

A literature review examining the association between the duration of hormone replacement therapy (HRT) and the risk of breast cancer in women

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Table of Contents

Introduction.....	1
Literature Review.....	9
Methodology.....	24
Discussion.....	25
References.....	29
Abstract.....	36

Chapter 1

INTRODUCTION

Ever since post-menopausal hormone replacement therapy (HRT) was introduced, there has been great concern that HRT could possibly increase the risk of breast cancer. The increased use of exogenous sex hormones to alleviate menopausal symptoms, has been suggested as having an unfavorable influence on breast cancer risk due to a possible growth-promoting effect on breast cancer cells (Benshushan & Brzezinski, 2002). Evidence of a small but significant increase in breast cancer risk that appears with long-term current post-menopausal hormone use has been established by over 60 observational studies and two randomized trials. (Kenemans & Bosman, 2003).

Menopausal hormone use (sometimes referred to as hormone replacement therapy or postmenopausal hormone use) can be defined as the peri-menopausal and post-menopausal use of estrogens either alone or in combinations with progestogens (Kenemans & Bosman, 2003). HRT is most often used to relieve vasomotor symptoms and vaginal atrophy in menopause that manifest as hot flashes, vaginal dryness, mood swings, sleep disorders, and decreased sexual desire (National cancer institute, 2007a). HRT medication may be taken in the form of a pill, a patch, or vaginal cream. 'Natural menopause' usually occurs between 45 and 55 years of age, with variations in timing among individual women (National cancer institute, 2007b). Women who undergo bilateral oophorectomy (surgery to remove both ovaries) experience surgical menopause - an immediate end to menstruation caused by lack of hormones produced by the ovaries. Estrogen output decreases significantly by the time a woman reaches natural menopause. Although estrogen is produced by other organs after menopause,

the levels are only about ten percent of the level found in pre-menopausal women.

Progesterone is nearly absent in menopausal women (National Cancer institute, 2007c).

According to a survey performed between 1988 and 1994 by the National Center for Health Statistics, almost half of all postmenopausal women in the U.S reported having ever used hormone replacement therapy (Brett & Chong, 2001). Although most women started using HRT around the time of menopause, about 25 percent began HRT five or more years after menopause (Brett & Chong, 2001). Women with surgical menopause were much more likely to have used HRT and also currently using it in comparison to women with natural menopause. Among women who were at least ten years post-menopausal, 14% had taken HRT pills for about ten years (Brett & Chong, 2001).

Doctors may recommend menopausal hormones to prevent some long-term conditions that are more common in postmenopausal women, such as osteoporosis (National cancer institute, 2007d). In women with an intact uterus, a significant increase in risk for endometrial cancer with exposure to post-menopausal estrogen replacement has been established (Marsden, 2003). To reduce endometrial cancer risk, combined HRT regimen with an addition of progestin is offered to women with an intact uterus, and women who have undergone a hysterectomy are generally given estrogen alone due to the absence of risk for endometrial cancer (Marsden, 2003).

HRT preparations

HRT encompasses a varied range of regimens consisting of natural or synthetic hormones, none of which precisely mimic the pre-menopausal milieu in women. The varied range of regimens may lead to differing effects on breast cancer incidence and prognosis (Marsden, 2003). In addition to estrogen and progestogen, other HRT substances such as tibolone, raloxifene and androgens, are increasingly being used in post-menopausal hormone therapy. These agents may also contribute to breast cancer risk in ways that differ from classical estrogens and progestogen regimens (Kenemans & Bosman, 2003). Most HRT regimens consist of a 28-day cycle where either conjugated equine estrogen or estradiol, typically 0.625 mg and 50 micrograms respectively, is administered daily. In combined HRT, the progestin component can be administered in a continuous or cyclical pattern, and the class of progestin prescribed may vary (Marsden, 2003). With continuous HRT, progestin is administered 28 days of the cycle and in cyclical HRT, it is given ten to 14 days in a 28-day cycle. Synthetic progestins are classified based on whether they are similar to testosterone (19-nor testosterone derivatives) or progesterone (21 progesterone derivatives) (Marsden, 2003).

How does menopausal hormone replacement therapy affect breast cancer risks?

The best evidence for the risks and benefits of menopausal hormone use comes from the Women's Health Initiative (WHI), a large randomized, double-blind, placebo-controlled disease prevention clinical trial including post-menopausal women aged 50-70, sponsored by the National Institutes of Health. The WHI trials started in 1993, enrolled 161,809 women, ages 50-79 in 40 different medical centers. The study was

intended to examine the health benefits and the risks of hormone replacement therapy, including the risk of developing breast cancer, heart attacks, strokes, and blood clots (Writing group for the WHI steering committee, 2002). The study consisted of two arms: one arm of the study assigned 8,506 women randomly to receive a single daily tablet of 0.625 mg conjugated equine estrogen plus 2.5 mg of medroxyprogesterone acetate, while 8,102 women received a matching placebo (Chlebowski, et al, 2003). The other arm included an estrogen-alone component between 1993 and 1998 with 10,739 postmenopausal women (including 23% of minority race/ethnicity), aged 50-79 years, with prior hysterectomy. These women were randomly assigned with 5,310 women who received 0.625 mg/day of conjugated equine estrogen and 5,429 women received a placebo (Writing group for the WHI steering committee, 2004).

In July 2002, the component of the WHI which studied the use of estrogen and progestin in women who had a uterus was stopped early because the health risks exceeded the health benefits (Writing group for the WHI Investigators, 2002). The main reason for stopping the estrogen-progestin study was because of a 26% (relative risk =1.26, 95% CI: 1.00-1.59) increased risk of invasive breast cancer in the treatment arm (estrogen plus progestin) after 5.2 years of use. The increased risk was strong for women using HRT more than five years (Writing group for the WHI Investigators, 2002). In April 2004, the WHI published results from the second arm, which studied estrogen-only therapy in women who no longer had a uterus due to hysterectomy. These results did not find any increased risk of breast cancer with a hazard ratio of 0.77 (95% CI: 0.59-1.01), (Writing group for the WHI Investigators, 2004) and provided strong evidence that use of unopposed estrogen for a duration of 6.8 years or less does not

alter breast cancer risk. In the WHI study, among women who had used HRT for several years before entering the study, the risk of breast cancer was significantly higher (Luukainen, 2003). The results of the WHI study, has led physicians to revise their recommendations regarding HRT.

In a meta-analysis of five studies conducted between 1992 and 1997 by Nelson, Humphrey, Nygren, Teutsch and Allan (2002) relating HRT use to cancer risks, there was found to be an increased breast cancer risk with longer duration of HRT use with relative risks ranging between 1.23 and 1.35. Increased breast cancer risk (relative risks between 1.21-1.40) with current use of estrogen was also identified in 3 meta-analysis (Nelson, et al, 2002). Marsden (2003) states that observational data that suggests a slight increase in breast cancer risk with combined HRT use of over 15 years is also supported by results from randomized large-scale HRT trials.

Purpose and Scope of the Literature Review:

Breast cancer is the most commonly occurring cancer in the United States with one out of eight women being affected during their lifetime (American cancer society, 2005). It ranks second only to lung cancer as a cause of cancer deaths among women (American cancer society, 2005a). In 2005, the American cancer society estimated 211,240 new cases of breast cancer diagnosis and 40,410 breast cancer deaths in women (American cancer society, 2005b). It is estimated that the median age at diagnosis for cancer of the breast was 61 years of age (American Cancer Society, 2005c). Many of these women diagnosed with breast cancer are also on HRT. The Food and Drug Administration estimates that ten million postmenopausal women in the United States currently use estrogen and combination estrogen with progesterin products

for relief of menopausal symptoms and prevention of postmenopausal osteoporosis (US FDA, 2003). Given that this is an area of concern affecting a large number of women, extensive research has been published to date on the relationship between HRT and breast cancer. Observational studies primarily examining unopposed estrogen preparations have suggested an eight percent to 30% increase in breast cancer with extended use (WHI steering committee, 2004). Steinberg, et al (1991) carried out a meta-analysis reviewing 16 studies to quantify the effect of estrogen replacement therapy on breast cancer risk. The researchers found that after 15 years estrogen use, there was a 30% increase in risk for breast cancer (relative risk 1.3, 95% CI: 1.2 to 1.6).

In the last decade, the most convincing evidence of the risk of breast cancer with use of hormone replacement therapy was brought together by the Collaborative Group on Hormonal Factors in Breast Cancer. This study involved the re-analyses of individual data on 52,705 women with breast cancer and 108,411 women without breast cancer from 51 epidemiological studies in 21 countries published between 1980 and 1997. Among the 53,865 post-menopausal women included in the main analysis, 33% had used HRT at some time and 34% of ever-users had used HRT for five years or longer. It was found that breast cancer risk was greater with a relative risk of 1.35 (95% CI: 1.21-1.49) among women who had used HRT for five years or longer (Collaborative group on Hormonal factors in breast cancer, 1997). However, use of HRT in general, for less than 5 years was not associated with altered risks of breast cancer. The findings also revealed that HRT use increased breast cancer risk by 2.3% for each year of use (Vecchia, 2004). Further, epidemiologic studies of HRT use and breast cancer

have suggested that HRT use and increased risk of breast cancer become significant after five years of use (American College of Obstetrics and Gynecology, 2002).

The purpose of this literature review was to identify the degree of breast cancer risk when compared with the length or duration of HRT use. Although it has been known that HRT use, particularly combined estrogen and progesterone, is associated with an increase in breast cancer risk, one cannot determine what duration of HRT use is absolutely safe in women. Since most women on HRT are in primary care, these questions are of interest to health care professionals in general practice. This review is an attempt to clarify some of these concerns related to HRT. The review will also detail breast cancer risk in women with recent, current and past HRT use, as well as women with no prior history of HRT use.

Research Questions and Hypotheses:

Research Question #1: Is there an increase in breast cancer risk with an increase in the duration or length of post-menopausal hormone replacement therapy? Is there an optimum duration of HRT use beyond which breast cancer risks far outweigh the benefits of HRT?

Hypothesis #1: The risk of breast cancer is increased with five or more years of HRT use.

Research Question #2: Are current users of HRT more at risk for breast cancer compared to past HRT users or women who have never used HRT?

Hypothesis #2a: Current HRT users are not at more risk for breast cancer compared to women who have used HRT in the past.

Hypothesis #2b: Current HRT users are at an increased risk for breast cancer compared to women who have never been on HRT.

Chapter 2

LITERATURE REVIEW

Hormone replacement therapy has been identified as a risk factor for breast cancer development. Recently, randomized controlled trials and large studies have shown that a woman's risk of developing breast cancer is affected by both type and duration of HRT use (Coombs, Taylor, Wilcken and Boyages, 2005). The longer the use of HRT, the greater the breast cancer risk, with relative risks ranging between 1.05 and 1.16 for estrogen alone, and 1.24-1.45 for combined estrogen and progesterone use associated with five years of use (Dixon, 2003). The following review will report studies published since the year 2000 which associate breast cancer risk with duration of HRT use.

Histological types of breast cancer and HRT use

In the last three decades, there has been an increase in the incidence of lobular breast cancer than ductal breast cancer, and this increase has been associated with the rise in menopausal hormone use (Li, Anderson, Daling, Moe, 2003; Rosenberg, et al, 2006). Rosenberg, et al (2006), conducted a population-based case-control study in Sweden between 1993 and 1995, to evaluate the impact of different hormone therapy regimens on risks of the three most common histological types of breast cancer. This study included women between the ages of 50 and 74 years. Based on tumor histology, 1,888 of the total population (N=2643) of women in the group with invasive breast cancer had ductal cancer, 308 women had lobular cancer, and 93 of the total women who participated in the study had tubular cancer. The control group consisted of a total of 3,065 women who were frequency matched by the expected age distribution among

cases. In the control group, 1,707 women had not used any form of hormone replacement therapy. Results of the study indicated that more than five years of estrogen-only HRT yielded odds ratio (OR) of 2.9 (95% CI :1.6-5.2) and 3.1 (95% CI : 1.0-9.5) for ductal and lobular breast cancer, respectively (Rosenberg, et al, 2006). Use of medium potency estrogen-progestin was found to be associated with increased risks of all three histological subtypes of breast cancer, with the highest risks being among women with at least five years of use. The risk was significantly higher among women with lobular (OR of 5.6, 95% CI: 3.2- 9.7) and tubular cancer (OR of 6.5, 95% CI: 2.8-14.9) compared to an OR of 2.3 (95% CI: 1.6 -3.3) for women with ductal cancer (Rosenberg, et al, 2006).

The risk of breast cancer by histopathology and post-menopausal hormone use was also examined by Newcomer, et al (2003), in women below the age of 75 years with newly diagnosed primary invasive breast carcinoma. The study was restricted to women who either had natural menopause or bilateral oophorectomy. Twenty-eight percent of the women in the control group reported postmenopausal hormone use versus 29% of the entire case group. Most of the women in both groups reported having prior postmenopausal estrogen use alone. Nineteen percent of the case group and 15% of the control group reported having had prior combined hormonal therapy. An increased risk of lobular cancer was associated with women who had prior use of any type of postmenopausal hormone therapy (OR: 1.5, 95% CI: 1.1-2.1), but not with risk of ductal cancer (OR: 1.1, 95% CI: 1.0-1.3) or any ductal subtypes (Newcomer, et al, 2003). Similarly, there was a positive association between the risk of lobular carcinoma to recent use of any type of postmenopausal hormone therapy (OR; 2.1, 95% CI: 1.4-

3.3) but not with risk of ductal carcinoma (OR: 0.9, 95% CI: 0.8-1.2). A higher risk of lobular carcinoma was seen in both the recent users of estrogen- only therapy (OR: 1.8, 95% CI: 1.0-3.4) and women who had prior use of estrogen only (OR: 1.6, 95% CI: 1.0-2.4). The risk for lobular cancer was slightly higher with the recent use of combined therapy- estrogen plus progestin (OR: 3.6, 95% CI: 1.8-7.6) than prior users of the combined therapy (Newcomer, 2003). There was no association of other histological types of breast cancer with prior or recent use of combined therapy. These findings are consistent with the results of another study by Chen, Weiss, Newcomb, Barlow, White (2002) which reported an increased risk of invasive lobular cancers (OR=3.9; 95% CI: 2.1-7.4) with current use of combination HRT, but not with invasive non-lobular cancers.

In another population-based case-controlled study comprising 975 women between 65-79 years of age, Li, et al (2003) found that women who used combined HRT for longer durations were at greatest risk for breast cancer. A combined HRT use of five to 14.9 years, had a 1.5-fold (95% CI, 1.0-2.3) and 15 years or longer had a 1.6-fold (95% CI, 1.0-2.6) increase in risk specifically of invasive ductal carcinoma. The risk of invasive lobular carcinoma was 3.7-fold (95% CI, 2.0-6.6) for five to 14.9 years of combined HRT use and 2.6- fold (95% CI :1.3-5.3) for 15 years and above of combined HRT use compared to never users (Li, et al, 2003). It was also observed that both former and current use of combined HRT of 6 months or longer was associated with an increase in risk with all histological breast cancer types. Conversely, women who had used estrogen replacement therapy alone were found to have a risk similar to HRT non-users, irrespective of duration of use (Li, et al, 2003).

In a large multi-center population-based case-control study, Newcomb, et al (2002), identified 5,298 post-menopausal women with invasive breast cancer and 5,571 randomly selected controls for comparison to investigate the type and duration of postmenopausal therapy and breast cancer risk. An increase in risk not only in lobular cancer, but also ductal breast cancer with relative risks (RR) of 2.01 (95% CI: 1.25-3.22) and 1.43 (95% CI: 1.14-1.79) respectively, in prior users of combined HRT was identified. However, the relative risks for ductal (RR=1.19, 95% CI: 0.88-1.61) and lobular (RR=1.22, 95% CI: 1.06-1.41) histological types were similar for estrogen-only HRT users. The relative risk for breast cancer also increased with longer durations of hormone use, with a relative risk of 1.57 (95% CI: 1.15–2.14) for recent and long term (> five years in duration) of estrogen-progestin use and a relative risk of 1.39 (95% CI: 1.17–1.65) for estrogen-alone use. Compared with women who had never used postmenopausal hormones, the estimated RR for prior use of estrogen-only therapy was 1.23 (95% CI: 1.09–1.39) and the RR for prior use of combined estrogen-progestin therapy was 1.43 (95% CI: 1.18–1.74).

Another large cohort study of postmenopausal women in Australia by Gertig, Erbas, Fletcher, Amos and Kavanagh (2003), included 2,200 women over 55 years of age with invasive breast cancer to investigate the association between duration of HRT use with tumor size and histologic grade of tumor. Early in the study, a survey of HRT use indicated that most women without hysterectomy used combined therapy and women who had undergone hysterectomy were estrogen only users. A borderline association between HRT use for more than five years when diagnosed with breast cancer and larger tumors was seen ($p= 0.07$). In women diagnosed with interval

cancers (cancer of the breast that are diagnosed between the time after a negative screen and before the next scheduled screening exam), a current HRT usage of five years or less was associated with smaller tumors ($p= 0.03$). However, this association was not observed ($p=0.84$) with longer durations of HRT use among these women (Gertig, et al, 2003). Compared with women who never used HRT, five years or more of HRT users were less likely to have a poorly-differentiated tumor ($p<0.001$). Short-term users of HRT (at most five years) were also less likely to have poorly differentiated tumors (OR= 0.48, 95% CI: 0.28-0.82), thereby indicating that there was no significant association between duration of HRT use and tumor size (Gertig, et al, 2003).

Duration of HRT use and breast cancer risk in different ethnic groups

Previous epidemiological studies have evaluated the relationship between postmenopausal hormone use and breast cancer risk primarily among White populations. In the WHI study, only 10% of the population was non-White (Writing group for the WHI Investigators, 2002). The results of the collaborative reanalysis of data from 51 observational studies included only 2% of non-White women (Collaborative group on hormonal factors in breast cancer, 1997).

Data from a prospective Black Women's Health study, a follow-up study of 32,559 US black women (40 years or older) from 1995 through 2003, using biennial questionnaires about female hormone use, breast cancer risk factors, and occurrence of breast cancer was analyzed by Rosenberg, Palmer, Wise and Campbell (2006). The results indicate that compared to prior use of HRT, the incidence rate ratio (IRR) for breast cancer in women with recent hormone use increased with duration of use for 10 or more years of use (IRR= 1.58, 95% CI :1.12-2.23). With estrogen alone use of 10

years or more, the incidence rate ratio (IRR) was found to be 1.41 (95% CI: 0.95-2.10). The IRR was 1.23 (95% CI: 0.82-1.84) for five to nine years of estrogen-only use and for five or more years of estrogen plus progestin use, an IRR of 1.45 (95% CI: 0.94-2.23).

In a multiethnic cohort prospective study by Lee, Kolonel, Wilkens, Wan, Henderson and Pike (2006), 55,371 African-American, Native Hawaiian, Japanese-American, Latina and White postmenopausal women were enrolled in the examination of dietary, environmental and genetic factors relationship to cancer and other chronic diseases. The women ranged from 45 to 75 years of age and were enrolled between 1993 and 1996 in Hawaii and California. They completed a 26-page questionnaire with detailed information about their diet, demographic factors, personal behaviors, prior medical conditions, use of medications, family history of common cancers, reproductive history, use of oral contraceptives and hormone therapy. Data analysis excluded women who had identified any previous cancer including in-situ breast cancer before the time of enrollment. Exclusion criteria included pre-menopausal status and simple hysterectomy before menopause. Only cases of invasive breast cancer as defined by ICD-O classification of histology (ductal cancer, pure lobular cancer and mixed lobular/ductal cancer) were included in the data analysis. Over a seven year mean length of follow-up, 1,615 cases of invasive breast cancer were identified. An increased risk of breast cancer in current estrogen plus progestin HRT use for all durations was seen with a 29% (RR= 1.29, 95% CI: 1.23-1.35) increase in risk per five years of use in all ethnic groups (Lee et al, 2006). A 10% increase in risk per five years of current estrogen use (RR= 1.10, 95% CI: 1.05-1.16) was also seen in all ethnic groups. A

significant increase in risk with past estrogen and progestin therapy use was also observed in the African-American group (RR= 1.82, 95% CI: 1.30-2.55) but not in any of the other ethnic groups (Lee et al, 2006).

Breast cancer risk with past versus current HRT use

Use of HRT by 50-64 year old women in United Kingdom in the 1980s was estimated to have resulted in an extra 20,000 incidences of breast cancer, including 15,000 attributable to combined estrogen-progestin therapy (Banks, Beral, Bull, Reeves, 2003). A cohort study of British women aged between 50 and 64 years, called as the Million Women Study, aimed to investigate the effects of specific types of hormone-replacement therapy on breast cancer incidence and mortality. Between 1996 and 2001, the National Health Service Breast Screening Program (NHSBSP) recruited 1,084,110 UK women who had not been registered as having had cancer. Following collection of relevant personal details and information about their use of HRT, these women were followed up for breast cancer incidence and death by routine screening every three years (Banks, et al, 2003). Deaths due to cancer were automatically flagged on the National Health Service register. Validation studies were done for a sample of the study population by comparing self-reported data with information in the records of family physicians. During enrollment into the study, participants were classified according to their reported use of HRT, menopausal status and other relevant factors. Information collected about HRT use included: ever-use, current use, age at first and last use, name of the HRT preparation used most recently and total duration of its use (Banks, et al, 2003) The main analyses ultimately included 828,923 postmenopausal women. About 9,364 incidences of invasive breast cancer and 637

breast cancer deaths were registered after an average of three to four years of follow-up, respectively. The breast cancer risk was significantly higher with a relative risk (RR) of 1.43 (95% CI: 1.36-1.50) among prior users of HRT than never users (Banks et al, 2003). Current users of HRT at recruitment were more prone to develop breast cancer and die from it, with a relative risk of 1.66 (95% CI: 1.60-1.72) than never users. It was also found that there was significant relative risks of breast cancer involved with current users of estrogen-only, estrogen-progestogen and tibolone preparations with relative risks of 1.30 (95% CI: 1.21-1.40), 2.00 (95% CI: 1.88-2.12) and 1.45 (95% CI: 1.25-1.68) respectively (Banks et al, 2003). In addition, the relative risk among current users revealed an increasing risk with longer duration of use of different HRT combinations. Among current estrogen-only users, the RR for one to four years of use was 1.25 (95% CI: 1.10-1.41), five to nine years of use was 1.32 (95% CI: 1.20-1.46) and more than 10 years was 1.37, 95% CI: 1.22-1.54 (Banks et al, 2003). Similarly, with estrogen-progestogen combinations, the RR for one to four years of use was 1.74 (95% CI: 1.60-1.89), five to nine years of use was 2.17 (95% CI: 2.03-2.33) and ≥ 10 years of use was 2.31 (95% CI: 2.08-2.56). However, among past HRT users, there was no significant difference compared to never users, whose use had ceased less than five years, five to nine years or 10 or more years previously (Banks et al, 2003). The results also indicated that the effects of current use of HRT substantially decreased, if not completely, within five years of stopping HRT use. Ten years of HRT use was estimated to result in five additional breast cancers per one-thousand estrogen-only users and 19 additional breast cancers per one-thousand users of combined estrogen-progestin (Banks et al, 2003). Among current HRT users, breast cancer risk increased

with total duration use of both estrogen alone, and estrogen plus progesterone combined therapy. In addition to confirming prior findings that current and recent use of HRT increased the risk of breast cancer, this study also provided new and reliable information about the effects of HRT on breast cancer incidence and mortality (Banks et al, 2003).

Weiss, et al (2002) reported results of a multi-center, population-based, case-control study designed to examine the relationship between HRT and breast cancer risk based on the regimen, duration and recentness of use. This study conducted in five US metropolitan areas from 1994 to 1998, obtained data from 3823 white and black postmenopausal women (1870 cases and 1953 controls) who were between 35-64 years of age. It was found that current use of combined HRT for five or more years conferred a significant increase in risk with an odds ratio of 1.37 (95% CI: 1.06 -1.77). This increase was confined to those women who used continuous combined HRT (OR=1.54; 95% CI: 1.10 -2.17). Among current users, a statistically significant trend indicating an increase in breast cancer risk with longer duration of combined HRT was also found, $p = 0.003$ (Weiss et al, 2002). Compared to never users, the odds ratio for two to five years of combined HRT use was 1.34 (95% CI: 1.05-1.70) and five or more years of use was 1.27 (95% CI: 1.03-1.56). The odds ratio for continuous combined HRT use for five or more years was 1.45 (95% CI: 1.09-1.91) compared with never users (Weiss, et al, 2002). Breast cancer risk decreased once HRT use was discontinued. There was a decreased risk in short-term users (less than 6 months) of combined HRT and estrogen-only therapy. There was no association between an

increased risk of breast cancer and estrogen replacement therapy regardless of duration of use or how recently HRT was used (Weiss et al, 2002).

Breast cancer risk in prior versus never HRT users

Epidemiological studies indicate a modestly increased risk of breast cancer in women who have prior HRT use, and also with current use of HRT (Stahlberg, et al, 2004). A Swedish study by Olsson, Bladstrom, Ingvar and Moller (2001) examined the breast cancer risk in a cohort study relationship to time of exposure to HRT and family breast cancer history. A total of 40,000 randomly selected 25 to 65 year old women from the South Swedish Health Care Region were interviewed between 1990 and 1992 regarding risk factors of malignant melanoma and breast cancer. Of these 29,508 interviewees, one-thousand women from each birth year were invited to participate in the study. The women were followed until December 1999, when the data showed that although the number of malignant tumors did not increase, there was a small increase in incidence of breast cancer. Among 3,663 prior users of HRT, there was a significant increase in breast cancer with an IR of 1.35 (95% CI: 1.09-1.64) compared to never users with an IR of 1.07, 95% CI: 0.96-1.19 (Olsson, 2001).

A German population-based case-control study was conducted in the Bonn metropolitan area and neighboring German districts to evaluate factors which might modulate HRT-related breast cancer risk. Between August 1, 2000 and October 31, 2002, the study included 688 breast cancer cases and 724 controls. It was found that there was an increase in breast cancer risk among women in natural menopause with a significant linear trend for duration of use with odds ratio of 1.46 (95% CI: 0.86-2.48) with five to 10 years of use and 1.79 (95% CI: 1.12-2.87) with greater than 10 years of

use (Pesch, et al, 2005). The OR was 1.05 (95% CI: 1.02-1.09) for each year of HRT use among this group. There was however, no such risk among women in surgical menopause even after at least 10 years of HRT use. An increased risk among women in natural menopause who were current, long-term users of HRT (OR 2.04, 95% CI: 1.24-3.36) compared to never users was also observed (Pesch, et al, 2005).

The World Health Organization recommends mammography as a screening for breast cancer. Currently, among women between 50 and 69 years of age, most breast cancers are diagnosed by screening (Hofvind, Moller, Thoresen, Ursin, 2006). The Norwegian Breast Cancer Screening program, a large prospective study undertaken to determine the risk of breast cancer (detected at screening and between mammographic screens) associated with HRT use, enrolled 296,651 women between the ages of 50 and 69 years between 1995 and 2004. After a mean enrollment period of four years, invasive screening detected breast cancer (cancer diagnosed as a result of a diagnostic work-up following a positive mammographic screening), was found in 1,512 women. Also, invasive interval breast cancer, defined as a breast cancer diagnosed between the date of a negative mammographic screen result and the next scheduled mammographic screening, was found in 814 women (Hofvind, Moller, Thoresen, Ursin, 2006). Data collected from this study showed that compared to never users, women who had prior post-menopausal hormone therapy use were at a 58% increased risk of breast cancer with a hazard risk (HR) ratio of 1.45 (95% CI:1.29-1.63) for screen detected cancer and HR of 1.89 (95% CI: 1.61-2.23) with interval cancer (Hofvind, Moller, Thoresen, Ursin, 2006). The hazard risk of breast cancer also increased with duration of hormone replacement for both screen detected and interval cancers in comparison to never users.

The HR ratios for less than one year HRT use was 1.12 (95% CI: 0.95-1.33), one to four years of use was 1.55 (95% CI: 1.39-1.73), five to nine years of HRT use was 2.03 (CI: 1.76-2.35) and at least 10 year HRT use was 2.23 (955 CI: 1.83-2.72) respectively (Hovind, Moller, Thoresen, Ursin, 2006).

Stahlberg, et al (2004) conducted the Danish Nurse Cohort study consisting of 10,874 nurses over the age of 44 years, to investigate the magnitude of breast cancer risk due to different HRT regimens in Scandinavia among post-menopausal women. The nurses completed a mailed questionnaire detailing the past, current, and duration of HRT use. Women who were excluded in the analysis at the beginning of the study in 1993 included cases of identified breast cancer, carcinoma in situ of the breast and other invasive cancers, except melanoma, and surgical menopause or bilateral oophorectomy (Stahlberg, et al, 2004). The follow-up of the sample group continued until 1999 during which a total of 244 women developed breast cancer. There was found to be a significantly increased risk of breast cancer following the prior use of HRT with a relative risk of 1.91 (95% CI= 1.45-2.50) and the current use of HRT with a relative risk of 2.42 (95% CI= 1.81-3.26). Additionally, it was found that there is overall no significant increased risk in breast cancer with longer duration of use. However, the use of continuous combined HRT for 10 years or longer had a relative risk of 6.78 (CI= 3.41-13.48), which was 6-fold in comparison to never users.

For cancer incidence, a population-based cohort study known as the Norwegian women and cancer study (NOWAC) followed 31, 451 postmenopausal women between the ages of 45 and 64 years with prior versus never use of HRT. Among these women, there were 624 cases of breast cancer with relative risk (RR) of 1.9 (95% CI: 1.5-2.5)

which was significantly higher in prior users than never-users of HRT (Bakken, Alsaker, Eggen, Lund, 2004). The risk was also increased in current users of HRT ($p=0.002$) than past users. Among current users, the risk increased with longer durations of HRT use with relative risks of 2.3 (95% CI: 1.5-3.1) for five to nine years of use and 1.9 (95%CI: 1.1-3.2) for 10 or more years of use (Bakken, Alsaker, Eggen, Lund, 2004). This trend of increased risk with longer duration of HRT use was also seen among prior users but not among past users. It was also estimated that 27% of the total breast cancer risk among Norwegian women 45 to 64 years of age was due to current use of HRT (Bakken, Alsaker, Eggen, Lund, 2004).

Breast cancer and type of HRT regimen

A key concern with HRT regimens is whether the varied treatment modes such as, cyclical or continuous addition of progestins, or the androgenicity of progestins, may influence breast cancer risk to a different degree (Stahlberg, et al, 2004). The women's health in the Lund area (WHILA) study by Jernstrom, Bendahl, Lidfeldt, Nerbrand, Agardh and Samsioe (2003) was designed to establish whether breast cancer risk depended on the type of HRT formula used. This study on women from Lund (Southern Sweden) included all women ($n=10,766$) born in the decade between December 2, 1935 and December 1, 1945 and living in the Lund area. The women ranged in age from 50 to 64 years at study entry between December 1995 and February 2000. The analysis in this cohort study included 6,586 women with no reported cancer at inclusion in the study, who completed questionnaires related to HRT use. Between inclusion and December 2001, 101 women developed breast cancer. The authors found a significant difference in prior use of HRT between cases and controls (76.3%

versus 61.6%; $p=0.003$). Only the prior use of continuous combined estrogen plus progestin (CCEP) differed significantly between women who did and did not develop breast cancer (45.2% versus 23.5%; $p=0.000001$). Compared with never users after adjustment for age at study entry and time of follow-up, women who used the CCEP exclusively showed the highest hazard ratio (HR= 3.3, 95% CI: 1.9-5.6). The next highest HR was seen among women who had used CCEP in addition to other HRT formulas (HR= 2.8, 95% CI: 1.4-5.5). No significant increase was seen in women who used other HRT formulas exclusively ($p=0.19$). The study concluded that CCEP therapy conferred more than three times the risk of developing breast cancer as compared with never users and more than doubled the risk of other HRT regimens (Jernstrom, et al, 2003).

A definitive and detailed population-based, case-control study aimed at determining the effects of combined HRT on breast cancer risk was published by Ross, Paganini-Hill, Wan and Pike (2000). The study was based on interviews with 2429 control subjects and 2653 breast cancer patients identified by the Cancer Surveillance Program (CSP) based in Los Angeles county. Breast cancer cases were ascertained in three diagnostic groups: (Group I) White (including Hispanic) women born in North America or western Europe aged 55 to 64 at first diagnosis who were diagnosed during March 1, 1987 to December 31, 1989; (Group II) White (including Hispanic) and African-American women born in the US aged 55 to 69 who were first diagnosed during January 1, 1992 through December 31, 1992; (Group III) White (including Hispanic) and African-American women born in the US aged 55 to 72 at first diagnosis, who were diagnosed during September 1, 1995 through April 30, 1996. In this study, the change

in targeted age range over time maximized the likelihood of long-term use of combined HRT. Statistical analysis was conducted using standard conditional multivariate logistic regression techniques. Breast cancer increased 10% for every five years of HRT use (OR=1.10; 95% CI: 1.02-1.18, $p=0.015$). There was a steady increase in risk with duration of HRT use with a 36% increase in risk after 15 years of use (Ross, et al, 2000). For combined HRT use, the risk was substantially higher (OR=1.24; 95% CI: 1.07-1.45) than for ERT use (OR=1.06; 95% CI: 0.97-1.15). The belief that progestins protect against breast cancer development was disproved in this study, which showed that progestins substantially increase the small ERT-related increase in breast cancer. This study argues that the adverse breast cancer risk from combined HRT outweighs the protection provided to the endometrium (Ross, et al, 2000).

Schairer, Lubin, Troisi, Sturgeon, Brinton and Hoover (2000) retrospectively reviewed data on 46,355 post-menopausal women to examine the effect of combined estrogen-progestin HRT on the risk of breast cancer compared to estrogen only use in a cohort study. These women from 29 screening centers across the United States were monitored for 15 years in the Breast cancer detection demonstration project. Between 1980 and 1995, 2,082 incident cases of breast cancer were identified. Among women with current or recent, within the past 4 years estrogen-only use, 1.2 times (95% CI: 1.0-1.4) increased risk was found versus 1.4 times (95% CI: 1.1-1.8) increased risk in women on estrogen and progesterone for 4 years (Schairer, et al, 2000). There was also a 0.01 (95% CI: 0.002-0.03) increased relative risk estrogen-only treatment and a relative risk of 0.08 (95% CI: 0.02-0.16) with each year of estrogen-progestin treatment among recent users (Schairer, et al, 2000).

Chapter 3

METHODOLOGY

This project reviewed scientific literature published from the year 2000 to the present in research journals pertaining to the topics discussed. Various search engines were utilized to obtain scientific articles, research and review papers for this purpose. These search engines were: Medline, PubMed, CINAHL, and Ohiolink. The search terms used included: breast cancer, breast neoplasm, breast cancer risk, breast cancer incidence, hormone therapy, hormone replacement therapy, menopause, estrogen use, combined hormone therapy, estrogen-progesterone use.

Chapter 4

DISCUSSION

Duration and regimens of HRT use with breast cancer risk

In the 1990s, the comprehensive analysis of available worldwide studies by the Collaborative Group of Hormonal risk factors in Breast Cancer (1997) concluded that breast cancer risk increases with long-term exposure to HRT, and with current long-term use of HRT. This finding is corroborated by the majority of studies reviewed in this project which indicate a concomitant increase in breast cancer risk with longer duration of HRT use. Studies conducted to evaluate HRT use over five to ten, 10 to 15 and over 15 years indicated a proportionate increase in risk with duration of use, with the maximum risk being at or over 15 years of use. The risks were also higher among women on longer durations of combined estrogen-progesterone HT use compared to women on longer durations of estrogen-only use. However, this finding was contradicted by Weiss, et al (2002) who found that prolonged estrogen-only use did not have any associated breast cancer risks. This is supported by data from Li, Malone, et al (2003) which concluded that irrespective of the duration of estrogen-only use, the breast cancer risks were similar to HRT non-users. A similar finding by Stahlberg, et al (2004) was that there was no risk with longer duration of HRT use except in women on continuous combined HRT for over 10 years wherein the risk was six-fold to never users. The findings on continuous combined HRT use among current long-term users were consistent with the findings from the WHI randomized controlled trial. The German study in the Bonn metropolis (2005) further suggested that among women in natural

menopause, there was high risk with longer duration of HRT use, but among women in surgical menopause, there was no such risk even with 10 years or more of HRT use.

Almost all the studies reviewed indicate that prior users of HRT are more at risk for breast cancer compared to never-users. This risk was highest among women who had prior use of continuous combined estrogen-progesterone preparations.

Recent or Current HRT versus total lifetime use and breast cancer risk

The million women study (2003) reported higher risks among current users of both estrogen only and estrogen-progestin users, compared to past users of HRT who had no significant risk even after ceasing HRT use less than five years earlier. However, the risk was highest among current combined HRT users. Also, among current users the overall risk increased with duration of use compared to never users according to data from all the studies that were reviewed. Weiss, et al (2002) also reported an increase in breast cancer risk with current use of combined HRT over five years or more. The multi-ethnic cohort study by Lee, Kolonel, et al (2006) assessing current HRT usage in ethnic groups found that the risk per five years of HRT use was high in all ethnic groups with highest risk among combined HRT users. However, African-American women were seen to be at particularly high risk with past use of estrogen-progesterone combined therapy, although this risk with past use was absent in all other ethnic groups.

Among the histological types of breast cancer, three types- ductal carcinoma in-situ (DCIS), lobular carcinoma in-situ (LCIS) and atypical hyperplasia have a high risk of invasive breast cancer. It is believed that DCIS is a pre-invasive condition that most likely results in invasive ductal carcinoma over time, unlike LCIS which is usually not

considered as a pre-invasive condition and is largely asymptomatic and found incidentally (Hollingsworth, Singletary, Morrow, et al, 2004).

There is strong evidence that HRT use increases the incidence of lobular breast cancer more than the ductal type. Recent or prior estrogen-only use over a period exceeding five years was associated with lobular breast cancer. On the other hand, combined estrogen and progesterone use of five years or more was linked to the ductal type of breast cancer. However, the findings of Li, Malone, et al (2003) suggest that former and current use of combined estrogen and progesterone therapy for over 6 months resulted in an increase of all histological types of breast cancer. These findings are similar to those by Newcomb, et al (2002) who found an increase in both lobular and ductal types with prior use of combined HRT.

Gertig, Erbas, et al (2003) reported that greater than 5 years of HRT use was less likely to result in poorly differentiated tumors compared to never users of HRT. There was no association between larger tumor size and longer duration of HRT use.

This discussion leads to the following conclusions:

- 1) The risk of breast cancer is increased with five or more years of HRT use.

Hypothesis #1 is therefore accepted.

- 2) Current HRT users are more at risk for breast cancer than past users of HRT.

Hence, hypothesis #2a is rejected.

- 3) Current users of HRT are at more risk for breast cancer than women who have never used HRT. Hypothesis #2b is accepted.

In summary, the body of literature yields evidence that there is a small increase in breast cancer risk with HRT use (particularly combined estrogen-progestin therapy),

and a possible increase in risk with longer duration of use (greater than 5 years). Short-term users of less than 6 months have a decreased risk of breast cancer (Weiss, et al, 2002). Therefore, short-term hormone replacement therapy in menopausal women, with a duration definitely not exceeding five years at the minimum possible dosage required to alleviate menopausal symptoms is recommended for consideration. Breast cancer risk falls following the cessation of HRT, irrespective of type, and by 5 years is no greater than that observed in women without any HRT exposure (Collaborative Group of Hormonal risk factors in Breast Cancer, 1997). Women need adequate counseling about duration of HRT use and the relative risk for breast cancer.

Most of the studies presented in this review support the premise that breast cancer risk increases with the duration of both estrogen only and estrogen-progesterone combined regimens use. Some studies in this review may have been confounded by other variables such as race, ethnicity, socioeconomic status, menopausal and oophorectomy factors and mammographic density. A limitation to the literature review is that, despite making every attempt to find all published articles associated with the review topic, there is the possibility that some relevant studies may not have been included in this project.

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Abstract

Objective. This literature review is a comprehensive review of research published since the year 2000 pertaining to the association between duration of post-menopausal hormone replacement therapy and breast cancer risk.

Methods. Search engines such as Medline, PubMed, and Ohiolink were used between September 2006 and September 2007 to complete this literature review.

Results. HRT use for greater than 5 years is associated with a significant increase in breast cancer risk with women on combined HRT more at risk than estrogen-only users. Women who have prior hormone replacement use are also at more risk than never users. The risk decreases upon cessation of HRT irrespective of the type of HRT regimen.

Conclusions. Breast cancer risk increases with longer durations of HRT use. Short-term HRT use for five years or less is therefore recommended in post-menopausal women to minimize their risk for breast cancer.