

Hormone Replacement Therapy in Cancer Survivors



Melissa Moffitt, MD
Assistant Professor of Oncology,
Department of Gynecology
Roswell Park Comprehensive Cancer Center

Activity Overview

This presentation is a review of the literature on estrogen use in female cancer survivors and previvors.

Target Audience

This activity is intended for primary care, gynecologist, and oncologists.

Instructions to Receive Credit

To receive credit, read the introductory CME material, watch the webcast, and complete the evaluation, attestation, and post-test, answering at least 70% of the post-test questions correctly.

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Melissa Moffitt, MD
Assistant Professor of Oncology
Department of Gynecology
Roswell Park Comprehensive Cancer Center
Buffalo, NY

Activity Planners

Ashley Snowden

Director, Physician and Corporate Relations
Roswell Park Comprehensive Cancer Center
Elm & Carlton Streets
Buffalo, NY

Danielle M. Fleischmann, CPC

Physician Relations Liaison
Roswell Park Cancer Institute
Elm & Carlton Streets
Buffalo, NY

Samantha Gordon, MS

Accreditation Manager
Med-IQ
Baltimore, MD

Amy Sison

Director of CME
Med-IQ
Baltimore, MD

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Upon completion, participants should be able to:

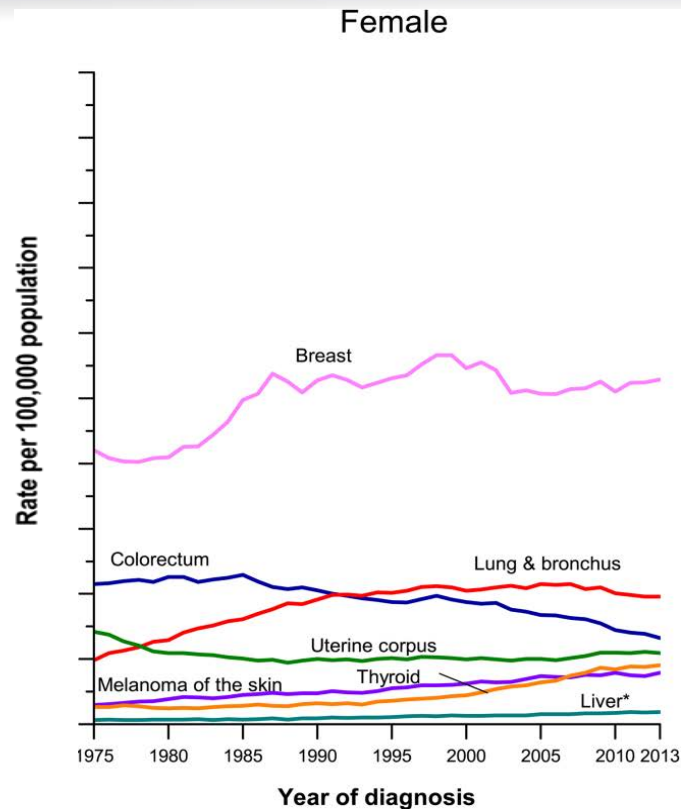
- Review the literature for estrogen use in the most common American women's malignancies as well as gynecologic malignancies

Outline

- Define Survivors and Previvors
- Review literature and guidelines for HRT in:
 - Previvors
 - Breast cancer survivors
 - Lung cancer survivors
 - Colon cancer survivors
 - Uterine cancer survivors
 - Ovarian cancer survivors
 - Cervical cancer survivors

WHO IS A CANCER SURVIVOR?


Cancer statistics, 2017



Cancer statistics, 2017

Estimated New Cases


Females



Breast	252,710	30%
Lung & bronchus	105,510	12%
Colon & rectum	64,010	8%
Uterine corpus	61,380	7%
Thyroid	42,470	5%
Melanoma of the skin	34,940	4%
Non-Hodgkin lymphoma	32,160	4%
Leukemia	25,840	3%
Pancreas	25,700	3%
Kidney & renal pelvis	23,380	3%
All Sites	852,630	100%

Estimated Deaths

Females



Lung & bronchus	71,280	25%
Breast	40,610	14%
Colon & rectum	23,110	8%
Pancreas	20,790	7%
Ovary	14,080	5%
Uterine corpus	10,920	4%
Leukemia	10,200	4%
Liver & intrahepatic bile duct	9,310	3%
Non-Hodgkin lymphoma	8,690	3%
Brain & other nervous system	7,080	3%
All Sites	282,500	100%

1990> 2014

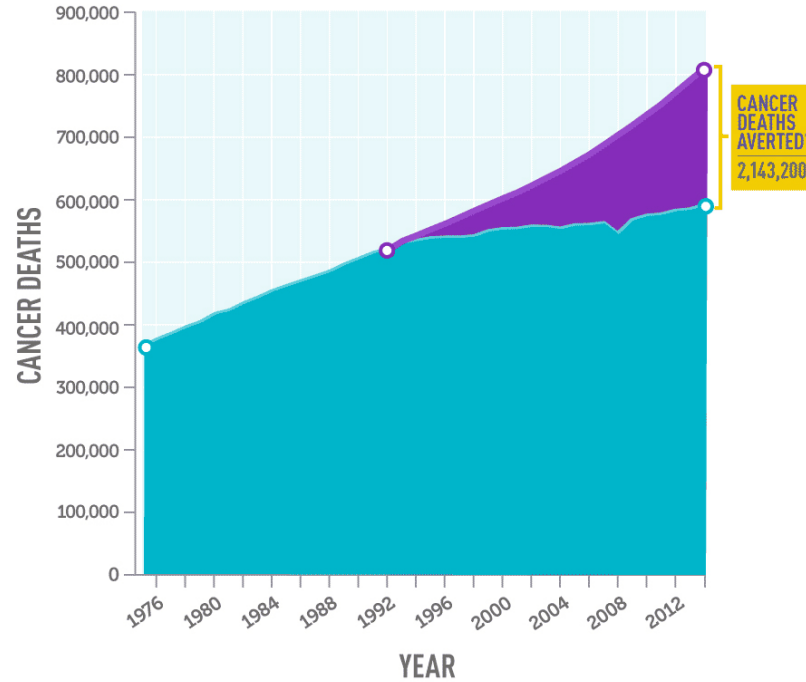
THE OVERALL CANCER DEATH RATE
IN THE UNITED STATES

FELL BY

↓ 25%

Source: SEER Cancer Statistics Review (CSR) 1975-2014
cancer.gov

Cancer Deaths Averted in Men & Women from 1991 to 2014



■ OBSERVED CANCER DEATHS

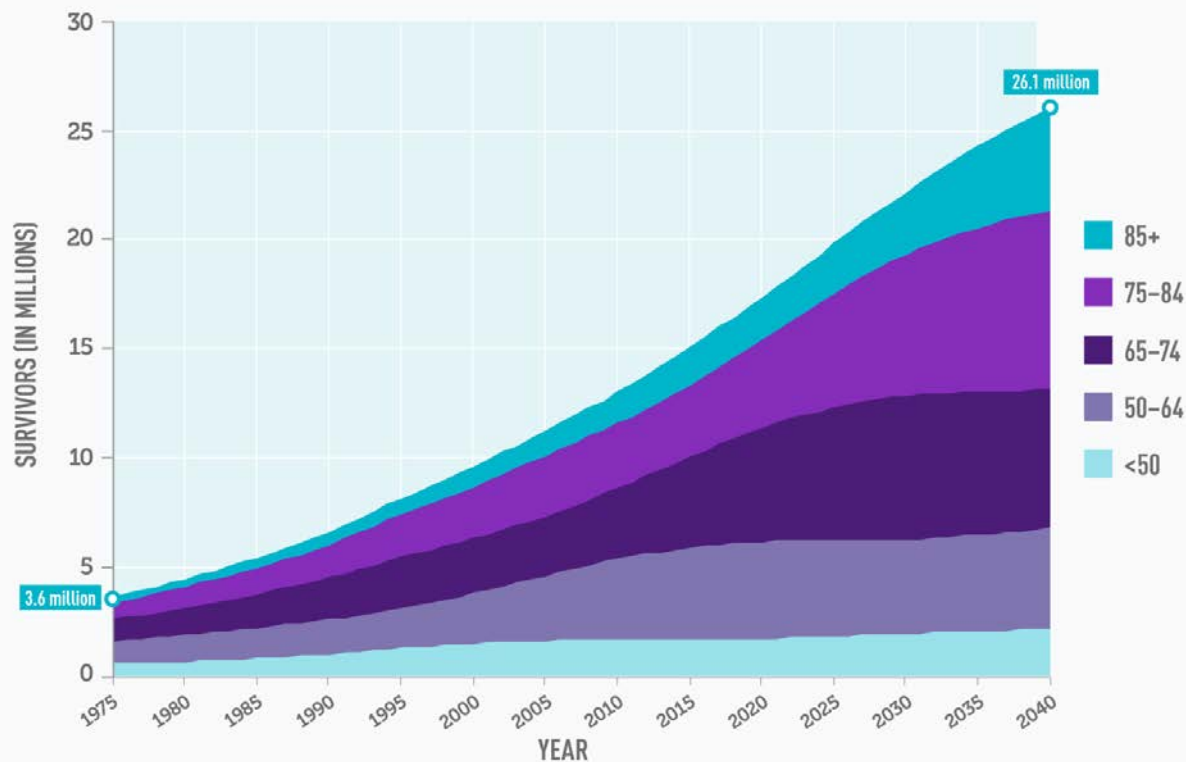
■ PROJECTED CANCER DEATHS

* Represents the difference between the number of observed cancer deaths and the number of projected cancer deaths that would have occurred had cancer death rates remained at their peak.

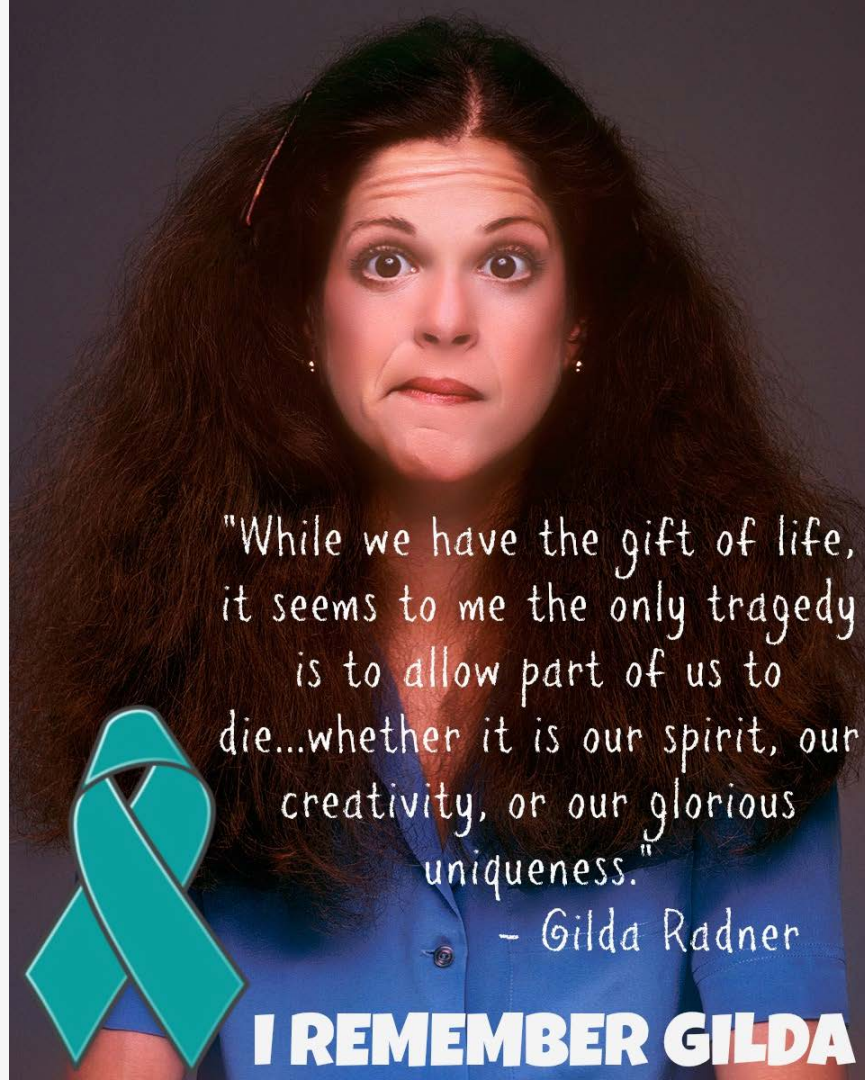
Adapted from: Siegel RL et al, Cancer Statistics, 2017. CA Cancer J Clin 2017;67:7-30. John Wiley & Sons, Inc. © 2017 American Cancer Society

cancer.gov

A Surge in Older Survivors: Estimated Number of U.S. Cancer Survivors by Age Group



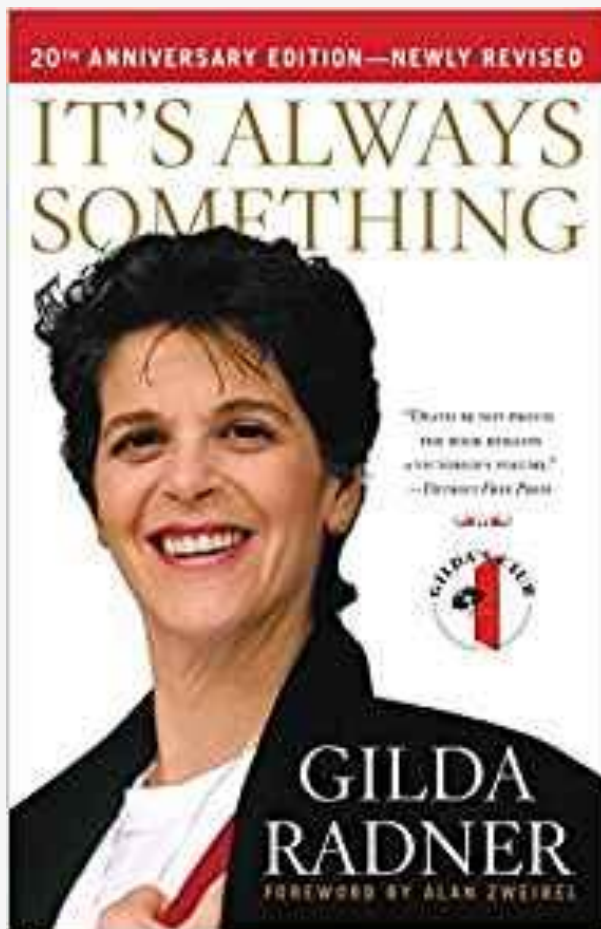
Source: Bluethmann SM et al. Cancer Epidemiol Biomarkers Prev. 2016 Jul;25(7):1029-36.
cancer.gov



"While we have the gift of life,
it seems to me the only tragedy
is to allow part of us to
die...whether it is our spirit, our
creativity, or our glorious
uniqueness."

- Gilda Radner

I REMEMBER GILDA



WHO IS A CANCER PREVIVOR?

Royalties to benefit *Gilda's Club* and
The Gilda Radner Familial Ovarian Cancer Registry



GILDA'S DISEASE

SHARING PERSONAL EXPERIENCES
AND A
MEDICAL PERSPECTIVE ON
OVARIAN CANCER

M. STEVEN PIVER, M.D.

One of the nation's leading ovarian oncologists:

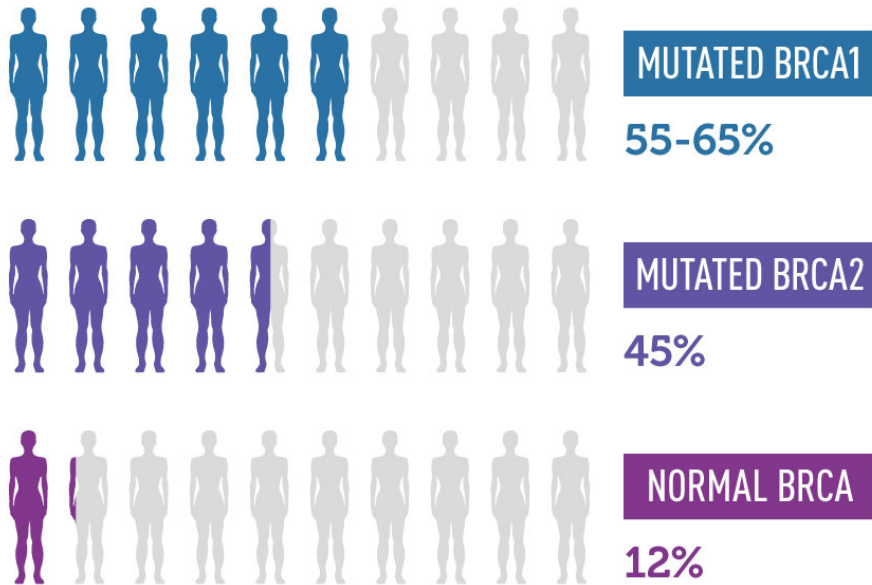
Roswell Park Cancer Institute

with

GENE WILDER

NATIONAL CANCER INSTITUTE CHANCES OF DEVELOPING BREAST CANCER BY AGE 70

Specific inherited mutations in the BRCA1 and BRCA2 genes increase the risk of breast and ovarian cancers. Testing for these mutations is usually recommended in women without breast cancer only when the person's individual or family history suggests the possible presence of a harmful mutation in BRCA1 or BRCA2. Testing is often recommended in younger women newly diagnosed with breast cancer because it can influence treatment decisions and have implications for their family members.





The New York Times

"MY CHANCES OF DEVELOPING
BREAST CANCER HAVE DROPPED
FROM 87 PERCENT TO UNDER
5 PERCENT."

Angelina Jolie in "My Medical Choice"
Published on May 14, 2013



ANGELINA JOLIE UNDERGOES DOUBLE MASTECTOMY
Reveals she carries gene that increases cancer risk



R CHANCES OF DEVELOPING BREAST CANCER HAVE DROPPED TO 5 PERCENT. | DOW ▲ 123.57

LYNCH SYNDROME FACTS

CANCER RISK WITH LYNCH SYNDROME

Lynch syndrome is the most commonly inherited colon cancer syndrome. People with Lynch syndrome have an increased lifetime risk of colon, uterine, ovary, gastric, small bowel, pancreas, brain and skin cancer.



THE NUMBER OF COLON CANCERS DUE TO LYNCH SYNDROME



1 IN 35

THE NUMBER OF AMERICANS WHO HAVE LYNCH SYNDROME

1 in 370

FAMILY COMMUNICATION OF GENETIC INFORMATION



CONNECT ON KINTALK

Kintalk allows family members to securely share their genetic information, connect with others from around the world who have Lynch syndrome and stay current with research in Lynch syndrome.



Previvors



Women with genetic predisposition to developing cancer

- BRCA 1
- BRCA 2
- Lynch
- BRIP 1, etc

Previvors



Undergo risk reducing BSO 35-55 depending on genetic mutation

- Reduces their risk of ovarian cancer down to near baseline
- Reduces all cause mortality
- Some studies show BSO reduces their risk of breast cancer by 50%
- Goal is to prolong life, decrease risk of life-shortening malignancy

Latrogenic menopause

- BSO at age < 45-50 without HRT increases all cause mortality
 - Osteoporosis, dyslipidemia, atherosclerosis, CVD, dementia
- Symptoms of surgical menopause are worse than those of natural menopause

Iatrogenic menopause

- HRT can prolong life, nearly resolved other increased risks and increase quality of life

HRT in menopause

- WHI:
 - 27347 women 50-79y
 - E vs no E x7y; EP vs no EP x5y
 - Follow x5 y
 - E and EP increased risks of CHD, VTE and breast cancer
 - EP vs no EP: CHD (HR 1.29, adjusted 95%CI 0.85-1.97), VTE (HR 2.11, 95% CI 1.26-3.55) and breast cancer (HR 1.26, 95% CI 0.83-1.92)
 - EP decreased risks of colon cancer (HR 0.63, adjusted 95% CI 0.32-1.24), hip fractures (HR 0.66, 95% CI 0.33-1.33), all cause mortality (HR 0.98, 95% CI 0.70-1.37)

HRT in menopause

- WHI:
 - 27347 women 50-79y
 - E vs no E x7y; EP vs no EP x5y
 - Follow x18 y
 - No increased cancer mortality (HR 1.03, 95% CI 0.95-1.12; 8.2% with hormone therapy vs 8% with placebo) or all-cause mortality (HR 0.99; 95%CI 0.94-1.03; 27.1% in hormone therapy vs 27.6% in placebo group)

Previvors



Multiple observational studies have shown no change in risk reduction for breast cancer in BSO pts using HRT



Multiple observational studies have shown no change in risk reduction for breast cancer in BSO pts using HRT

- T.R. Rebbeck, et al. Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: the PROSE study group. *J. Clin. Oncol.*, 23 (2005), pp. 7804-7810,
- A. Eisen, et al. Hormone therapy and the risk of breast cancer in BRCA1 mutation carriers. *J. Natl. Cancer Inst.*, 100 (2008), pp. 1361-1367,
- Domchek SM, et al. Mortality after bilateral salpingo-oophorectomy in BRCA1 and BRCA2 mutation carriers: a prospective cohort study. *Lancet Oncol.* 2006 Mar;7(3):223-229.

NAMS

Recommendations for
Previvors

- HRT does not increase risk of breast cancer in women with:
 - a family history of breast cancer
 - a genetic predisposition to developing breast cancer

NCCN

Recommendations for
Previvors

- Use HRT with caution in mutation carriers following BSO

ACOG

Recommendations for
Practitioners

- HRT is the most effective therapy for vasomotor symptoms
 - Increased risks of breast cancer and VTE
- Individualize care, consider non-hormonal options
- Local estrogen treatment for genitourinary syndrome of menopause

Previvors



Recommendations

- Use HRT for young women with
 - Risk reducing BSO
 - Genetic predisposition to developing ovarian/breast cancer
 - Continue until normal age of menopause



Photo credit: [HRTtp://www.clickforhope.net/blog/2016/10/21/sharis-story](http://www.clickforhope.net/blog/2016/10/21/sharis-story)

ACOG

Recommendations for
Breast Cancer Survivors

- HRT is the most effective therapy for vasomotor symptoms
 - Increased risks of breast cancer and VTE
- Individualize care, consider non-hormonal options
- Local estrogen treatment for genitourinary syndrome of menopause

ACOG

Recommendations for Breast Cancer Survivors

- Given conflicting evidence on safety, use non-hormonal options in women with hormone-positive breast cancer
- Non-hormonal treatment for genitourinary syndrome of menopause
 - Short term use of local estrogen is ok if other methods fail, pts should be counseled regarding risks

NAMS

Recommendations for
Breast Cancer Survivors

- HRT not generally advised.
 - Observational studies report both neutral effects and increased risk of breast cancer recurrence
- Local estrogen treatment can be used if non-hormonal options fail and in consultation with oncologist

NCCN

Recommendations for Survivors

- HRT is the most effective treatment for vasomotor symptoms
- Contraindicated in patients with hormonally dependent cancers
 - Use non-hormonal options
 - After consideration of the risks and benefits to the individual survivor, HRT could be used

Breast cancer



- HRT increases risk of breast cancer
- HRT users' breast cancer tends to be earlier stage and lower grade with improved survival rates
- Increased risk returns to baseline after discontinuation of HRT

Breast cancer



HRT after breast cancer diagnosis leads to lower mortality in multiple large observational studies

- O'Meara, Ellen S, et al. 2001. Hormone replacement therapy after a diagnosis of breast cancer in relation to recurrence and mortality. *J Natl Cancer Inst.* 93, 754-762
- Durna, E.M., et al. 2002. Hormone replacement therapy after a diagnosis of breast cancer: cancer recurrence and mortality. *Med J Aust.* 177,347-351.
- Brewster, Abenaa M., et al. 2007. Relationship between epidemiologic risk factors and breast cancer recurrence. *J. Clin. Oncol.* 25 (October 28) 4438-4444.

Breast cancer



Stockholm Trial

- 378 women with hx of breast cancer
- HRT vs no HRT, follow x10y
- No difference in recurrence (HR 1.3, 95% CI 0.9-1.9; $P = 0.18$)
- No difference in mortality (HR 1.1, 95% CI 0.6-2.0; $P = 0.83$)

Breast cancer



Hormonal Replacement After Breast Cancer – Is It Safe? (HABIT trial)

- 442 women with hx of breast cancer
- HRT vs no HRT, follow x4y
- Increased risk of recurrence in HR arm
 - HR 2.4, 95% CI 1.3-4.2; $P = 0.003$
- No difference in mortality ($P = 0.51$)

Breast cancer



Recommendations

- Use HRT for young women with
 - a hx of breast cancer
 - suffering from systemic menopausal symptoms
 - failed non-hormonal options
 - ***after consultation with oncologist***

Lung cancer



- Surgical menopause increases risk of lung cancer
- Earlier natural menopause increases risk of lung cancer

Lung cancer



- Synergistic effect between HRT and smoking

Lung cancer



In two studies

- HRT decreases survival in pts with lung cancer, particularly those over 60 years old with a history of smoking
 - Ganti--survival in patients with no HRT compared with patients who received HRT (79 vs 39 months, respectively; hazard ratio 1.97; 95% CI, 1.14 to 3.39)
 - Chlebowski--Deaths from lung cancer increased in the HRT group (73 vs 40 deaths, respectively, HR 1.71, 95% CI 1.16, 2.52, $P=0.01$)

Lung cancer



In two other studies

- There is no difference in outcomes noted
 - Huang—no difference in survival (hazard ratio, 1.09; 95% confidence interval, 0.82-1.44)
 - Ayeni--No difference in survival, median survival being 14 months for HRT recipients and 13 months for HRT non-recipients (log-rank $p = 0.6$).

Lung cancer



- Anti-estrogen endocrine therapy has not shown clinical benefit

Lung cancer



Recommendations

- Use HRT for young women with
 - a hx of lung cancer
 - suffering from systemic menopausal symptoms
 - failed non-hormonal options

Colon cancer



HRT decreases risk of colorectal cancer

- WHI: estrogen and progesterone replacement conferred risk reduction
 - 43 invasive colorectal cancers in hormone group vs 72 in the placebo group (HR 0.56, 95% CI 0.38-0.81; $P = 0.003$)

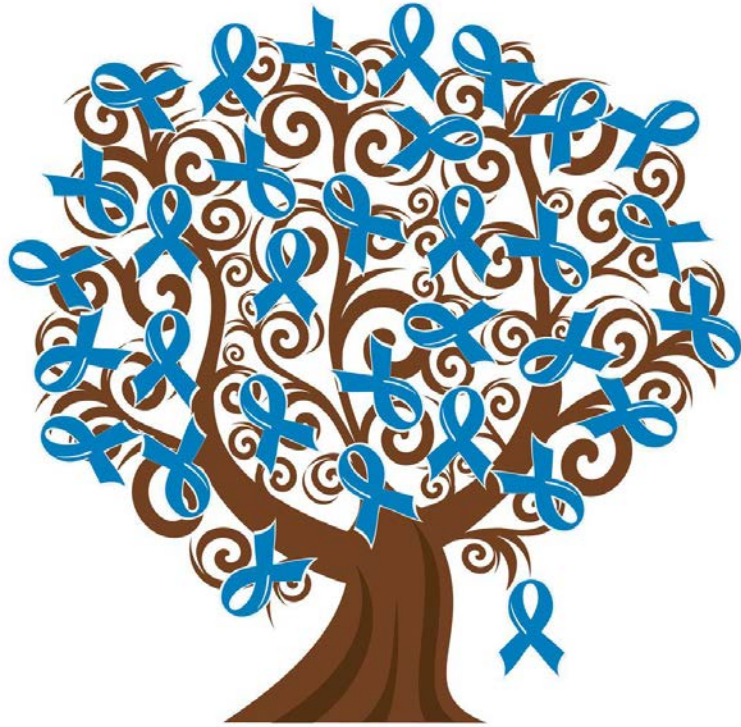
Colon cancer



HRT decreases risk of death from colorectal cancer

- WHI: estrogen and progesterone replacement conferred risk reduction
 - Death from colorectal cancer in HRT users vs never-users was lower (HR, 0.63, 95% CI 0.47-0.85; $P=0.002$)

Colon cancer



Recommendations

- Use HRT for young women with
 - a hx of colon cancer
 - suffering from systemic menopausal symptoms

Endometrial cancer



- Estrogen increases risk
- WHI: continuous estrogen + progestogen decrease risk of endometrial cancer
 - Fewer endometrial cancers in the HRT vs placebo group (66 vs 95 patient cases; HR = 0.65, 95% CI 0.48-0.89; $P = 0.007$)

Endometrial cancer



RCT

- 1236 women with stage I, II eac
- HRT or no HRT (placebo)
- Follow x36 mos
- Closed early due to WHI
- Low recurrence rate in both arms (2.1% vs 1.9 NS)

Endometrial cancer



Meta-analysis

- 896 endometrial cancer survivors using HRT and 1079 non users
- No increased risk of recurrence in survivors using HRT vs control group (OR: 0.53; 95% CI 0.3-0.96)

Endometrial cancer



Recommendations

- Use HRT for young women with
 - Endometrial cancer
 - suffering from systemic menopausal symptoms
 - failed non-hormonal options

Uterine sarcomas



Recommendations

Use HRT for young women with

- Leiomyosarcoma, endometrial stromal sarcoma
- suffering from systemic menopausal symptoms
- failed non-hormonal options
- ***after consultation with oncologist***

Ovarian cancer



- WHI showed no increase incidence
 - HR for invasive ovarian cancer in women assigned to HRT vs placebo (HR 1.58; 95% CI 0.77-3.24)
- Meta-analysis of 52 studies found increased risk (relative risk of 1.37; 95% CI 1.29-1.46; $P<0.0001$)

Ovarian cancer



Multiple studies on HRT after ovarian cancer diagnosis show:

- No impact or improved survival
- Improved quality of life

Ovarian cancer



RCT

- 139 with ovarian cancer under 59y
 - HRT or no HRT starting 6 wx postop
 - Follow x48 mos
- No impact on length of remission or overall survival ($P = 0.354$)

Ovarian cancer



Meta-analysis

419 ovarian cancer survivors
using HRT and 1029 non-users

- Does not impact prognosis
- Improves quality of life

Ovarian cancer



Meta-analysis

419 ovarian cancer survivors
using HRT and 1029 non-users

- Does not impact prognosis
- Improves quality of life

Ovarian cancer



LMP?

- HRT before or after diagnosis had no impact on overall survival
 - Before diagnosis (multivariate HR = 0.83, 95% CI 0.65-1.08)
 - After diagnosis (multivariate HR 0.57, 95% CI 0.42-0.78)

Ovarian cancer



Recommendations

Use HRT for young women with

- high grade serous carcinoma
- LMP
- malignant germ cell tumor
- suffering from systemic menopausal symptoms

Ovarian cancer



Recommendations

Use HRT for young women with

- Low grade serous carcinoma
- endometrioid or clear cell ovarian cancer
- sex cord stromal tumors
- suffering from systemic menopausal symptoms
- failed non-hormonal options
- ***after consultation with oncologist***

Cervical cancer



- 70% diagnosed in women under 55y
- Estrogen may be associated with increased risk of cervical adenocarcinoma
 - Compared to never users, relative risk of cervical cancer increased with increasing duration of use—for 10 or more years $RR = 2.2$ (95% CI 1.9-2.4)

Cervical cancer



RCT

- 120 cervical cancer survivors younger than 45y
- 80 received HRT, 40 no HRT
 - No difference in recurrence rates (20% and 32% NS)
 - No difference in survival rates (80% and 65%, insignificant difference)

Cervical cancer



Recommendations

- Use HRT for young women with
 - a hx of cervical cancer
 - suffering from systemic menopausal symptoms
 - Continue until normal age of menopause

Contrast

- Alcohol increases risk of breast cancer recurrence
 - HR 1.35, 95% CI 1.00-1.83

Physician prescribing

88% of German physicians preferred non-hormonal treatment for endometrial cancer pts suffering from menopausal symptoms

75% believed HRT to be contraindicated in high grade EAC

Physician prescribing

Only 63% of Swedish gynecologists would offer HRT to young ovarian cancer patients with iatrogenic menopause, while 92% of gyn oncologist would offer it.

Key Points

- Very little evidence that HRT is harmful to cancer survivors
- Lots of evidence that HRT is helpful in cancer survivors and previvors

In conclusion

- Focus on the patient as a whole
 - Quality of life
 - Length of life

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