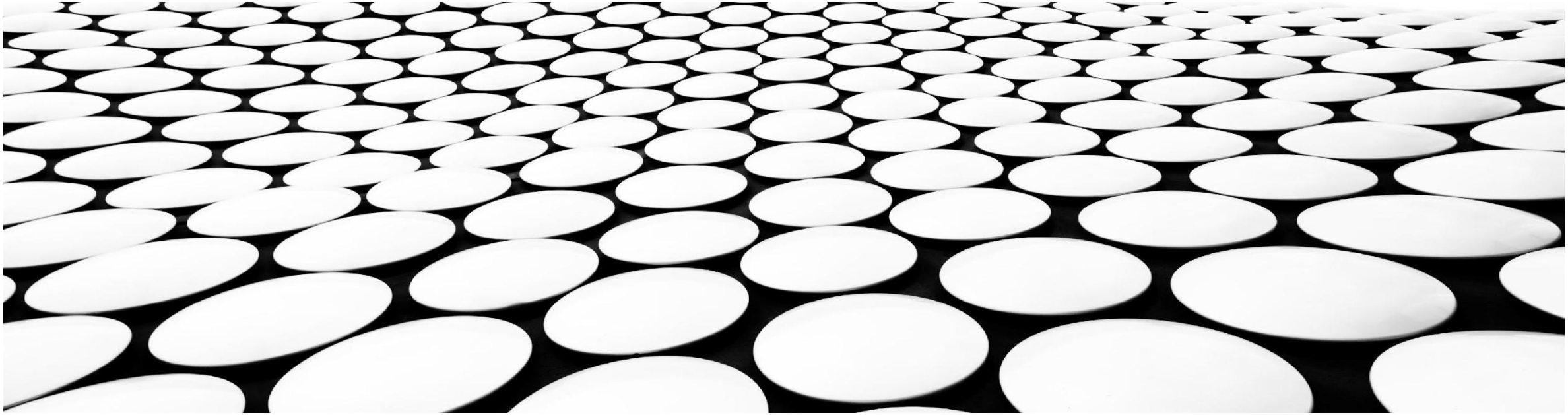
Hormone Replacement Therapy in Cancer Survivors – Review of the Literature

Tamás Deli[1] · Mónika Orosz[1] · Attila Jakab[1]

Pathology & Oncology Research

Received: 23 July 2018 / Accepted: 18 December 2018 / Published online: 8 January 2019

REPORTER : 許越涵　　SUPERVISOR : 黃貞瑜主任 & 顏明賢主任



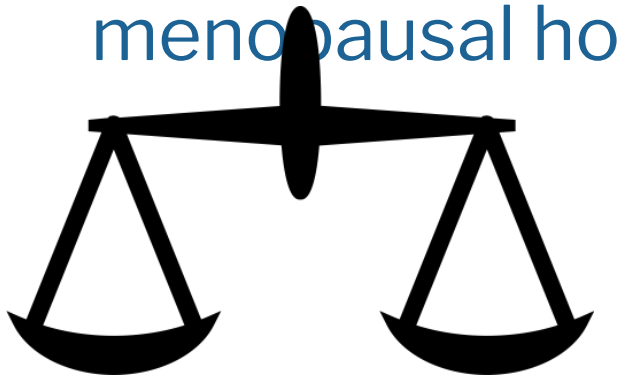
increasing survival of oncologic patients

menopause

vasomotor symptoms
cardiovascular effects
skeletal effects

hormone replacement therapy (HRT)

menopausal hormone the

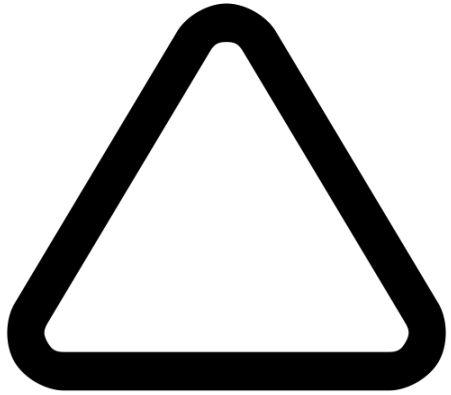


From in vitro experiments to clinical studies

Gynecologic & Non-gynecologic cancers

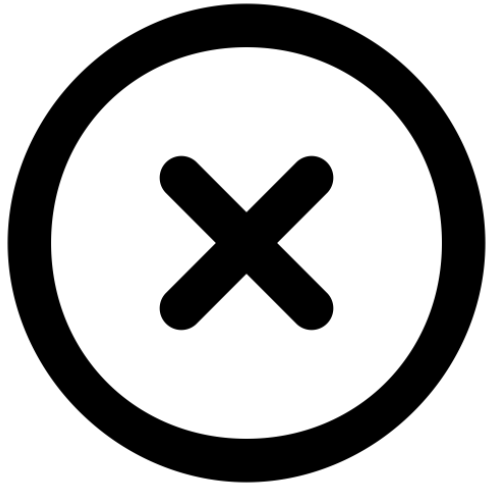
Grouping

advantageous



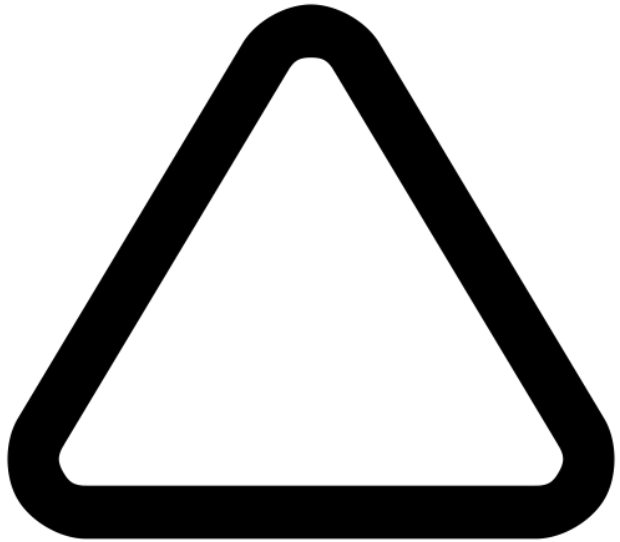
neutral

relatively contraindicated



contraindicated

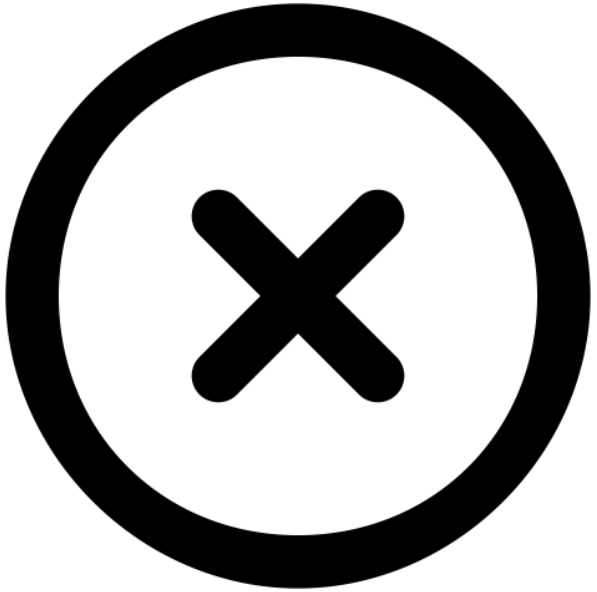
- Endometrial cancer type I
- Cervical adenocarcinoma
- Haematologic malignancies
- Local cutaneous malignant melanoma
- Colorectal cancer
- Hepatocellular cancer



- BRCA 1/2mutation carriers without cancer
- endometrial cancer type II
- uterine carcinosarcoma and adenosarcoma
- certain types of ovarian cancer
- cervical, vaginal and vulvar squamous cell carcinoma
- prolactinoma
- kidney cancer
- pancreatic cancer
- thyroid cancer

relatively contraindicated

- Leiomyosarcoma
- Certain types of ovarian tumors
- Brain tumors
- Advanced metastatic malignant melanoma
- Lung cancer
- Gastric cancer
- Bladder cancer



contraindicated

- Breast cancer
- Endometrial stroma sarcoma
- Meningioma
- Glioma
- Hormone receptor positive gastric cancer
- Hormone receptor positive bladder cancer

to induce tumors

cancer recurrence and progression

premature ovarian failure

- genetic diseases
- autoimmune diseases
- the consequence of other benign ovarian pathology

physiological menopause around the age of 50 y/o

Cancer

- the organ
- histologic type
- molecular characteristics
- grade
- stage
- therapy
- time of survival since therapy
- endocrine caracteristics
- surrounding stromal tissue
- immune response

HRT

- estrogenic and progestagenic compound type
- dose
- sequential or continuous
- route
- duration

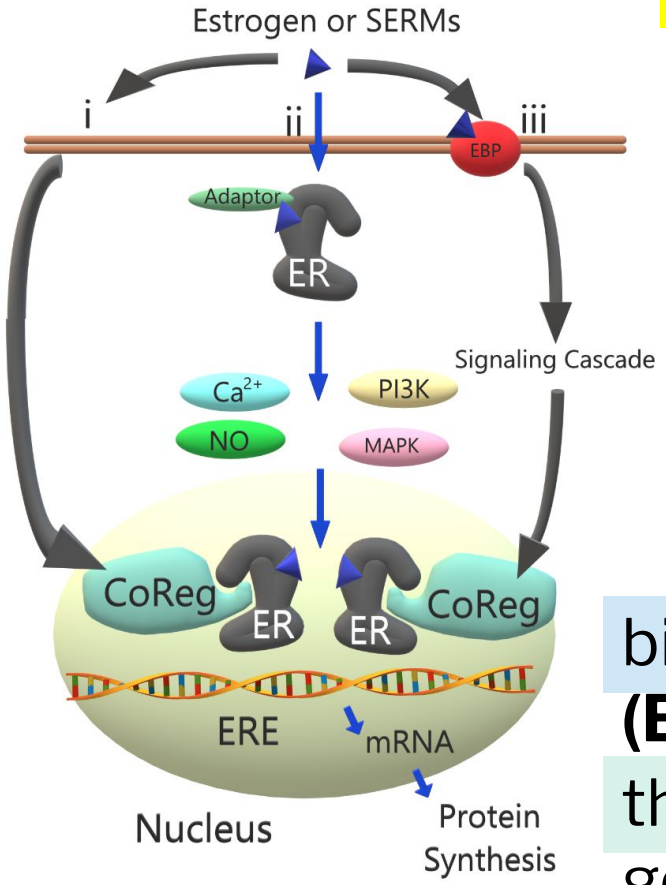
Individualized
decision-making

- preclinical research
- case reports
- retrospective studies
- randomized controlled trials
- meta-analyses

Determinants of Estrogen Effect on Tissues

Estrogen ⟷ estrogen receptors (ERs)
ERα and ERβ

dimerization



- direct
- by transcription factors (TFs)

binding to **estrogen response elements (ERE)**

the promoter and regulatory regions of their target genes

Estrogen sensitivity & ERE mediated activation of cells or genes

- the addition of estrogen → gene upregulation

> 1000 estrogen sensitive genes

- identifying EREs in the promoter region of genes

ERE databases ------- available online

example : EBAG9, c-fos, OXT, F12, TFF1, LTF, CTSD, PFDN2, TGF-α, AGT, GREB1, KIAA1243, NRIP1, MADH9, NME3, TPD52L, and ABCG2

Estroge
n

Estrogen
receptor

not enough to predict the effect of estrogen in any cell type

Estrogen and progesterone receptor status

Estrogen receptor overexpression

- Breast cancer
- Endometrial cancer
- Ovarian cancer

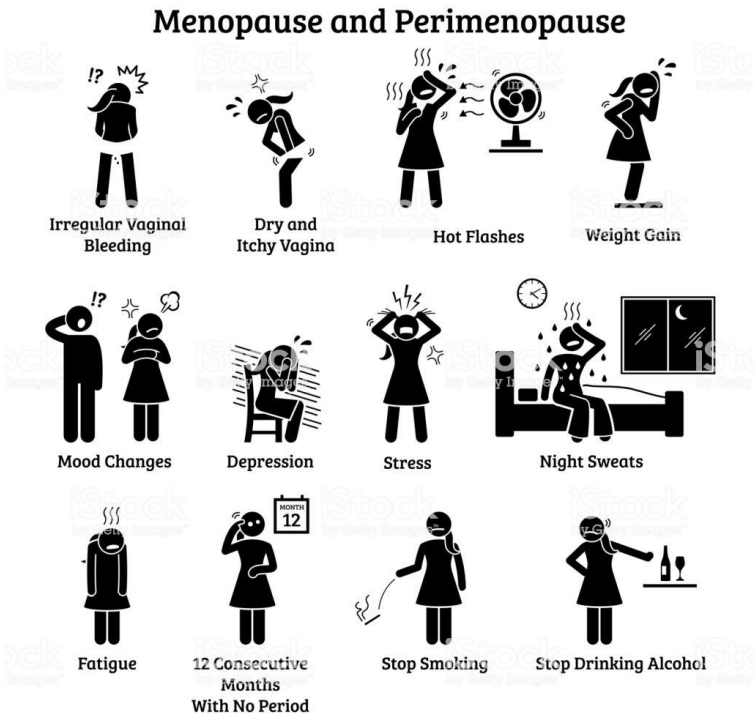
ERα : induce estrogen dependent proliferation

ER β

Altered estrogen and / or progesterone receptor expression

- thyroid cancer
- Hodgkin's lymphoma
- B-cell malignancies
- brain tumours
- prolactinoma
- melanoma
- lung cancer
- colorectal cancer
- gastric cancer
- liver cancer

Determinants of Progesterone Effect on Tissues



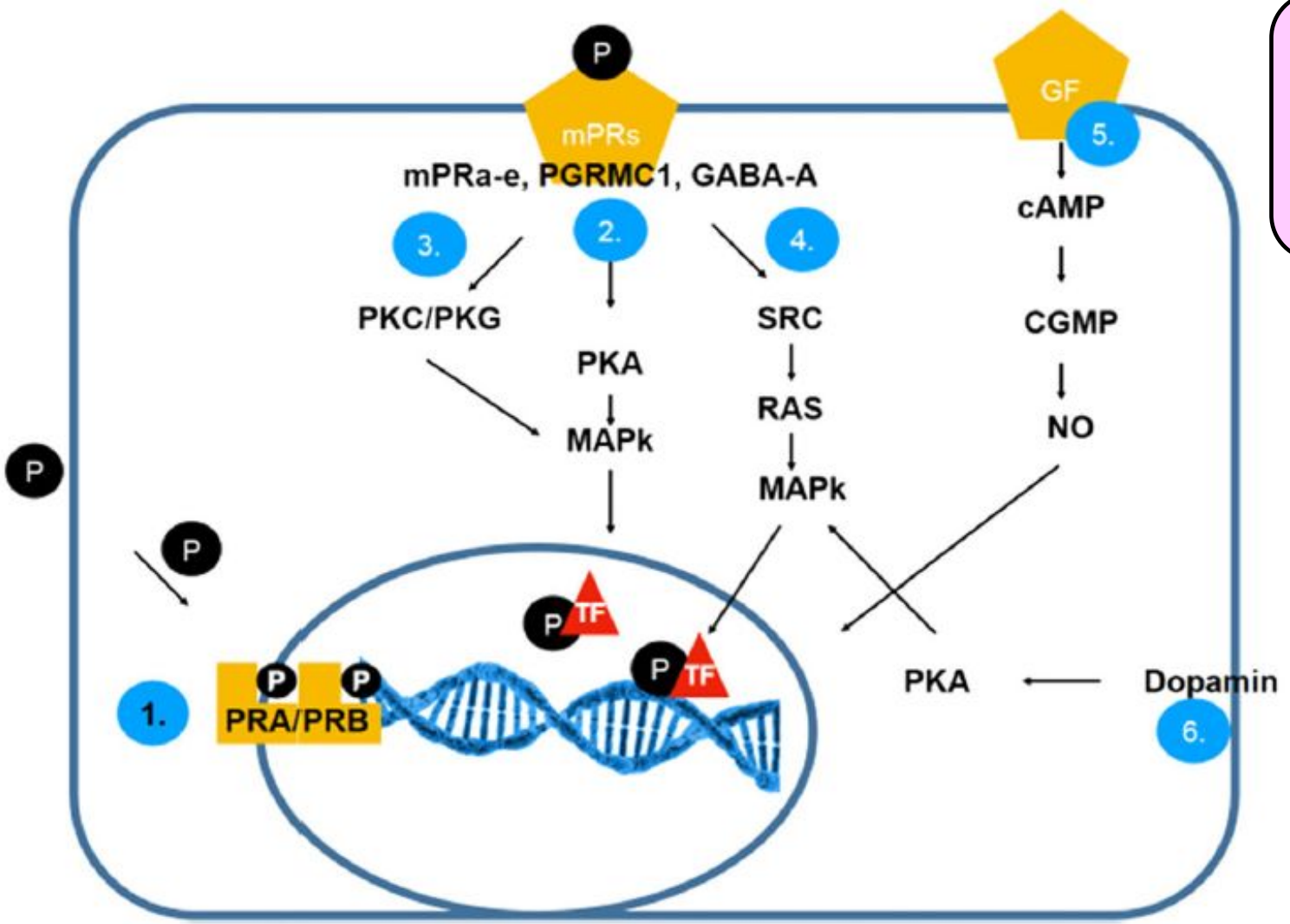
Estroge
n

Progestogenic
compounds

Pure progesterone-like effect (except for micronised progesterone)

Other steroid hormone receptors (androgen, mineralocorticoid, glucocorticoid)

<u>prediction</u> of E P HRT effect on tissues simply based on receptor expression and signalling is **nearly impossible**



'Non-classical' progesterone signalling

'Classical' progesterone signalling

Table 1 The most common cancer types in childhood, young adults and females. American Cancer Society, 2015-2016 [43]

Childhood cancer	Young adult cancer	Female cancer (new cases)
Leukemia	Breast cancer	Breast cancer
Brain and spinal cord tumours	Lymphoma (Hodgkin / non-Hodgkin)	Lung cancer
Neuroblastoma	Melanoma	Colorectal cancer
Wilms tumour	Sarcoma	Uterine corpus
Lymphoma (Hodgkin / non-Hodgkin)	Female genital tract cancers	Thyroid cancer
Rhabdomyosarcoma	Thyroid cancer	Non-Hodgkin lymphoma
Retinoblastoma	Testicular cancer	Melanoma
Bone cancer (osteosarcoma, Ewing sarcoma)	Colorectal cancer	Leukemia
	Leukemia	Pancreatic cancer
	Brain and spinal cord tumours	Kidney cancer

- Breast cancer
- Gynecologic cancers
- Other common non-gynecologic cancers

Breast Cancer

antiestrogenic endocrine therapy

No hormone replacement therapy

Nonhormonal methods

- lifestyle changes
- behavioral therapy
- Gabapentine
- venlafaxine or fluoxetine (SSRI)

HABITS (Hormone Replacement Therapy After Breast Cancer – Is it Safe?)

the first large randomized, controlled trial (RCT)

2.1 years □ stopped in **2003**

increased risk of breast cancer recurrence
n=434
HRT group : recurrence 26 cases
non-HRT group : 7 cases
HR: 3.3

HABITS (Hormonal Replacement Therapy After Breast Cancer--Is It Safe?), a Randomised Comparison: Trial Stopped

L Holmberg [1], H Anderson, HABITS steering and data monitoring committees

Randomized Controlled Trial > J Natl Cancer Inst. 2008 Apr 2;100(7):475-82.

doi: 10.1093/jnci/djn058. Epub 2008 Mar 25.

Increased Risk of Recurrence After Hormone Replacement Therapy in Breast Cancer Survivors

Lars Holmberg [1], Ole-Erik Iversen, Carl Magnus Rudenstam, Mats Hammar, Eero Kumpulainen, Janusz Jaskiewicz, Jacek Jassem, Daria Dobaczewska, Hans E Fjosne, Octavio Peralta, Rodrigo Arriagada, Marit Holmqvist, Johanna Maenpaa, HABITS Study Group

In the extended follow-up of HABITS :
RR of recurrence of 2.4
(n=442, mean HRT duration 24 months, follow-up **5 years**, recurrence **22.2%** HRT user vs. **8.0%** non-user)

The Effects of Tibolone in Older Postmenopausal Women

Steven R. Cummings, M.D., Bruce Ettinger, M.D., Pierre D. Delmas, M.D., Ph.D., Peter Kenemans, M.D., Ph.D., Victoria Stathopoulos, Ph.D., Pierre Verweij, Ph.D., Mirjam Mol-Arts, M.D., Lenus Kloosterboer, Ph.D., Lori Mosca, M.D., Ph.D., M.P.H., Claus Christiansen, M.D., John Bilezikian, M.D., Eduardo Mario Kerzberg, M.D., et al., for the LIFT Trial Investigators*

The LIFT (Long-Term Intervention on Fractures with Tibolone) study:

- Decrease fracture risk
- Reduces **invasive breast cancer** risk significantly (odds ratio 0.32)

Tibolone : a compound that is metabolized to an estrogenic, progestagenic and androgenic isomer

Randomized Controlled Trial > Lancet Oncol. 2009 Feb;10(2):135-46.
doi: 10.1016/S1470-2045(08)70341-3. Epub 2009 Jan 23.

Safety and Efficacy of Tibolone in Breast-Cancer Patients With Vasomotor Symptoms: A Double-Blind, Randomised, Non-Inferiority Trial

Peter Kenemans [1], Nigel J Bundred, Jean-Michel Foidart, Ernst Kubista, Bo von Schoultz, Piero Sismondi, Rena Vassilopoulou-Sellin, Cheng Har Yip, Jan Egberts, Mirjam Mol-Arts, Roel Mulder, Steve van Os, Matthias W Beckmann, LIBERATE Study Group

The LIBERATE (Livial Intervention Following Breast Cancer: Efficacy, Recurrence and Tolerability Endpoints) Trial :

- Bone mineral density (BMD) and climacteric symptoms significantly improved,
- **increased** recurrence risk □ **prematurely terminated**
- (n=3098, follow-up 3.1 years, breast cancer recurrence **15.2%** with tibolone vs. **10.7%** with placebo, HR: 1.4)

HRT is **generally contraindicated** in breast cancer

Tibolone

ER parallel endocrine oncotherapy

ER

- ER negative (HR: 1.15) : no significant relative risk elevation

parallel endocrine oncotherapy

- aromatase inhibitor (HR: 2.42)
- GnRH analogue (HR: 2.29)
- SERM (tamoxifen) (HR: 1.25) : no significant relative risk elevation

› Med J Aust. 2002 Oct 7;177(7):347-51.

Hormone Replacement Therapy After a Diagnosis of Breast Cancer: Cancer Recurrence and Mortality

Eva M Durna [1], Barry G Wren, Gillian Z Heller, Leo R Leader, Peter Sjoblom, John A Eden

Vaginal estrogen user breast cancer survivors :

- 9.1% recurrence in vaginal estrogen users
- 29.5% in non-HRT users (RR: 0.18; 0.04-0.75)

During adjuvant **aromatase inhibitor** therapy

any form of local estrogen application

the serum estrogen level has to be kept strictly at zero

› Menopause. Jul-Aug 2003;10(4):277-85. doi: 10.1097/01.GME.0000061806.76067.E9.

Estrogen Replacement Therapy in Breast Cancer Survivors: A Matched-Controlled Series

David A Decker [1], Jane E Pettinga, Nancy VanderVelde, Raywin R Huang, Larry Kestin, John H Burdakin

› Am J Clin Oncol. 2000 Dec;23(6):541-5. doi: 10.1097/00000421-200012000-00001.

Breast Cancer Survival and Hormone Replacement Therapy: A Cohort Analysis

P J DiSaia [1], W R Brewster, A Ziogas, H Anton-Culver

Duration of HRT

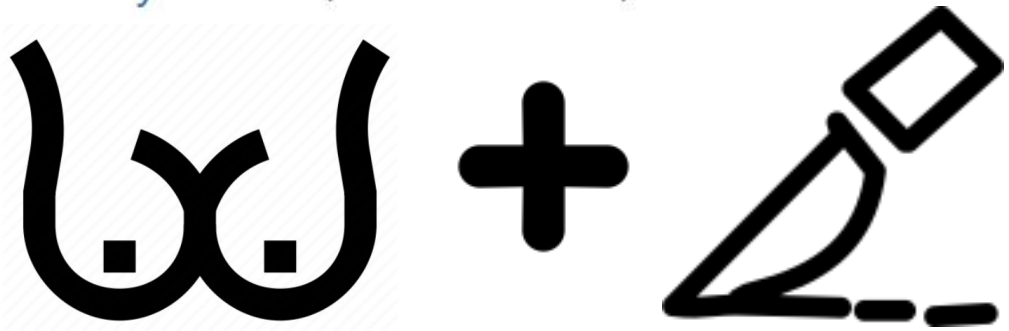
longer periods of MHT □ more recurrences □ **increased** mortality

24-42 months vs. 12-22 months

Womens Health (Lond). 2012 Sep;8(5):543-55. doi: 10.2217/whe.12.41.

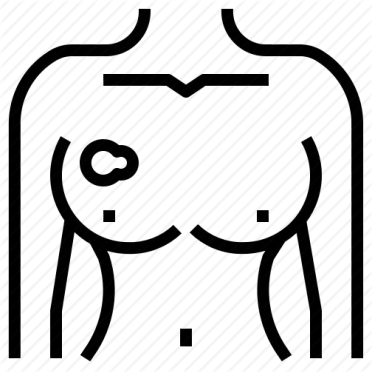
BRCA Carriers, Prophylactic Salpingo-Oophorectomy and Menopause: Clinical Management Considerations and Recommendations

Amy Finch [1], Gareth Evans, Steven A Narod



HR
T

age of natural menopause (50 y/o)

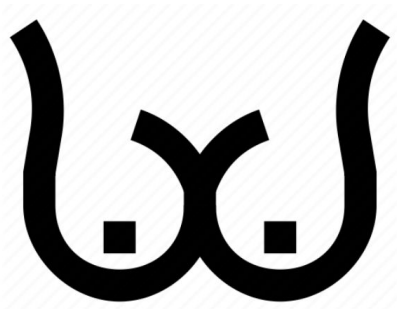


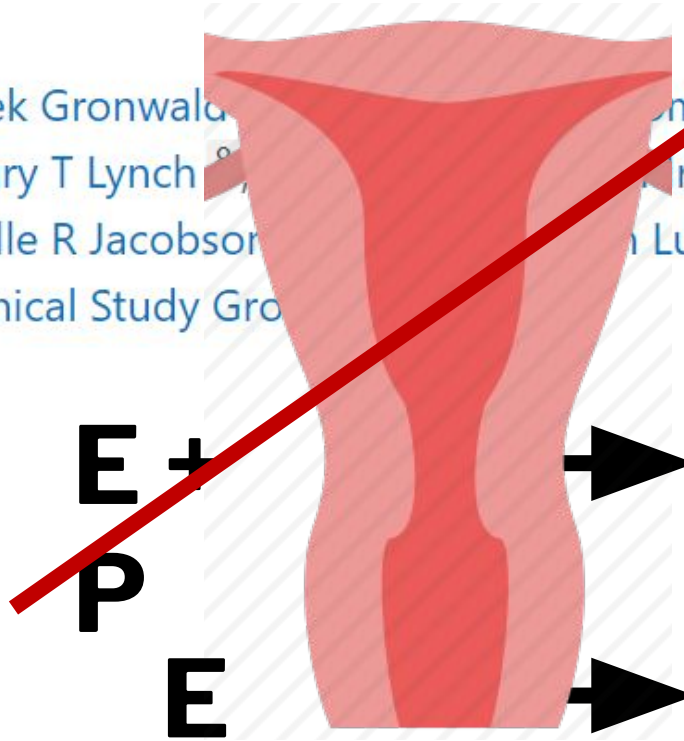
HRT is **contraindicated**

JAMA Oncol. 2018 Aug 1;4(8):1059-1065. doi: 10.1001/jamaoncol.2018.0211.

Hormone Replacement Therapy After Oophorectomy and Breast Cancer Risk Among BRCA1 Mutation Carriers

Joanne Kotsopoulos [1 2], Jacek Gronwald, ...masz Huzarski [3], Nadine Tung [5], Pal Moller [6], Susan Armel [7], Henry T Lynch [8], ...rea Eisen [10], Christian F Singer [11], William D Foulkes [12], Michelle R Jacobson, ...Lubinski [3], Steven A Narod [1 2], Hereditary Breast Cancer Clinical Study Gro...





risk of breast cancer

risk **not** increase

Ovarian Cancer

Estrogen replacement therapy for ovarian carcinoma survivors: A randomized controlled trial.	Guidozzi F1, Daponte A (1999)
Use of hormone replacement therapy before and after ovarian cancer diagnosis and ovarian cancer survival.	Mascarenhas C1, Lambe M, Bellocco R, Bergfeldt K, Riman T, Persson I, Weiderpass E (2006)
Adjuvant hormo cancer: results c	JP, Gore M, Mansi J, Williams C, Kitchener rie D, Harper P, Bliss
Hormone therap meta-analysis.	ouni E, Prodromidou A, a DN, Vlachos GD
Hormone replac	iltshaw E, Fryatt I, rd JH, Harmer CL, CE (1991)
Hormone replacement therapy after invasive ovarian **serous cystadenocarcinoma** treatment: the effect on survival.	Ursic-Vrscaj M, Bebar S, Zakelj MP (2001)
Reproductive factors and epithelial ovarian cancer survival in the EPIC cohort study.	Bešević J, et al. (2015)
Hormone therapy for ovarian cancer survivors: systematic review and meta-analysis.	Pergialiotis V, Pitsouni E, Prodromidou A, Frountzas M, Perrea DN, Vlachos GD

EOC ------ HRT :

(between 42 months to 19 years)

- does **not** increase recurrence of the malignant disease
- (in some studies, e.g. Mascharenas et al.) it even increases the overall survival

Endometrioid ovarian cancer

sensitive to estrogen → **avoidance** of HRT

Menopausal hormone therapy in cancer survivors: A narrative review of the literature

Carol L. Kuhle, Ekta Kapoor, Richa Sood, Jacqueline M. Thielen, Aminah Jatoi, Stephanie S. Faubion

Preventive Medicine, Occupational, and Aerospace Medicine, Medical Oncology, General Internal Medicine

Research output: Contribution to journal › Review article

Review › Maturitas. 2015 Nov;82(3):296-8. doi: 10.1016/j.maturitas.2015.07.006. Epub 2015 Jul 22.

Treatment of Climacteric Symptoms in Survivors of Gynaecological Cancer

Nicoletta Biglia [1], Valentina Elisabetta Bounous [2], Luca Giuseppe Sgro [2], Marta D'Alonzo [2], Martina Gallo [2]

endometrial adenocarcinoma survivors are candidates for HRT

germ cell tumors

Menopausal hormone therapy in cancer survivors: A narrative review of the literature

Carol L. Kuhle, Ekta Kapoor, Richa Sood, Jacqueline M. Thielen, Aminah Jatoi, Stephanie S. Faubion

Preventive Medicine, Occupational, and Aerospace Medicine, Medical Oncology, General Internal Medicine

Research output: Contribution to journal › Review article

no additional recurrence risk

granulosa cell tumor

the most common sex-chord stromal ovarian tumour

hormonally – endocrinologically active character

It may be safer **not** to initiate HRT in these patients.

(no direct evidence)

Review > Gynecol Oncol. 2017 Aug;146(2):427-435. doi: 10.1016/j.ygyno.2017.06.013. Epub 2017 Jun 16.

Management of Menopausal Symptoms in Women With Gynecologic Cancers

Marcela G Del Carmen [1], Laurel W Rice [2]

Review > Maturitas. 2010 Mar;65(3):190-7. doi: 10.1016/j.maturitas.2009.11.017. Epub 2009 Dec 16.

Hormone Replacement After Gynaecological Cancer

Piksi Singh [1], Martin K Oehler

Endometrial Cancer

Type I : estrogen sensitive

increased recurrence rate after the initiation of HRT

Estrogen replacement therapy in the patient treated for endometrial canc	Creasman WT, Henderson D, L
Estro endo	990)
Estro surv	K, ML
Estrogen replacement therapy in endometrial cancer patients: a matched control study.	Sunano KA, McHale M, McLaren CE, Li KT, Re A, DiSaia PJ (2001)
Does immediate hormone replacement therapy affect the oncologic	Ayhan A, Taskiran C, Simsek S,

- **Recurrence rate & disease free survival were not worse**
- **In most cases : be even better in HRT groups**
- stage I and II
- Follow-up times : 42-87 months
- E or E+P

Review > Eur J Cancer. 2014 Jun;50(9):1628-37. doi: 10.1016/j.ejca.2014.03.006.
Epub 2014 Mar 28.

Effects of Hormone Replacement Therapy on the Rate of Recurrence in Endometrial Cancer Survivors: A Meta-Analysis

Seung-Hyuk Shim [1], Sun Joo Lee [1], Soo-Nyung Kim [2]

E + P : had a **protective effect** against cancer recurrence
(OR: 0.23; 95% CI 0.08-0.66)

E : did not show this effect (OR: 0.35; 95% CI 0.06-2.10)

- **When to start HRT ?**

- **Duration ?**

HRT was initiated after between **1 to 60 months** of disease free survival (after surgery).
Most cases :after surgery --- between **3-12 months**

type II

No specific studies

not sensitive to estrogen

 it is logical to think that HRT use is not more dangerous

?

Uterine Sarcoma

- Leiomyosarcomas
- Carcinosarcomas
- Adenosarcomas
- Endometrial stroma sarcomas

Endometrial stroma sarcoma

overexpress estrogen and progesteron receptors

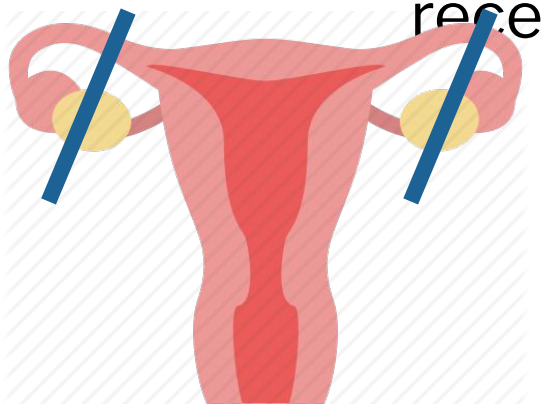
Gynecol Oncol. 2006 Jun;101(3):464-9. doi: 10.1016/j.ygyno.2005.11.010. Epub 2005 Dec 20.

Harm or Benefit of Hormonal Treatment in Metastatic Low-Grade Endometrial Stromal Sarcoma: Single Center Experience With 10 Cases and Review of the Literature

Daniel Pink [1], Tanja Lindner, Alicia Mrozek, Albrecht Kretzschmar, Peter C Thuss-Patience, Bernd Dörken, Peter Reichardt

estrogen HRT : adverse effect → **Avoid HRT**

often overexpress estrogen and progesteron receptors **as**



not improve the 5-year overall survival

Kapp DS, Shin JY, Chan JK (2008) Prognostic factors and survival in 1396 patients with uterine leiomyosarcomas: emphasis on impact of lymphadenectomy and oophorectomy. Cancer 112(4): 820–830

REVIEWS

Estrogen therapy in gynecological cancer survivors

F. Guidozzi

Pages 611-617 | Received 06 Feb 2013, Accepted 14 May 2013, Published online: 16 Aug 2013

V

not hormone sensitive and HRT may be given

Review > Gynecol Oncol. 2017 Aug;146(2):427-435. doi: 10.1016/j.ygyno.2017.06.013. Epub 2017 Jun 16.

Management of Menopausal Symptoms in Women With Gynecologic Cancers

Marcela G Del Carmen [1], Laurel W Rice [2]

X

lack of direct data to support or refute its safety

Review > Climacteric. 2013 Dec;16(6):611-7. doi: 10.3109/13697137.2013.806471.
Epub 2013 Aug 16.

Estrogen Therapy in Gynecological Cancer Survivors

F Guidozzi [1]

Carcinosarcomas & Adenosarcomas

HRT can be used

Cervical Cancer

squamous cell carcinoma

80-90% of cervical cancer

not estrogen dependent

Clinical Trial > Gynecol Oncol. 1987 Feb;26(2):169-77. doi: 10.1016/0090-8258(87)90270-8.

Hormonal Replacement Therapy in Patients After Cervical Cancer Treatment

E Ploch

Both E or E + P : advantageous

	HRT group	Control group
Recurrence rate	**20%**	32%
5-year overall survival rate	**80%**	65%

Cervical adenocarcinoma

10-20% of cervical cancer

its biological behavior resembles **endometrial cancer**

HRT and probably it is beneficial to chose a combined **E+P** regimen

Treated cervical cancer is **not** a contraindication for HRT

Vaginal and Vulvar Cancer

Most : squamous cell carcinomas

behave similarly to squamous cell cervical cancer

MHT is not contraindicated

==========

Vaginal (clear-cell) adenocarcinoma

diethylstilbestrol

vulvar adenocarcinoma

can develop from Bartholin's glands

HRT ?

Haematologic Malignancies

- acute and chronic lymphoid leukaemia
- acute and chronic myeloid leukaemia
- Hodgkin lymphoma
- non-Hodgkin lymphoma
- myeloma multiplex

haemopoietic cells

beneficial effect of estrogen

- **Pregnancy** : against the development of **Hodgkin lymphoma**
- **former HRT** : decreases the risk of **B-cell non-Hodgkin lymphomas**
- **Estrogen** : improves the disease-free and overall survival in **diffuse large-cell lymphomas**

haemopoietic cells

beneficial effect of estrogen

- **Pregnancy** : against the development of **Hodgkin lymphoma**
- **former HRT** : decreases the risk of **B-cell non-Hodgkin lymphomas**
- **Estrogen** influences the proliferation, differentiation and survival of B-linage precursors and by <u>decreasing local IL-6 production,</u>

  improves the disease-free and overall survival in **diffuse large-cell lymphomas**

Observational Study > Climacteric. 2017 Jun;20(3):268-273.
doi: 10.1080/13697137.2017.1309382. Epub 2017 Apr 11.

Hormone Therapy for Premature Ovarian Insufficiency Patients With Malignant Hematologic Diseases

X Yang [1], C Wang [1], X He [2], J Wei [2], Y Wang [3], X Li [2], L-P Xu [4]

- No increase in the recurrence of the disease or excess mortality
- Significant alleviation of menopausal symptoms

Neutral effect of HRT on malignant haematologic diseases

Brain Tumors

meningioma

- more common in women than in men
- grow faster in the **luteal phase** of the cycle & **pregnancy**
- the role of **progesterone effect.**
- 58-83% express progesterone receptor
- 0-8 % expressing estrogen receptor

na by 30-80 %

Review > Int J Cancer. 2015 May 15;136(10):2369-77. doi: 10.1002/ijc.29274. Epub 2014 Nov 12.

Menopausal Hormone Therapy and Central Nervous System Tumor Risk: Large UK Prospective Study and Meta-Analysis

Victoria S Benson [1], Oksana Kirichek, Valerie Beral, Jane Green

Estrogen-only HRT increased the risk of brain tumors, glioma and meningioma

J Neurooncol. 2018 Jan;136(2):327-333. doi: 10.1007/s11060-017-2656-9. Epub 2017 Oct 28.

Progesterone-only Contraception Is Associated With a Shorter Progression-Free Survival in Premenopausal Women With WHO Grade I Meningioma

Tessa A Harland [1], Jacob L Freeman [1], Monica Davern [1], D Jay McCracken [2], Emma C Celano [3], Kevin Lillehei [1], Jeffrey J Olson [2], D Ryan Ormond [4]

WHO Grade I meningioma

- progesterone-only contraception
  - shorter progression-free survival in premenopausal women

meningioma

glioma

HRT

E

P

growth recurrence

HRT should be avoided

Prolactinoma

Estrogen inhibited dopaminergic system □ prolactin ↑

microprolactinoma

macroadenoma

- pregnancy
- low-dose (<30 ug) ethynil estradiol contraceptive

→ growth rare (1-2%)

→ 30-40% grow during pregnancy

- **Micro**prolactinoma should therefore **not** be considered a contraindication for HRT
- **Macro**prolactinoma : very close monitoring

Prolactinoma

Estrogen inhibited dopaminergic system → prolactin ↑

hyperprolactinemia ?????

microprolactinoma

macroadenoma

- pregnancy
- low-dose (<30 ug) ethynil estradiol contraceptive

→ growth rare (1-2%)

→ 30-40% grow during pregnancy

- **Micro**prolactinoma should therefore **not** be considered a contraindication for HRT
- **Macro**prolactinoma : very close monitoring

Malignant Melanoma

controversi
al

estrogen receptor-β
(ERβ)

ERα : proliferative and tumor promoting effect

Erβ : antitumor effect---------- inhibition of the PI3K/Akt pathway

ERβ expression □ better prognosis
Decreased ERβ expression □ poorer prognosis and the metastatic state

use of **estrogen** or **ERβ agonists** in the treatment of melanoma

ERβ-rich tumors : estrogen supplementation might even be advantageous

advanced, metastatic cases : the safety is unclear

Lung Cancer

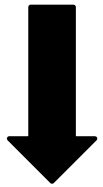
estrogen-depend

Non-small cell lung cancer :

ERβ --- tumor promoter

via interactions with receptor splice variants, EGFR receptor signalling and G-protein coupled estrogen receptors

application of **antiestrogenic agents** and **aromatase inhibitors** in the treatment of lung cancer



MHT should **not** be used in lung cancer patients

Colorectal Cancer

protective effect of female hormones

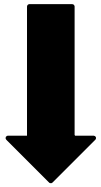
- Less severe forms in women than in men
- Estrogen **decreases** the incidence of colorectal cancer and decreases the progression of the disease
- **ERβ** : anti-tumor effect
  positive prognostic marker

MHT has a positive effect on colorectal cancer

Kidney Cancer

Reproductive factors and kidney cancer risk in 2 US cohort studies, 1993-2010.	Karami S, et al. (2013)
Reproductive, menstrual, and other hormone-related factors and risk of renal cell cancer.	Zucchetto A, et al. (2008)
Reproductive factors and risk of renal cell cancer: the Nurses' Health Study.	Lee JE, Hankinson SE, Cho E (2009)
Reproductive characteristics and risk of kidney cancer: IowaWomen's.	Molokwu JC, Prizment AE, Folsom AR (2007)
Risk factors for kidney cancer in New South Wales, Australia. II. Urologic disease, hypertension, obesity, and hormonal factors	McCredie M, Stewart JH (1992)

no relation between MHT and kidney cancer



Survivors of kidney cancer can be offered HRT

Gastric Cancer

ER positivity ---- poor outcome

Postoperative survival rates :

- ER+ vs. ER- cases : 15 % vs. 62%

Matsui M, Kojima O, Kawakami S, Uehara Y, Takahashi T(1992) The prognosis of patients with gastric cancer possessing sex hormone receptors. Surg Today 22(5):421–425

- ERα and ERβ isoforms : prognostic markers
  - ERα66 : poorly differentiated gastric cancer
  - ERα36 : more often in lymph node metastases
  - ERβ1 : associated with low grade tumors
- Androgen receptor : poor prognosis & progress free survival

MHT to gastric cancer survivors should be **avoided**

(especially in ER + or PR +)

Liver Cancer

Estrogen ----- antioxidant and anti-inflammatory effect

preventing **fibrosis** as a key step towards **liver carcinogenesis**

Estrogen ----- inhibit the progression of **HBV** infection

inhibiting hepatocellular carcinoma

HRT

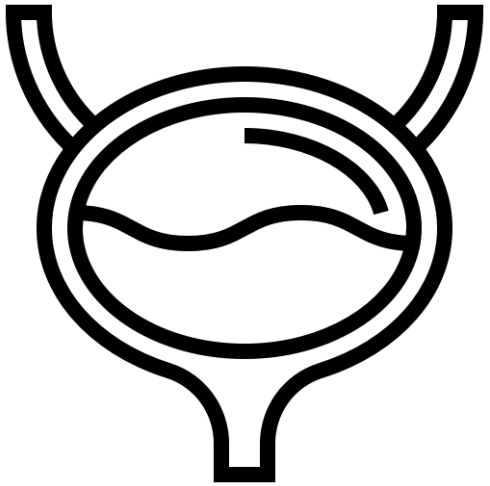
decreased incidence of hepatocellular cancer & better overall survival rate

Bladder Cancer

should be considered an **estrogen sensitive** tumor

- More aggressive in women then in males
- **Tamoxifen** in bladder cancer seems to be effective
- Former use of MHT was reported to **double the risk** of bladder cancer

Fernandez E, Gallus S, Bosetti C, Franceschi S, Negri E, La Vecchia C (2003) Hormone replacement therapy and cancer risk:
a systematic analysis from a network of case-control studies. Int J Cancer 105(3):408–412



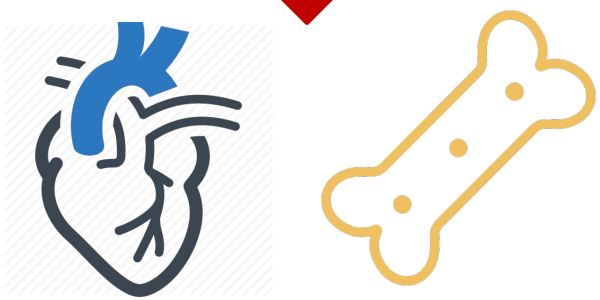
MHT should **not** be prescribed
(no direct clinical evidence is available)

Thyroid Cancer

- More common in women than in men
- **No** strong evidence of relation between MHT & thyroid cancer
- ER + or PR + ===== thyroid cancer : positive and negative associations

Survivors : thyroxine --------- subclinical hyperthyroidism

 suppress TSH decrease recurrence risk



V Thyroid cancer should **not** be considered a contraindication to MHT

Pancreatic Cancer

Meta-Analysis > Medicine (Baltimore). 2015 Feb;94(7):e177.
doi: 10.1097/MD.0000000000000177.

Relationship Between Female Hormonal and Menstrual Factors and Pancreatic Cancer: A Meta-Analysis of Observational Studies

Bo Tang [1], Jiannan Lv, Yang Li, Shengguang Yuan, Zhenran Wang, Songqing He

The risk of pancreatic cancer is **not** associated with exogenous hormone use (oral contraceptives or MHT) or menstrual factors (age at menarche, age at menopause, hysterectomy or oophorectomy).

V Pancreatic cancer should **not** be considered a contraindication to MHT

European Menopause and Andropause Society (EMAS) and International Gynecologic Cancer Society (IGCS) position statement on managing the menopause after gynecological cancer: focus on menopausal symptoms and osteoporosis

Margaret Rees[a,*], Roberto Angioli[b], Robert L. Coleman[c], Rosalind Glasspool[d], Francesco Plotti[b], Tommaso Simoncini[e], Corrado Terranova[b]

[a] *John Radcliffe Hospital, Oxford, UK*
[b] *Campus Bio-Medico University of Rome, Italy*
[c] *MD Anderson Cancer Center, Houston, TX, USA*
[d] *The Beatson West of Scotland, Cancer Centre, Glasgow, UK*
[e] *Department of Clinical and Experimental Medicine, University of Pisa, Italy*

low-grade, early-stage endometrial cancer : systemic or topical estrogens
more advanced disease : non-hormonal approaches

Uterine sarcomas : may be hormone dependent
estrogen and progesterone receptor testing
 to guide decisions

nonserous epithelial ovarian cancer and **germ cell tumors :**
not appear to be associated with harm and does not decrease overall or disease-free survival

serous and granulosa cell tumors : hormone dependence
 non-hormonal options

cervical, vaginal or vulvar cancer :
no evidence to contraindicate the use of systemic or topical menopausal hormone

Surgically induced menopause often leads to the immediate onset of vasomotor symptoms: **more severe** than after natural menopause

.

- Age
- tumor type and stage
- the use of anti-estrogen therapies (hormone dependent)
- concomitant morbidities

- Ex: women who are taking **aromatase inhibitors**, estrogen-based therapies are contraindicated
- vasomotor symptoms ：**selective serotonin reuptake inhibitor**s and **serotonin norepinephrine reuptake inhibitors**

Vulvovaginal atrophy :

- lubricants and bioadhesive moisturizers
- Laser therapy for vulvovaginal atrophy : larger, long-term studies are required

Osteoporosis :

- Bisphosphonates
- Calcium and vitamin D

Strategies need to be **holistic** and include maintaining a healthy weight, diet, exercise and lifestyle.

Endometrial Cancer

Low-grade, early-stage endometrial cancer : systemic or topical estrogens

More advanced disease : non-hormonal approaches

If **adjuvant treatment** is carried out, there should be a **6–12-month** waiting period before starting menopausal hormone therapy

Women with **Lynch syndrome :**
no long-term data regarding the safety of menopausal hormone therapy

Atypical endometrial hyperplasia Hysterectomy
 consider menopausal hormone therapy is reasonable (paucity of data)

Uterine sarcoma

Uterine sarcomas : may be **hormone dependent**

⬇

Estrogen and progesterone **receptor testing**

 to guide decisions

No clinical trial data are available to inform practice in women whose tumors are **steroid receptor negative** or who have smooth muscle tumors of **uncertain malignant potential**.

Ovarian Cancer

V **Nonserous epithelial ovarian cancer** and **germ cell tumors :**
not appear to be associated with harm and does not decrease overall or disease-free survival

X **Serous and granulosa cell tumors :** hormone dependence
 non-hormonal options

Borderline malignant tumors : paucity of data
with completely resected disease (**without invasive implants**)
 reasonable to consider HRT

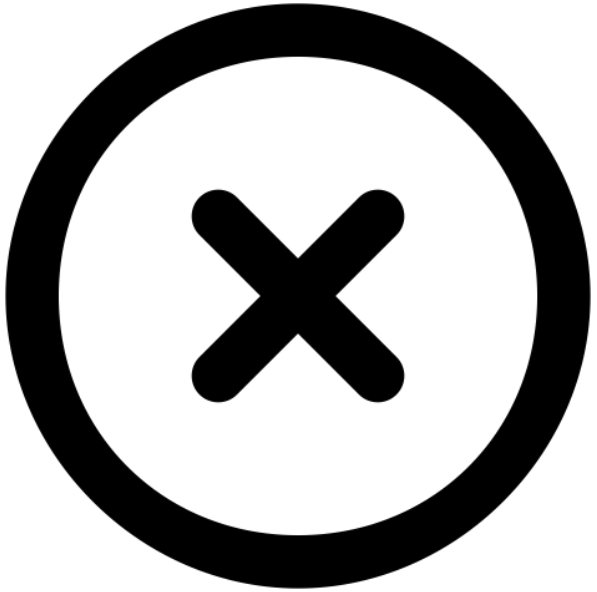
Cervical, vaginal and vulvar cancers

- **Cervical, vaginal or vulvar cancer :**
  no evidence to contraindicate the use of systemic or topical menopausal hormone

In women who have been treated with **radiotherapy**, rather than hysterectomy, for cervical cancer : E + **P**

advantageo
us

- Endometrial cancer type I
- Cervical adenocarcinoma
- Haematologic malignancies
- Local cutaneous malignant melanoma
- Colorectal cancer
- Hepatocellular cancer



contraindicated

- Breast cancer
- Endometrial stroma sarcoma
- Meningioma
- Glioma
- Hormone receptor positive gastric cancer
- Hormone receptor positive bladder cancer

- Individualized approach
- age, tumor type and stage, and concomitant therapies and morbidities
- Multidisciplinary team of health and allied health professionals
- Need for randomized trials and analysis of data registries to provide a stronger evidence base to inform practice

Thanks for your attention.