nature reviews clinical oncology

https://doi.org/10.1038/s41571-024-00934-7

Supplementary information

Translating biological insights into improved management of endometrial cancer

In the format provided by the authors and unedited

Supplementary Table 1 – Risk/protective factors associated with and potential interventions to modify the risk to develop endometrial cancer

A)

Risk factors	**Protective factors**
Exogenous estrogen sources	Reproductive
Unopposed estrogen therapy	Increasing gravidity and parity
Tamoxifen	Older age at last birth
Endogenous estrogen sources	Breast feeding
Obesity	Copper intra-uterine device
Chronic anovulation (e.g. polycystic ovarian syndrome)	Progestin-containing intra-uterine device
Estrogen-secreting tumors (e.g. granulosa cell tumor of the ovary)	Progesterone therapy (e.g. combined oral contraceptive or progesterone / progestin-only)
Early menarche/Late menopause	Lifestyle
Hereditary	Physical activity and diet
Lynch syndrome (MLH1, MSH2, MSH6, or PMS2 mutation)	Smoking
Cowden syndrome (PTEN mutation)	Surgical
BRCA mutation carrier	Hysterectomy
First-degree relative with endometrial cancer	
Other	
Pelvic radiation	
Diabetes	
Hypertension	

B)

Characteristic of population at high risk	Endometrial cancer prevention strategies for consideration
Obesity	Weight loss through -Diet and physical exercise -Bariatric surgery -Pharmacological (e.g. semaglutide)
Lynch Syndrome	-Progesterone/progestin-based therapy -Risk-reducing hysterectomy when childbearing complete
Chronic anovulation (e.g. polycystic ovarian syndrome)	-Combined hormonal contraception -Progesterone/progestin-based therapy
Tamoxifen use for breast cancer treatment	-Discussion for switching therapy to aromatase inhibitor and performing elective bilateral salpingo-oophorectomy

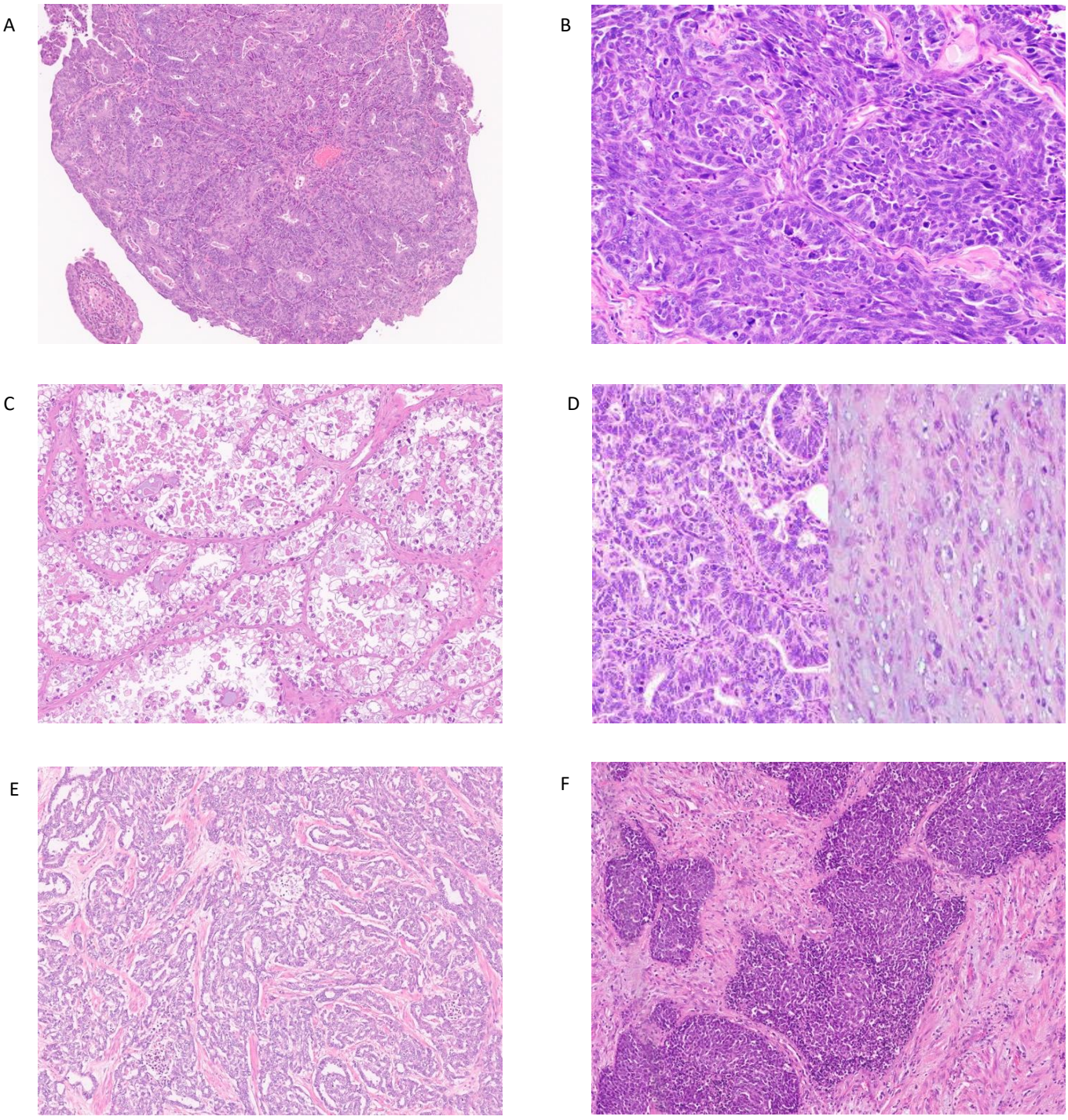
Supplemental Table 1A demonstrates risk/protective factors in the development of endometrial cancer.

Supplemental Table 1B demonstrates potential interventions/strategies to modify risk of endometrial cancer.

Supplementary Table 2 – 2020 WHO classification of tumors of uterine corpus[30]

Endometrial epithelial tumors and precursors
Precursor lesions
Endometrial hyperplasia without atypia
Endometrial atypical hyperplasia / endometrioid intraepithelial neoplasia
Endometrial carcinomas
Endometrioid carcinoma
Serous carcinoma
Clear cell carcinoma
Undifferentiated carcinoma
Dedifferentiated carcinoma
Mixed carcinoma
Other endometrial carcinomas
Carcinosarcoma
Tumor-like lesions
Endometrial polyp
Endometrial metaplasia
Arias-Stella reaction
Mesenchymal tumors
Smooth muscle tumors
Leiomyoma
Intravenous leiomyomatosis
Smooth muscle tumor of uncertain malignant potential
Metastasizing leiomyoma
Leiomyosarcoma
Endometrial stromal and related tumors
Endometrial stromal nodule
Low-grade endometrial stromal sarcoma
High-grade endometrial stromal sarcoma
Undifferentiated uterine sarcoma
Miscellaneous mesenchymal tumors
Uterine tumor resembling ovarian sex cord tumor
Perivascular epithelioid cell tumor
Inflammatory myofibroblastic tumor
Other mesenchymal tumors
Mixed epithelial and mesenchymal tumors
Adenomyoma
Atypical polypoid adenomyoma
Adenosarcoma
Miscellaneous tumors
Central primitive neuroectodermal tumor / CNS embryonal tumor
Germ cell tumors

Supplementary Figure 1 – Histological appearance of subtypes of endometrial cancer



Supplementary Figure 1A) endometrioid carcinoma 1B) serous carcinoma 1C) clear cell carcinoma 1D) carcinosarcoma (malignant epithelial and mesenchymal elements shown) 1E) Mesonephric-like carcinoma 1F) undifferentiated/dedifferentiated carcinoma

Supplementary Table 3 – Differences between FIGO 2009 and 2023

	FIGO 2009	FIGO 2023
Stage I	-Tumor confined to the uterine corpus, including endocervical glandular involvement -Stage I subdivided into IA or IB based on depth of myometrial invasion	-Tumor may involve uterine with or without ovarian structures based on specific criteria -Stage I is subdivided IA1 – IA3, IB, and IC based on aggressiveness of the histologic subtype, extent of myometrial invasion, and extent of LVSI. -Re-introduces criteria of absent myometrial invasion (part of FIGO 1988 staging). -Introduces concept of focal LVSI and dichotomous aggressive/non-aggressive terminology for histology -Introduces ovarian involvement based on specific criteria (stage IA3) -Introduces concept of stage modification with molecular profiling. If tumor molecular profiling reveals POLE mutation in an original stage I-II, then the stage will be down-staged to stage $IAm_{POLEmut}$, regardless of prior stage or other molecular features.
Stage II	-Tumor invading the cervical stroma but not extending beyond the uterus. -No stage subdivisions	-Tumor involves the cervical stroma and/or the uterus based on specific criteria -Stage II is subdivided into IIA, IIB, and IIC based on aggressiveness of the histologic subtype and extent of LVSI. -Introduces concept of extensive LVSI -If tumor molecular profiling reveals p53abn for original stage I or II tumors will be upstaged the tumor to stage $IICm_{p53abn}$, regardless of prior stage I – II or other molecular features (except in presence of POLE mutation).
Stage III	-Tumor involving the uterine serosa, adnexa, vagina, parametrium, or regional lymph nodes -Stage III is divided into stage IIIA (serosa or adnexa), IIIB (vagina or parametria), and IIIC (pelvic or para-aortic lymph nodes)	-Tumor involves uterine subserosa, uterine serosa, adnexa, vagina, parametria, pelvic peritoneum, or regional lymph nodes -Stage IIIA is subdivided IIIA1 and IIIA2 based on adnexal or (sub)serosal involvement (except when meeting stage IA3). Stage IIIB

		is subdivided IIIB1 and IIIB2 based involvement of vagina, parametria, or pelvic peritoneum. IIIC is subdivided into IIIC1i, IIIC1ii, IIIC2i, and IIIC2ii based on size and location of lymph node metastases. -Introduction of concept of uterine subserosa. -Introduces micro- and macrometastasis
Stage IV	-Tumor involving the mucosa of the bladder or rectum and/or distant metastasis -Stage IV is subdivided into invasion into the bladder/rectum (IVA) and peritoneal/distant metastases (IVB)	- Tumor involving the mucosa of the bladder or rectum and/or distant metastasis -Stage IV is subdivided into IVA – IVC -IVB and IVC are distinguished by peritoneal metastasis beyond the pelvis vs distant metastasis