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Prospects and Consequences of Hormone Replacement Therapy in Cancers A Review

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ABSTRACT
Hormone replacement therapy (estrogens with or without progestogens) is widely used medication therapy worldwide for alleviating post menopausal symptoms. The association of Hormone replacement therapy (HRT) and risk of cancers leads to many studies. A lot of controversial results regarding the risk of cancers arises which leads to many questions that are still unanswered and can be cleared by further extensive research. There is considerable uncertainty among general practitioners to balance the beneficial and harmful effects of long term HRT particularly regarding the risk of cancers (breast, ovarian, endometrial, colorectal, lung cancers, lymphoma's and leukaemia's). The goal of HRT is not only to normalize the follicle stimulating hormone value, but rather to use the minimum effective dosage to suppress vasomotor reactions, treat urogenital atrophy, prevent trabecular and cortical bone loss, and reduce cardiac risk. Use of HRT should be individualized for risks and benefits of each patient that is being taken into consideration.

Keywords: Hormone replacement therapy, menopausal symptoms, cancers, risks and benefits.

INTRODUCTION

Use of postmenopausal hormone replacement therapy (HRT) has fluctuated over the past 50 years due to changes in the perception of its risks and benefits. HRT refers to the use of estrogens or its analogues, with or without progestogen, primarily for the treatment of menopausal symptoms. [1] Although first approved in the 1940s; unopposed estrogen replacement therapy became widely used in the 1960s. Its application declined in the 1970s after the publication of reports of an association between estrogens use and risk of cancers. In the 1980's introduction of combined estrogen and progestin hormones help HRT regain its popularity owing to its less adverse effects and is being used currently in the clinical practice. [2] Currently, two hormone replacement regimens-a cyclic and a continuous regimen-are in widespread clinical use. [3] Surgical menopause and premature menopause without estrogen replacement are significant risk factors for coronary artery disease, diabetes (including
hypertriglyceridemia), family history, and advancing age. Likewise, natural menopause may be a risk factor for Postmenopausal
Estrogen/Progestin Intervention Trial (PEPI) demonstrated that HRT significantly lowered LDL- cholesterol levels even with the addition of medroxyprogesterone acetate (MPA) or micronized progesterone. [4] There is considerable uncertainty among general practitioners to balance the beneficial and harmful effects of hormone replacement therapy in the long term, particularly relating to its use for prevention of osteoporosis and cardiovascular disease. [5] The goal of HRT is not only to normalize the follicle stimulating hormone value, but also to use the minimum effective dosage to suppress vasomotor reactions, treat urogenital atrophy, prevent trabecular and cortical bone loss, and reduce cardiac risk.

Although HRT is helpful in postmenopausal women, its use for primary prevention of chronic diseases in women without menopausal symptoms is unjustified. [6] The largest HRT randomised clinical trial, the women's health initiative, indicated that long term use of oestrogen plus progestin HRT not only was associated with increased risk of cancer but, contrary to expectations, did not decrease, and may have increased, risk of cardiovascular disease. [7] Use of HRT should be individualized, the risks and benefits of HRT for each patient being taken into consideration. [8]

Impact of HRT on Cancers

Hormones may act to promote the late stages of carcinogenesis among postmenopausal women and to facilitate the proliferation of malignant cells. The effect of HRT on various neoplastic sites are summarised hereafter.

Breast cancer

The effect of estrogen replacement on the breast is controversial. Estrogen is a trophic growth hormone and

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therefore may promote the growth of a pre-existing breast cancer (BC). [4] The concern that postmenopausal HRT may cause cancer of the breast has lead to an enormous volume of research in epidemiology, endocrinology and tumour cell biology. The epidemiology has become extremely sophisticated because the anticipated effect is small and there are several confounding factors. The consensus today is that long-term HRT (>10 years) is associated with an increase in the risk of breast cancer which, on average, is equivalent to delaying menopause for the same period of time that the patient is on treatment. The risk is related to endogenous and exogenous oestrogen levels. [9-10]

A meta-analysis of major breast cancer studies did not show an increased risk of breast cancer in women who had ever received estrogen replacement therapy compared with those who had not. Women can certainly be assured of the safety of short-term HRT (< 5 years). Long-term HRT may slightly increase the risk of breast cancer, but the data suggesting this association are not compelling or consistent. Nevertheless, this is an important epidemiologic issue because the studies are recommending long-term HRT for more women.[3]Meta-analysis from the Collaborative Group on Hormonal Factors in Breast Cancer (CGHFBC) provides substantial evidence that HRT increases the risk of breast cancer. [11-12] It is evident that HRT-associated overall risk of Breast cancer. There is evidence that relative risks for BC by HRT particularly in EPT than in ET, have been increasing in recent years. [13]

However, HRT may not increase the risk of ductal and lobular carcinomas. This conclusion is borne out by the Iowa and several other studies. [14] Researchers have suggested that users of hormone replacement who get BC develop tumours with "favourable" pathological features compared with non-users and showed that grade 1 node negative tumours were more common in the users. [15] Despite a better prognosis in women diagnosed with BC (case fatality), its mortality is increased in users of HRT as compared with non users.

However, further studies with a longer follow-up time are needed to confirm these findings. The risk of developing both favourable and non-favourable prognostic types of BC is increased 2 to 4 fold in current users of HRT as compared with never/past users, except for hormone receptor negative tumours. [16] In a study it was showed that a monotonic gradient of increasing risk for interval cancers was found for each 25% increase in mammographic density. [17] Ross *et al.* reported that women using estrogen and progestin, compared with nonusers, have a 10% higher breast cancer risk for each 5 years of hormone use and women using continuous estrogen and progestin have no increased risk of breast cancer, while women using cyclic estrogen and progestin have a 38% higher risk with same duration. For women on ET, they find no increase in risk for the first 15 years of use and the adverse effect of HRT on the breast may outweigh the beneficial effect on the endometrium, at least in terms of cancer morbidity and mortality. [18]

A Swedish study reported that after 10 years of HRT use, the yearly BC risk was 3% with estrogens alone and 7% for estrogen plus a progestin. The risks of HRT taken for more than 10 years (estrogen alone or estrogen plus progestin) were not increased for those with a BMI more than 27 kg/m^2 as opposed to those with BMIs of 22-27 $kg/m^2$and less than 22 kg/m^2. [12] An increased rate of breast density was shown in women taking ET in PEPI trial. [19] In a survey 33% were found to be currently using HRT and 14% were found to be past users and concluded that women using HRT are more likely to experience reduced sensitivity and specificity of BC screening, compared with women not using HRT. [2] Bush *et al.* reviewed 65 epidemiologic studies, in 80% of the studies, the relative risk of BC in HRT users was 1.0, i.e., HRT was not associated with BC because there was no consensus in the literature regarding BC risk from HRT use, and that the variability in results could be due to sampling error from multiple repeated studies.

As for mortality, the Nurse's Health Study followed 91,523 women for 17 years and found that current HRT users had a 37% lower risk of death than women who had never taken HRT. The risk was still 20% lower even in those using HRT for more than 10 years. Among women with a first-degree relative with BC, the risk of death was 35% lower in HRT users than in nonusers. [20] Based on the results of the WHI trial, HRT use for 1 year in 10,000 healthy postmenopausal women is associated with 7 times more coronary artery disease (CAD) events, 8 times more invasive breast cancers, strokes, pulmonary emboli, 6 fewer colorectal cancers and 5 fewer hip fractures. [7] Both ET and EPT were associated with BC risks with the magnitude of increase varying according to body mass and clinical characteristics of the tumors. [21] The tumours of women with BC who used HRT have some better prognostic factors than those of women who have not used HRT. [22-23] Clinical studies evaluating HRT and hormonal contraceptives support the hypothesis that in combination with oestrogen, exogenous progestogens exert a mutagenic effect on the breast. For women using HRT and combined oral contraceptives (COCs), however, the risk of BC is small and any probable impact on long-term survival is likely to be very small. [24]

A study on 462 women with disease-associated germ line *BRCA1/2* mutations study was conducted and the data suggested that short-term HRT use does not negate the protective effect of bilateral prophylactic oophorectomy (BPO) on subsequent BC risk in *BRCA1/2* mutation carriers. [25] Using data from the Melbourne Collaborative Cohort Study authors recommend that analysis investigating the association between HRT and should present the results in two ways: excluding women with age at menopause missing and including the women using multiple imputations. For both methods, estimates of risk with and without the adjustment of age at menopause should be given. [26] The timing of exogenous hormone use is important. Women who used hormones before menopause had elevated risks, but the harmful effects began to decline with age after menopause. [27] The randomized HABITS study, which compared HRT for menopausal symptoms with best management without hormones among women with previously treated BC was stopped early due to suspicions of an increased risk of new BC events following HRT. After extended follow-up, there was a clinically and statistically significant increased risk of a new BC event in survivors who took HRT. [28] Evidence that long-term use of HRT is associated with increased risk of BC and decreased risk of colorectal cancer is supplied from a southern European population and findings which indicates that transdermal therapy might have lower effect than oral therapy in increasing BC risk. [29] Current hormone therapy use was associated with more favourable breast cancer characteristics for ductal tumours but had less effect

on prognostic characteristics in women with lobular tumors. [30]

It is evident from a study that, there was a link between declines in the use of HRT and BC incidence, in the absence of any change in mammography rates. [31-32] Whether the observed decline in BC incidence will be sustained (preliminary data from the USA suggests it might not be) and whether BC mortality will also decline, are important questions that currently remain unanswered. [33]

The three studies: collaborative reanalysis (CR), the Women's Health Initiative (WHI) and the Million Women Study (MWS) were evaluated for evidence of causality between HRT and BC showed that the studies did not adequately satisfy the criteria of time order, bias, confounding, statistical stability and strength of association, dose/duration response, internal consistency, external consistency or biological plausibility. Thus, HRT may or may not increase the risk of breast cancer, but the studies did not establish that it does. [34-37]

Endometrial cancer

There is extensive epidemiologic evidence that postmenopausal estrogen therapy substantially increases the risk for endometrial cancer. Since 1970, more than 30 epidemiologic studies have documented the strong association between unopposed estrogen use and increased endometrial cancer risk. Risk is increased with increasing dose of estrogen and particularly with long-term use, such that women with more than 10 years of unopposed use have about a 10-fold increased risk of endometrial cancer.

As showed in PEPI trial, estrogen increased endometrial hyperplasia at rate of 10% per year. [19] Pike *et al.* presented data which showed that both the cyclic and continuous hormone replacement regimens are associated with a much lower risk of endometrial cancer than estrogen used alone. The sharp distinction between the effects of less than 10 days, 10 days or more of progestin use in sequential EPRT suggests that the extent of endometrial sloughing may play a critical role in determining endometrial cancer risk. [38-39] A population based case-control study showed that among women with long-term use of ERT or combined HRT, the risk of endometrial cancer may be associated with functionally relevant genotypes that regulate steroid hormone sulfation. [40-41]

Cancer prevention study II nutrition cohort was conducted and showed that greater BMI increased risk of both ''type I'' (classic estrogen pathway) and ''type II'' (serous, clear cell, and all other high grade) cancers. [42] Prospective studies of BMI and incident endometrial cancer supported the hypothesis that hyperestrogenia is an important mechanism underlying the BMI-endometrial cancer association, whilst the presence of residual risk in HRT users points to the role of additional systems. [43]

Ovarian cancer

Knowledge about the impact of menopausal hormone therapy (MHT) on the risk of ovarian cancer (OvC) is insufficient, and studies are inconsistent. Mortality from OvC ranks highest among cancer sites in female reproductive organs. A meta-analysis showed that the risk of OvC is increased 1.28-fold by ET and 1.11-fold by EPT with a suggestion of greater risks with ET. ET as well as EPT, are risk factors for OvC. [44]

A nationwide case–control study showed ever users of ERT and sequentially added progestins (HRTsp) but not continuously added progestins (HRTcp) may be at increased risk of epithelial ovarian cancer (EOC). [45] A population-based study showed that long term used of unopposed estrogen is associated with increased risk of epithelial ovarian cancer but not by EPT. [46] Women taking HRT had increased risks of both serous tumours and endometrioid tumours but decreased risk of mucinous tumors. [47]

Colorectal cancer

The issue of colon cancer is also of interest, as the mortality is higher than that for BC, and there seems to be no public discussion on the potential benefit of HRT on this. [48] Of 12 case-control studies, five reported significant risk reductions among ever-users of HRT, while two investigations showed moderate, non-significant inverse associations and none showed a significant increased risk. Two recent meta-analyses showed a 20% reduction in the risk of colon cancer among current users.

Although these epidemiological observations are consistent, surveillance bias may account for part of the association. [49] Long-term use of HRT was related to decreasing risk of colon and rectal cancers. [50] More than 10 observational studies have showed reduced risk of colon cancer in women taking HRT. [19] Studies showed that estrogen plus progestin use, especially sequential regimen was associated with the largest overall reduction of colorectal cancer risk. [51-52] A study among 56,864 premenopausal or postmenopausal participants under 80 years of age with no prior colorectal cancer showed that Baseline-recent hormone therapy users were at 36% lower risk for colon cancer versus baseline-never users. [53]

Lung cancer

HRT use was associated with an overall reduced risk of 34% of lung cancer, after adjusting for age, ethnicity, smoking status, education, body mass index, and menopausal status. The use of ERT alone was associated with a 35% reduction in lung cancer risk and the use of EPRT was associated with a 39% reduction in lung cancer risk. Biological mechanism to explain these findings showed that HRT use was associated with lower insulin-like growth factor I levels for both cases and controls compared with non-HRT users. [54]

A prospective cohort on peri- and postmenopausal women aged 50 to 76 years showed that the use of EPT increased the risk of incident lung cancer in a duration-dependent manner, with an approximate 50% increased risk for use of 10 years or longer. These findings may be helpful for informing women of their risk of developing lung cancer and delineating important pathways involved in hormone metabolism and lung cancer. [55]

Others

A study was conducted to evaluate whether the use of HRT is associated with non-Hodgkin lymphoma (NHL) or chronic lymphocytic leukaemia (CLL). Compared with never users of HRT at baseline, current users were at increased risk of NHL after adjustment for age and other confounding factors and data also suggested that HRT is a risk factor for follicular NHL but not for diffuse or small lymphocyte NHL or CLL. [56]

For most menopausal women, the benefits of HRT outweigh the risks, despite the fears aroused by the unproven link to cancers. The role of HRT in breast, endometrial and ovarian cancers were controversial because the results of different studies vary. Some studies agreed with the risk and some don't, depending on confounding factors. The biological role

of HRT in colorectal and lung cancers remains understudied, and only extensive research can yield new insights into the mechanisms underlying protective effects of HRT. The currently available information from epidemiological studies concerning the association between HRT use and cancer occurrence is controversial and leaves many questions unanswered. Much future epidemiological study on cancers should require the pathological examination of the specimens so that a correlation between epidemiology and morphology can be made. It needs to address the phenomenon that increases or decreases the risk of cancers with HRT. Further genotype studies which identify populations at increased risk are advisable. A Perceived quality of life should be taken into account when deciding on HRT. As a role of physicians and health care providers are to clearly inform patients about both the benefits and the risks of HRT, taking into account patients' preferences and concerns. The above studies give us cautious optimism about prescribing hormone replacement therapy but the risk of cancers is still unjustified.

REFERENCES

1. Banks E. Hormone replacement therapy and the sensitivity and specificity of breast cancer screening: a review. J Med Screen 2001; 8:29-35.
2. Brett KM, Madans JH. Use of Postmenopausal Hormone Replacement Therapy: Estimates from a Nationally Representative Cohort Study. Am J Epidemiol 1997; 145:536-45.
3. Grady D, Ernster VL. Hormone Replacement Therapy and Endometrial Cancer: Are Current Regimens Safe? Journal of the National Cancer Institute 1997; 89(15):1088-1089.
4. Thacker HL. Current issues in menopausal hormone replacement therapy. Cleveland Clinic Journal of Medicine 1996; 63(6):344-353.
5. Wilkes HC, Meade TW. Hormone replacement therapy in general practice: a survey of doctors in the MRC's general practice research framework. BMJ 1991; 302:1317-20.
6. Minelli C, Abrams KR, Sutton AJ, Cooper NJ. Benefits and harms associated with hormone replacement therapy: clinical decision analysis. BMJ 2004; 328:1-6
7. Krieger *et al.* Hormone replacement therapy, cancer, controversies, and women's health: historical, epidemiological, biological, clinical, and advocacy perspectives. J Epidemiol Community Health 2005; 59:740-748.
8. Humphries KH, Gill S. Risks and benefits of hormone replacement therapy: The evidence speaks. CMAJ 2003; 168(8):1001-10.
9. Jacobs HS. Hormone replacement therapy and breast Cancer. Endocrine-Related Cancer 2000; 7; 53-61.
10. McCullough *et al*. Body Mass and Endometrial Cancer Risk by Hormone Replacement Therapy and Cancer Subtype. Cancer Epidemiol Biomarkers Prev 2008; 17(1):73-79.
11. Colditz GA. Relationship between Estrogen Levels, Use of Hormone Replacement Therapy, and Breast Cancer. J Natl Cancer Inst 1998; 90:814–23.
12. Santen RJ et al. Risk of Breast Cancer with Progestins in Combination with Estrogen as Hormone Replacement Therapy. JCE & M 2001; 86(1):16-23.
13. Greiser CM, Greiser EM, Dören M. Menopausal hormone therapy and risk of breast cancer:a meta-analysis of epidemiological studies and randomizedcontrolled trials. Human Reproduction Update 2005; 11(6):561-573.
14. Mayer ME. Hormone replacement and breast cancer: implications of the iowa women's health study. Cleveland Clinic Journal of Medicine 1999; 66(10): 608-613.
15. Stallard S, Litherland JC, Cordiner CM, Dobson HM, George WD, Mallon EA, Hole D. Effect of hormone replacement therapy on the pathological stage of breast cancer: population based, cross sectional study. BMJ 2000; 320:348-9.
16. Stahlberg *et al.* Breast cancer incidence, case-fatality and breast cancer mortality in Danish women using hormone replacement therapy- a prospective observational study. International Journal of Epidemiology 2005; 34:931-935.
17. Chiarelli *et al.* Influence of Patterns of Hormone Replacement Therapy Use and Mammographic Density on Breast Cancer Detection, Cancer Epidemiol Biomarkers Prev 2006; 15(10):1856-62.
18. Ross RK, Paganini-Hill A, Wan PC, Pike MC. Effect of Hormone Replacement Therapy on Breast Cancer Risk: Estrogen Versus Estrogen Plus Progestin. J Natl Cancer Inst 2000; 92:328–32.
19. Barrett-connor E, Stuenkel CA. Hormone replacement therapy-risks and benefits, Int.J.epidemiology 2001; 30:423-426.
20. Batur P, Thacker HL, Moore HCF. Discussing breast cancer and hormone replacement therapy with women. Cleveland Clinic Journal of Medicine 2002; 69(11):838-848.
21. Brinton *et al.* Menopausal Hormone Therapy and Breast Cancer Risk in the NIH-AARP Diet and Health Study Cohort. Cancer Epidemiol Biomarkers Prev 2008; 17(11):3150–60.
22. Ursin *et al.* Does Menopausal Hormone Replacement Therapy Interact With Known Factors to Increase Risk of Breast Cancer? J Clin Oncol 2002; 20:699-706.
23. Daling *et al.* Association of Regimens of Hormone Replacement Therapy to Prognostic Factors among Women Diagnosed with Breast Cancer Aged 50-64 Years. Cancer Epidemiol Biomarkers Prev 2003; 12:1175-1181.
24. Marsden J, A'Hern R. Progestogens and breast cancer risk: the role of hormonal contraceptives and hormone replacement therapy. Journal of Family Planning and Reproductive Health Care 2003; 29(4): 185-187.
25. 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 2005, 23:7804-7810.
26. Simpson JA, English DR, MacInnis RJ, Gertig DM, Hopper JL, Giles GG. A comparison of different methods for including 'age at menopause' in analyses of the association between hormone replacement therapy use and breast cancer. J Fam Plann Reprod Health Care 2007; 33(1): 11-16.
27. Shantakumar *et al.* Age and Menopausal Effects of Hormonal Birth Control and Hormone Replacement Therapy in Relation to Breast Cancer Risk. Am J Epidemiol 2007; 165:1187-1198.
28. Holmberg *et al.* Increased Risk of Recurrence after Hormone Replacement Therapy in Breast Cancer Survivors. J Natl Cancer Inst 2008; 100: 475-482.
29. Corrao *et al.* Menopause hormone replacement therapy and cancer risk: an Italian record linkage investigation. Annals of Oncology 2008; 19: 150-155.
30. Slanger *et al.* Menopausal Hormone Therapy and Risk of Clinical Breast Cancer Subtypes. Cancer Epidemiol Biomarkers Prev 2009; 18(4):1188–96.
31. Renard F, Vankrunkelsven P, Van Eycken L, Henau K, Boniol M, Autier P. Decline in breast cancer incidence in the Flemish region of Belgium after a decline in hormonal replacement therapy. Annals of Oncology 2010; 21: 2356-2360.
32. De P, Ineke Neutel C, Olivotto I, Morrison H. Breast Cancer Incidence and Hormone Replacement Therapy in Canada. J Natl Cancer Inst 2010; 102:1489-1495.
33. Zbuk K, Anand SS. Declining incidence of breast cancer after decreased use of hormone-replacement therapy: magnitude and time lags in different countries. J Epidemiol Community Health 2012; 66:1-7.
34. Shapiro S, Farmer RDT, Seaman H, Stevenson JC, Mueck AO. Does hormone replacement therapy cause breast cancer? An application of causal principles to three studies, Part 1. The Collaborative Reanalysis. J Fam Plann Reprod Health Care 2011; 37:103-109.
35. Shapiro S, Farmer RDT, Seaman H, Stevenson JC, Mueck AO. Does hormone replacement therapy cause breast cancer? An application of causal principles to three studies, Part 2. The Women's Health Initiative: estrogen plus progestogen. J Fam Plann Reprod Health Care 2011; 37:103-109.
36. Shapiro S, Farmer RDT, Seaman H, Stevenson JC, Mueck AO. Does hormone replacement therapy cause breast cancer? An application of causal principles to three studies, Part 3. The Women's Health Initiative: unopposed estrogen. J Fam Plann Reprod Health Care 2011; 37:103-109.
37. Shapiro S, Farmer RDT, Stevenson JC, Burger HG, Mueck AO. Does hormone replacement therapy cause breast cancer? An application of causal principles to three studies, does hormone replacement therapy cause breast cancer? An application of causal principles to three studies, Part 4. The Million Women Study. J Fam Plann Reprod Health Care 2012; 38:102-109.

38. Pike *et al.* Estrogen–Progestin Replacement Therapy and Endometrial Cancer. J Natl Cancer Inst 1997; 89:1110-6.
39. Strom *et al.* Case-Control Study of Postmenopausal Hormone Replacement Therapy and Endometrial Cancer. Am J Epidemiol 2006; 164:775-786.
40. Rebbeck *et al.* Estrogen Sulfation Genes, Hormone Replacement Therapy, and Endometrial Cancer Risk J Natl Cancer Inst 2006; 98: 1311 – 20.
41. Razavi P, Pike MC, Horn-Ross PL, Templeman C, Bernstein L, Ursin G. Long-term Postmenopausal Hormone Therapy and Endometrial Cancer. Cancer Epidemiol Biomarkers Prev 2010; 19(2); 475-83.
42. McCullough *et al*. Body Mass and Endometrial Cancer Risk by Hormone Replacement Therapy and Cancer Subtype. Cancer Epidemiol Biomarkers Prev 2008; 17(1):73-79.
43. Crosbie EJ, Zwahlen M, Kitchener HC, Egger M, Renehan AG. Body Mass Index, Hormone Replacement Therapy, and Endometrial Cancer Risk: A Meta-Analysis. Cancer Epidemiol Biomarkers Prev 2010; 19(12): 3119-30.
44. Greiser CM, Greiser EM, Do¨ren M. Menopausal hormone therapy and risk of ovarian cancer: systematic review and meta-analysis. Human Reproduction Update 2007; 13(5):453-463.
45. Riman T, Dickman PW, Nilsson S, Correia N, Nordlinder H, Magnusson CM, Weiderpass E. Hormone Replacement Therapy and the Risk of Invasive Epithelial Ovarian Cancer in Swedish Women. J Natl Cancer Inst 2002; 94:497-504.
46. Rossing MA, Cushing-Haugen KL, Wicklund KG, Doherty JA, Weiss NS. Menopausal Hormone Therapy and Risk of Epithelial Ovarian Cancer. Cancer Epidemiol Biomarkers Prev 2007; 16:2548-2556.
47. Morch LS, Løkkegaard E, Andreasen AH, Kjær KS, Lidegaard Ø. Hormone Therapy and Different Ovarian Cancers: A National Cohort Study. Am J Epidemiol. 2012; 175(12):1234-1242.
48. Dietel M, Lewis MA, Shapiro S. Hormone replacement therapy: pathobiological aspects of hormone-sensitive cancers in women relevant to epidemiological studies on HRT: a mini-review. Human Reproduction 2005; 20(8):2052-2060.
49. Fernandez E, Franceschi S, Vecchia CL. Colorectal cancer and hormone replacement therapy: a review of epidemiological studies. Menopause Int 2000; 6: 8-14.
50. Fernandez E, Vecchia CL, Braga C, Talamini R, Negri E, Parazzini F, Franceschi S. Hormone replacement therapy and risk of colon and rectal cancer. Cancer epidemiology, biomarkers and prevention 1998; 7:329-333.
51. Johnson *et al.* Menopausal Hormone Therapy and Risk of Colorectal Cancer. Cancer Epidemiol Biomarkers Prev 2009; 18(1):196-203.
52. Rennert G, Rennert HS, Pinchev M, Lavie O, Gruber SB. Use of Hormone Replacement Therapy and the Risk of Colorectal Cancer. J Clin Oncol 2009; 27:4542-4547.
53. Henderson *et al.* Menopausal Hormone Therapy Use and Risk of Invasive Colon Cancer The California Teachers Study. Am J Epidemiol 2010; 171:415-425.
54. Schabath MB, Wu X, Vassilopoulou-Sellin R, Vaporciyan AA, Spitz MR. Hormone Replacement Therapy and Lung Cancer Risk: A Case- Control Analysis. Clin Cancer Res 2004; 10:113-123.
55. Chien JW, Au DH, Satia JA, White E. Lung Cancer and Hormone Replacement Therapy: Association in the Vitamins and Lifestyle Study. J Clin Oncol 2010; 28:1540-1546.
56. Cerhan *et al.* Hormone Replacement Therapy and Risk of Non-Hodgkin Lymphoma and Chronic Lymphocytic Leukemia. Cancer Epidemiol Biomarkers Prev 2002; 11:1466-1471.