAGe, the patient arm of ESGO.

For the 2024 Uterine Cancer Awareness Month, the IGCS issued a global call to action to address disparities in uterine cancer care jointly by all stakeholders (from healthcare providers and employers to governments to patients and their families) (227). The five central themes of the call to action were:

- Raise public awareness
- Overcome barriers to diagnosis
- Improve access to treatment
- Support survivors
- Increase diversity in clinical research

A large-scale international initiative for endometrial cancer could follow in the footsteps of the WHO's Global Breast Cancer Initiative. It could be centered around a handful of key strategies to achieve the objectives of reducing incidence and improving survival. This could include a focus on (i) health promotion with an emphasis on overweight/obesity, (ii) timely diagnosis, (iii) and comprehensive management. The ESGO quality indicators for the surgical treatment of endometrial cancer from 2021 (see section 4.1) could serve as a reference for such a global initiative. While an international initiative currently seems out of reach, a first step for individual countries could be to review the possibility of including the ESGO quality indicators as quality metrics in endometrial cancer care in their respective health systems.

Table 16: Policy initiatives for endometrial cancer

Description	Objective	Country or region	Source
Uterine Cancer Awareness Month (UCAM) • In 2023, the International Gynecologic Cancer Advocacy Network along with support from patient advocacy organizations worldwide initiated a global effort to raise awareness by declaring June as Uterine Cancer Awareness Month. • In this month there are activities aiming to increase knowledge about the risks of uterine cancer and encourage research.	Increase awareness	Global	(226)
World Gynecologic Oncology Day • Since 2019, the World Gynecologic Oncology Day or "World GO Day" is observed on September 20, being organized by ENGAGe, the patient arm of ESGO. • It is an annual event dedicated to raising awareness about gynecological cancers (ovarian, uterine, cervical, vulvar, and vaginal cancer). It emphasizes the importance of education, awareness, and advocacy, encouraging participation from members, healthcare professionals, policymakers, affected women, and the general public. The day serves as a platform to reinforce findings, share new insights, and highlight the necessity of emphasizing certain areas within the field of gynecologic oncology. • In 2022 the topic was "protect your health every day" with a focus on endometrial cancer.	Increase awareness	Global/ Europe	(228), (229)
OPTEC (Ohio Prevention and Treatment of Endometrial Cancer) • Identifies women with endometrial cancer at increased risk for other types of cancer due to their genetic makeup. • Offers free screening to women for Lynch syndrome. • Provides all women with complimentary tumor testing to detect molecular changes in their endometrial cancer.	Prevention and targeted treatment	United States	(230)
Uterine cancer part of WTC-related health conditions • In 2023, uterine cancer was recognized as a World Trade Center (WTC)-related health condition. Under this program, women diagnosed with uterine cancer, which can be linked to exposure on or after the September 11 attacks, are eligible for treatment coverage. • The treatment coverage is certified and ensures no out-of-pocket expenses for the affected individuals.	Access to treatment	United States	(231)

Apart from the lack of policy initiatives, endometrial cancer faces relative shortfalls in public research funding. In general, gynecological cancers, including uterine cancer, are substantially underfunded relative to other cancer sites by the National Cancer Institute (NCI) in the US. A study covering the years 2007-2014, adjusting research funding for cancer site lethality (using years of life lost), placed uterine cancer near the bottom of the funding list, at place 14 out of

18, with a lower funding than ovarian and cervical cancer (232). Additionally, the trend of funding relative to lethality for uterine cancer was decreasing in this period, a pattern not observed in many other cancers (e.g., breast cancer, leukemia, melanoma, pancreatic cancer).

The funding landscape for uterine cancer research in the US has remained largely unchanged in recent years. The NCI, which serves as the federal government's primary entity for cancer research and training (233), has not seen a significant increase in its allocation for uterine cancer research since 2015; see Figure 34. The research funding is and has been below other gynecological cancers. In 2021, uterine cancer research funding was US$14.4 million, whereas it was US$73.7 million for cervical cancer and US$134.7 million for ovarian cancer (234). Interviewed experts noted that the disadvantaged position of endometrial cancer in public research funding probably also applies to Europe.

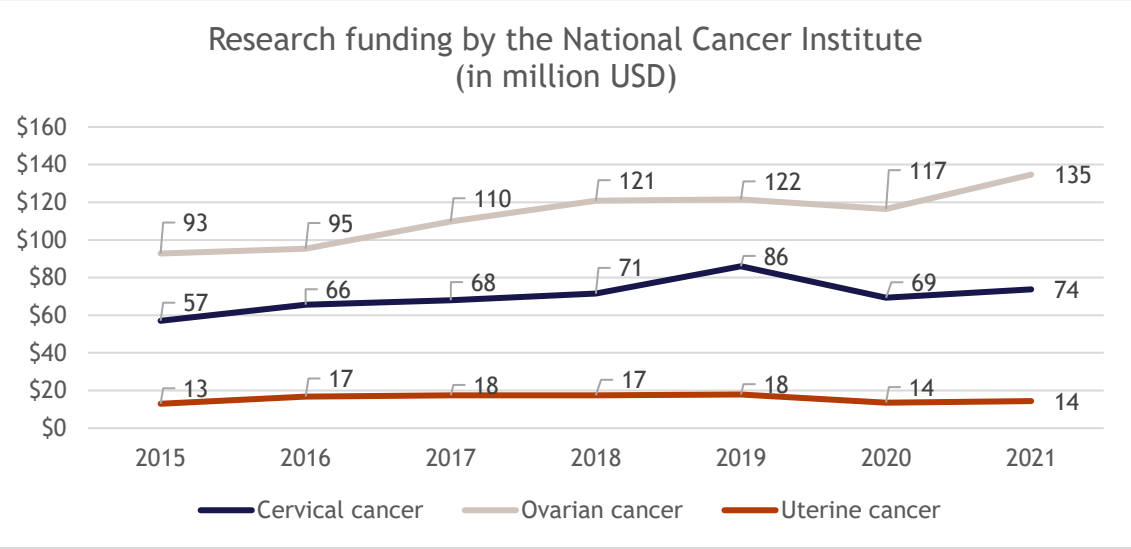

Figure 34: Research funding by the National Cancer Institute in the US, 2015-2021.

Notes: Funding for 2020 and 2021 are estimates from the NCI. Source: NCI (234).

5.2 Recommendations

Endometrial cancer is a common cancer type affecting women, yet it receives comparatively less attention in terms of public awareness and research funding than other cancer types. Women diagnosed with endometrial cancer may encounter numerous obstacles in their care journey such as lack of knowledge about the disease, the need to undergo multiple diagnostic tests, no access to gynecologic oncologists, and long-term side effects of their treatments. This report concludes with broad recommendations for the improvement of endometrial cancer care and the lives of patients and survivors. They are grouped into five areas.

5.2.1 Area 1: Raise awareness

Endometrial cancer is the most prevalent type of gynecological cancer and ranks as the fourth most common cancer among women. The incidence rates have been on the rise in many Western countries, a trend expected to continue due to demographic changes and exacerbated by the increasing prevalence of major risk factors such as overweight and obesity. Notably, in the US, the incidence rates in women under 50 years have been increasing more rapidly than in other age groups. Unlike many other cancer types, endometrial cancer is distinguished by increasing mortality rates in certain countries, including the US. Despite these concerning trends, awareness about endometrial cancer remains low among women, and healthcare providers may often mistakenly attribute its symptoms to less serious conditions. This underscores the critical need for raising awareness among women of all ages as well as healthcare providers.

Action	Why?
Raise awareness among women 	Raising awareness among women about the signs, symptoms, and risk factors of endometrial cancer is essential for early detection. This is particularly important for pre-menopausal women who might not fit the traditional profile for endometrial cancer, making them susceptible to being overlooked by healthcare professionals. Similarly, perimenopausal women might also be dismissed by healthcare providers, attributing symptoms to normal menopausal changes. In addition, it is important for women to understand that Pap smears do not screen for endometrial or other gynecological cancers besides cervical cancer, underscoring the need for increased awareness and vigilance regarding their gynecological health.
Strengthen the knowledge of GPs and gynecologists 	Primary care professionals and gynecologists typically serve as the initial point of contact for women suspecting gynecological health issues, positioning them as central figures in improving patient outcomes. Primary care professionals and gynecologists should be equipped with the necessary training to recognize early signs of the disease and understand its risk factors (overweight/obesity, polycystic ovary syndrome, Lynch syndrome, etc.). Knowledge of risk factors is especially crucial for the early detection of endometrial cancer in pre-menopausal women where symptoms like abnormal uterine bleeding might not immediately signal a significant concern.
Overcome weight bias in diagnosis 	It is not uncommon for primary care professionals or gynecologists to overlook or disregard various symptoms of endometrial cancer, attributing symptoms solely to a patient's overweight condition. A narrow focus on weight can prevent or at least delay a comprehensive evaluation and the consideration of other crucial symptoms, ultimately affecting the timely and accurate diagnosis.

5.2.2 Area 2: Provide patient-centered support and information

Recognizing the multifaceted challenges faced by patients, it is important to adopt an approach that addresses the medical aspects along with the emotional, social, and practical dimensions of patient care. This entails facilitating access to supportive communities where patients can share experiences and gain strength. It also includes delivering clear and comprehensive information about the treatment's impact on health and well-being as well as discussing personalized treatment options that respect patients' future life plans, including fertility.

Action	Why?
Facilitate access to support groups 	Facilitating access to patient groups and support networks is important in the journey of endometrial cancer patients. These networks serve as platforms for support, offering patients the opportunity to connect with women who understand their experiences firsthand. Such interactions and the sharing of personal stories can be incredibly empowering, providing emotional support, practical advice, and coping strategies. Beyond the emotional and social support, these groups act as a source for new information. Patients can learn about the latest treatments, research developments, and insights into managing side effects and the recovery process. This exchange of information can help patients make informed decisions about their care and treatment options.
Provide clear information to patients 	Healthcare professionals should provide comprehensible and comprehensive information about the expected impact of endometrial cancer treatment on aspects of health and well-being to help patients and their families cope with the new circumstances. For women of reproductive age, the implications of treatment on fertility and family planning, and the transition into menopause following a hysterectomy can have profound effects on physical and emotional health. Side effects such as difficulties in maintaining body weight and hair loss due to hormonal changes or treatment effects require attention as well. Sexual function is another critical area impacted by treatment. Patients should be counseled on potential changes in libido, postcoital bleeding, discomfort during intercourse, etc. Healthcare providers can offer solutions and create a space for open discussions about intimacy and relationships.
Discuss fertility-sparing treatment 	The prospect of undergoing a hysterectomy can be deeply distressing for young women who still wish to have children. Clinical guidelines, such as those by ESGO/ESHRE/ESGE, recommend providing fertility-sparing treatments in cases of endometrial cancer where this is feasible. These treatments typically start with the hysteroscopic resection of the tumor, followed by hormonal therapy, offering a chance to preserve the uterus during the early stages of the disease. It is crucial for physicians to be well-informed about these options so they can present women with appropriate alternatives to hysterectomy.
Leverage nursing capabilities 	Nurses can enhance oncology care by receiving specialized training on patient education, symptom management, and emotional support. To address specific patient concerns effectively, nurses could be offered certification programs in areas such as sexual health, menopause management, and fertility counseling. Furthermore, nurse-led support groups and educational workshops can provide platforms for patients and their families. These sessions can cover a range of topics, including side effect management, nutritional guidance, and strategies for coping with emotional and psychological impacts. Additionally, nurses can facilitate discussions on intimacy and relationships, creating safe spaces for patients to explore sensitive issues.

5.2.3 Area 3: Ensure optimal care delivery

Timely and comprehensive diagnostics followed by appropriate treatment are vital to increase the survival prospect of endometrial cancer patients. Challenges that hamper the provision of optimal care include slow referrals from primary care to diagnostic services and specialized care, shortages of gynecologic oncologists, incomplete biomarker testing, high copayments for medical services, and lack of patient involvement in decision-making along the care pathway.

Action	Why?
Ensure treatment decisions are made by an MDT 	Ensure that treatment decisions are made by an MDT that involves relevant specialists and jointly with the patient. MDTs are collectively usually more informed about the latest research, clinical trials, and emerging treatment options, which can be beneficial for patients. The diagnosis of endometrial cancer can be particularly challenging due to the multidimensional consequences involved in treatment (early menopause, infertility, problems with sexual life, family life, work life, etc.). MDTs can navigate these complexities, if they draw on a diverse array of professionals including psychosocial support specialists, dieticians, and others. By encompassing a holistic approach, MDTs can address the multifaceted needs of both patients and their families, ensuring comprehensive and tailored care.
Strive to minimize waiting times 	Timely intervention is critical for achieving optimal outcomes in endometrial cancer. Delays in diagnosis and treatment can permit cancer progression, potentially resulting in a poorer prognosis or complications. Both Sweden and the UK are examples that have established specific timeframes for endometrial cancer care and gynecological cancer care, respectively, to facilitate prompt diagnosis and treatment. While having standardized care protocols is essential for optimal diagnostic and treatment pathways, the utmost importance lies in adhering to these timelines.
Incorporate comprehensive biomarker testing 	Current guidelines from ESGO/ESTRO/ESP, ESMO, and NCCN recommend classifying endometrial cancer in four molecular subtypes. Comprehensive biomarker testing allows for the personalization of treatment plans, and it is expected to play a bigger role in the development of targeted therapies in the future. Certain molecular characteristics, such as dMMR, MSI-H, and TMB-H, have been shown to be predictive of response to specific treatments, particularly immunotherapy. Identifying these features can help oncologists select the most appropriate treatments, potentially leading to better outcomes. National health systems need to increase their capabilities and resources for comprehensive biomarker testing and include the testing in the diagnostic process.
Enable access to new treatments 	The last few years have witnessed the introduction of new medical treatment options that are increasingly targeted, designed for specific molecular characteristics of tumors. New cancer medicines, in particular immunotherapies, have been included in guidelines from ESGO/ESTRO/ESP, ESMO, and NCCN in the metastatic setting as first-line and second-line therapies. Clinical trials of immunotherapies in the early-stage setting are underway. Patient access to new cancer medicines depends on reimbursement decisions by public payers in Europe and inclusion in the benefit list of private insurances and Medicaid/Medicare in the US.

5.2.4 Area 4: Foster research

Despite being the most prevalent form of gynecological cancer, endometrial cancer garners significantly less focus in the broader dialogue on women's health issues. This discrepancy exists even though the incidence of endometrial cancer keeps increasing and survival rates have shown no or little progress in the last two decades in the Nordic countries and the US. There is a need for a realignment of research priorities and funding to reflect the prevalence of endometrial cancer and its impact on women's health.

Action	Why?
Evaluate the impact of quality indicators 	The evaluation of quality indicators for endometrial cancer care is critical to inform their inclusion in clinical guidelines and support their incorporation in clinical practice. An evaluation should be conducted to examine the effects of compliance with ESGO quality indicators for surgical treatment on the recurrence and survival rates of endometrial cancer patients. This exploration could mirror efforts like the SUCCOR quality validation study conducted for cervical cancer and published in 2022, which demonstrated that care centers with high adherence to ESGO surgical quality indicators were associated with a reduced risk of relapse and decreased mortality risk.
Monitor adherence to quality indicators 	ESGO quality indicators could be considered to be included in national clinical protocols and patient care pathways. In addition, a country-wide system for continuous monitoring and evaluation of compliance with national/international quality indicators for endometrial cancer care could be established. This would help to uncover disparities in the treatment provision between regions, hospitals, and patient demographics.
Promote research and visibility of nurses 	Encourage and fund research that specifically studies the impact of nursing interventions on endometrial cancer prevention and care outcomes. Publish and disseminate findings that highlight nurses' role in cancer care, enhancing their visibility and the recognition of their contributions.
Increase research funding 	Endometrial cancer, despite being one of the most common gynecological cancers, has not received research funding proportional to its prevalence and lethality. This underfunding has negative implications for the advancement of the understanding, diagnosis, and treatment of the disease, which may ultimately delay improvements in patient outcomes. In a first step, public funding for clinical research on endometrial cancer could be elevated to bring it at least on par with funding for cervical and ovarian cancer.

5.2.5 Area 5: Reduce health disparities

Factors such as education level, health insurance coverage, community wealth, ethnicity, and income have been shown to significantly affect the stage at which endometrial cancer is diagnosed, as well as recurrence rates and overall survival. For example, in Sweden, lower education levels are associated with later stages of diagnosis. In the US, African American women often receive diagnoses at more advanced stages and experience lower survival rates. Additionally, in the US, insurance status is closely linked to survival outcomes, with privately insured patients typically having better results than those without insurance. Generally, women from lower socioeconomic backgrounds and certain ethnic groups are more prone to be diagnosed with advanced stages of endometrial cancer and tend to have poorer survival rates and higher recurrence probabilities. It is essential to address these disparities to enhance health outcomes in endometrial cancer care for everyone.

Action	Why?
Improve health coverage 	Expanding health insurance coverage would ensure that women of all socioeconomic backgrounds and ethnicities have affordable access to timely and effective cancer care. This expansion could benefit earlier diagnoses and higher survival rates, especially for underinsured groups currently experiencing worse outcomes. In the US, Medicaid expansion has already shown benefits in access and timeliness of treatment for women with gynecological cancers.
Overcoming language barriers 	Language barriers further exacerbate challenges for marginalized groups in receiving adequate care. Effective communication between healthcare providers and patients is crucial for successful diagnosis and treatment. Misunderstandings can lead to inappropriate treatment plans, non-compliance with treatment protocols, and others. Providing multilingual support through interpreters, translated materials, and culturally competent healthcare professionals can help to overcome language barriers and enhance the patient's understanding and management of their illness.

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Appendix

Table A1: Risk groups with unknown and known molecular classification based on 2009 FIGO

Risk group	Molecular classification unknown	Molecular classification known
Low risk	Stage IA endometroid + low grade	Stage I-II POLEmut no residual disease Stage IA dMMR/NSMP + low grade
Intermediate risk	Stage IB endometroid + low grade Stage IA endometroid + high grade Stage IA non-endometroid	Stage IB dMMR/NSMP + low grade Stage IA dMMR/NSMP + high grade Stage IA p53abn and/or non-endometroid
High-intermediate risk	Stage I endometroid + spread into blood or lymph vessels Stage IB endometroid + high grade Stage II	Stage I dMMR/NSMP + substantial spread into blood or lymph vessels Stage IB dMMR/NSMP + high grade Stage II dMMR/NSMP
High risk	Stage III-IVA with no residual disease Stage I-IVA non-endometroid + myometrial invasion with no residual disease	Stage III-IVA dMMR/NSMP with no residual disease Stage I-IVA p53abn + myometrial invasion no residual disease Stage I-IVA NSMP/dMMR non-endometroid with no residual disease
Advanced metastatic	Stage III-IVA with residual disease Stage IVB	Stage III-IVA of any molecular subtype with residual disease Stage IVB of any molecular subtype

Notes: This table is an adaptation of Table 2 on prognostic risk groups from the ESGO/ESTRO/ESP 2021 guidelines. Low-high grade indicates the grade of the tumor, with low-grade tumors being less aggressive and high-grade tumors being more aggressive. Endometrioid cancers arise from the cells that line the uterus and often have a pattern similar to the normal endometrial lining. Non-endometroid includes several less common types of endometrial cancer, such as serous carcinoma, clear cell carcinoma, and carcinosarcoma. Abbreviations POLEmut: Polymerase epsilon mutated, dMMR: Deficient Mismatch Repair, NSMP: No specific molecular profile, p53abn: Abnormal p53 gene. Source: (28).

Table A2: Comparison of staging systems of endometrial cancer

AJCC (2018) with previous FIGO 2009 classification			FIGO 2023
Stage	FIGO 2009	Description	Changes compared to FIGO 2009
Stage I	I IA IB	Cancer is confined to the uterus. All Stage I classifications have not spread to nearby lymph nodes or distant sites. IA: Cancer is limited to the endometrium with less than half of the underlying muscle (myometrium) involved. IB: Cancer has grown more than halfway through the myometrium but remains within the uterus.	*Introduces stage IC for aggressive histological types limited to a polyp or confined to the endometrium.* *Adds IA POLEmut.*
Stage II	II	Cancer has extended to the cervical tissue but remains within the uterus without any spread to nearby lymph nodes or distant sites.	*Adds classifications IIA, IIB, and IIC, differentiating based on the type of histology and the presence of cancer cells in blood vessels near the tumor.* *Adds IIC p53abn.*
Stage III	III IIIA IIIB IIIC1 IIIC2	Cancer has spread outside the uterus. But none of the stage III classifications have distant metastasis. IIIA: Involves the uterine serosa and/or adnexa. IIIB: Cancer has spread to the vagina or parametrium. IIIC1: Includes spread to pelvic lymph nodes. IIIC2: Cancer has spread to para-aortic lymph nodes.	*Subdivisions (IIIA, IIIB, IIIC) offer more detailed categories based on exactly where the tumor has spread within the regional structures.*
Stage IV	IVA IVB	Indicates advanced disease with significant spread. IVA: Cancer has invaded the bladder or rectal mucosa, with possible lymph node involvement but no distant metastasis. IVB: Cancer can be of any size and might have spread to lymph nodes, with distant metastases to the groin, upper abdomen, involvement of the peritoneal cavity, or more distant organs like the lungs, liver, or bones.	*Adds a stage IVC specifically for distant metastases including to locations beyond the pelvis like the lungs, liver, brain, or bone.*

Notes: For an overview of the 2023 FIGO staging system, please refer to Table 14. Source: (68, 174).

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