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Systematic Review

Does Unopposed Peri-menopausal or Post-menopausal Estrogen Protect against Breast Cancer? A Systematic Review

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Abstract

Globally, breast cancer is the most common incident cancer and cause of cancer deaths in women. The incidence of breast cancer suddenly increases from age 40 and continues to increase until age 84 years. These coincide with perimenopause and menopause periods.

Hormone Replacement Therapy (HRT) is recognized to cause breast cancer. This causal association has become assumed with unopposed Estrogen Replacement Therapy (ERT) which is used for women who require HRT but do not require the Progestogen component. This systematic review assessed the evidence behind the belief that unopposed ERT had a causal relationship with breast cancer.

Established databases were searched to August 2017 for publications that examined the relationship between unopposed ERT and breast cancer in cohort studies (prospective and retrospective), case control studies and randomized controlled studies. Unopposed ERT could be oral, transdermal patch or gel, subcutaneous or intranasal routes.

All the studies were systematically assessed for the risk of bias and the measures of effect such as appropriate measures of effect [relative risk for randomized controlled studies, incidence ratio/rate for prospective cohort studies and odds ratio for retrospective cohort studies and case control studies. The quality of the evidence was assessed with GRADE methods [1].

We report on the general direction of the evidence from different types of studies over different decades in different countries using different types of unopposed Estrogens at different doses, to show whether the evidence is consistent in its direction that unopposed Estrogens do not increase the risk of Breast cancer in peri-menopausal or post-menopausal women.

The evidence does not support that unopposed ERT increases the risk of breast cancer. Where an association has been reported, there was methodological association because the study was either a retrospective study as case control study or cohort study which are not study designs that are valid to show cause and effect relationships. Moreover the only randomized studies in the short term and long term show no cause and effect relationship.

The implication is that as unopposed ERT does not increase the risk of breast cancer, more women can consider its use and benefits.

Introduction

The basic elements for the association between non-contraceptive Estrogens and the risk of Breast cancer are present because Estrogens initiate breast tissue. Estrogen is produced by the ovaries in the first half of the menstrual cycle. It stimulates the growth of milk ducts in the breasts. The increasing level of Estrogen leads to ovulation halfway through the cycle. Next, the hormone Progesterone takes over in the second half of the cycle.

Therefore there should be a higher risk of breast cancer in young girls with or without the contraceptive pill who use higher doses of estrogen or in menstruating women or pregnant women who have to bear long intervals of powerful strong Estrogens. By the fifth or sixth month of pregnancy,

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the breasts are fully capable of producing milk. As in puberty, Estrogen controls the growth of the ducts and Progesterone controls the growth of the glandular buds.

By the time a woman reaches her late 40s and early 50's, peri-menopause is starting or is well underway. At this time, the levels of Estrogen and Progesterone begin to change. Estrogen levels dramatically decrease. This leads to many of the symptoms commonly linked to menopause.

Without Estrogen, the breast's connective tissue becomes dehydrated and is no longer elastic. The breast tissue, which was prepared to make milk, shrinks and loses shape. This leads to the "saggy" breasts associated with women of this age.

This connection points a finger to Estrogens as a potential cause of breast cancer. However, certain cogent studies have contributed consistent research that have directed us to this current scientific search for the evidence to support or dispel the association between unopposed Estrogen use and risk of breast cancer.

HRT is known to be beneficial for all manner of things, including hot flashes, vaginal dryness, urinary symptoms, bone protection and memory. However it is generally alleged that the overriding fear of breast cancer might deter women and their families. More so, that it has been traditionally contraindicated in women with a previous diagnosis of Breast cancer because of fear that it may increase the risk of recurrence.

Menopausal women might suffer from vasomotor symptoms which include hot flushes, sweats and night sweating which can then affect sleep. Other women have psychological and psychiatric symptoms such as anxiety and depression. Others still, suffer from extreme tiredness and lack of energy and from collagen effects such as thin hair, skin cartilage and bone or from genitourinary symptoms with urinary and vaginal problems [2].These can be isolated symptoms or occur in symptom combinations.

The amelioration of some or all these symptoms can be achieved with menopausal Hormone Replacement Therapy (MHRT). Women who still have a womb are treated with a combination of Estrogen and Progestogen Hormone Replacement Therapy (HRT). When there is no uterus, women are treated with unopposed Estrogen Replacement Therapy (ERT).

Many studies have shown an increased risk of breast cancer with menopausal Hormone Replacement Therapy (MHRT) [3,4]; Women's Health Initiative (WHI study) [5-8].

There are also multiple plausible biologic basis for how the Estrogen component of HRT or MHRT can either initiate breast cancer or promote breast cancer [9] and increase the incidence of breast cancer. However, this increase in risk of breast cancer has not been consistently demonstrated in women on unopposed Estrogen or Estrogen alone HRT or Estrogen Replacement Therapy (ERT) in Randomized controlled studies [10] and in detailed analysis using causal analysis [11]. This suggests that there might be an alternative cause for the increase in risk of Breast cancer not directly related to Estrogen or completely unrelated to the Estrogen component of HRT.

Some earlier observational studies had shown that unopposed Estrogen did not increase the risk of breast cancer [12-14]. In some studies, the risk of Breast cancer was even unchanged following prolonged follow-up of 10-15 years [13, 15]. The aim of this systematic review was to determine whether unopposed peri-menopausal or post-menopausal Estrogens increased or protected against the risk of breast cancer. If the risk was not increased, more women can avail of the benefits without fear of breast cancer, but possibly with the confidence of additional protection against Breast cancer.

Literature review

In both observational and randomized controlled trials of Menopausal HRT, the risk of Breast cancer is consistently elevated WHI, 2002 [4,5]; Million Women Study [6-8]. However, while this is consistent for combined Estrogen plus Progestogen Menopausal Hormone Therapy, the same consistency for reports on breast cancer risk has not been shown for unopposed ERT which was used mainly in the 1970's in all women and more recently, solely in women who have no uterus [4,7]. Apart from one observational retrospective Finnish study which reported an increased risk of breast cancer when measured as an incidence ratio, a measure of effect of prospective observational studies which this was not, clinical practice with unopposed Estrogens after 5 years of use (Lyytinen, et al. 2006 [16], [Incidence Ratio 1.44 95%CI: 1.29 –1.59]), deviated from most earlier observational studies when ERT was used predominantly, which showed that unopposed post-menopausal Estrogen did not increase the risk of breast cancer (Kaufman, et al. 1984 [12] [RR 0.9, 95% CI 0.7-1.1]; Palmer, et al. 1991 [13] [RR 0.90, 95% CI 0.4-1.9]; Ross, et al. 2000 [14] [OR 1.06, 95% CI: 0.97-1.15]; Zhang, et al. 2007 [15] [HR 1.11, 95% CI: 0.79, 1.56]; Lyytinen, et al. 2006 [16] [Incidence ratio for less than 5 years use was 0.93 [95% CI: 0.80 –1.04]); Brinton & Hoover, 1981 [17] [RR 1.24, 95% CI: 1.0–1.5]; Persson, et al. 1997 [18] (RR 1.24, 95% CI: 1.0–1.5). In one review, the use of unopposed ERT was not found to be significantly associated with Breast cancer risk (OR 1.00, 95% CI: 0.7–1.4) (Li, et al. 2004) [19]. In some studies the risk of breast cancer was unchanged and even reduced much further for longer duration of use of unopposed Estrogens (Greiser, et al. 2005 [7] [RR 0.99, 95% CI: 0.84-1.17]; Kaufman, et al. 1991 [20] [RR for use of at least 15 years duration was 0.9, 95% Cl 0.5-1.9]). However, these earlier results were challenged by larger observational studies.

In the collaborative re-analysis of 51 studies, the risk of breast cancer was elevated [4]. A critical evaluation [21] showed that there were methodological faults that do not allow this study to validly contribute to a cause and effect relationship.

The Women's Health Initiative randomized controlled trial of unopposed Estrogen versus placebo showed a risk reduction for Breast cancer (Manson, 2013 [22]: HR 0.79; 95%CI, 0.65-0.9;). When a critical cause and effect evaluation was applied to this study, it was concluded that there was a causal link between use of unopposed Estrogens and reduced risk of Breast cancer [11]. A subsequent observational follow-up for a further 10 years confirmed the risk reduction of Breast cancer from unopposed Estrogen compared to placebo (Chlebowski, 2019

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[23]: RR 0.77; 95% CI: 0.59–1.01). Previous observational and randomized controlled trials of unopposed Estrogens versus placebo have been combined in either a review [19] or a meta-analysis of selected studies [7]. Studies after 2005 have not been added into any systematic review. This systematic review will achieve that objective.

This report synthesizes the study results to August 2017 to determine if the association between unopposed ERT in perimenopausal and post-menopausal women and the risk of Breast cancer, irrespective of study design, shows 'increased risk', 'no risk' or 'reduced risk'.

Methodology

Search strategy

The search strategy evolved from Greiser, et al. [7]. This meta-analysis of epidemiological studies suggested that a scoping review based on the following keywords Estrogen therapy, ERT, Breast cancer, singly and in combination would identify relevant studies. This proposal did not limit the search to study types like 'case control study' or 'cohort study' or randomized/randomized controlled clinical trials. It explored all study types.

Search Keywords

The search keywords were firstly coined from the title: "Unopposed Peri-menopausal or Post-menopausal Estrogens Protect against Breast Cancer". In Stage 1, the Search keywords were Estrogen, Estrogen only HRT, Unopposed Estrogen, perimenopausal or post-menopausal and Breast cancer risk. In Stage 2, these keywords were combined in a Boolean way with 'and' to give 'Estrogen and 'Breast cancer risk', 'Estrogen replacement therapy' and 'Breast cancer risk' 'Estrogen only HRT' and 'Breast cancer risk', 'Unopposed Estrogen' and Breast cancer risk'. In Stage 3, the addition of 'Post-menopause' made little difference to stage 2 search terms.

Inclusion and exclusion Criteria

This systematic review looked at quantitative studies that had reported the risk of Breast cancer associated with unopposed Estrogen only HRT The research paradigm for this systematic review stems from a positivist tradition. It aims to bring objectivity, rigor, transparency, replication & elimination of bias to the process of synthesizing evidence. The systematic review process will allow multiple studies to be combined by meta-analysis, where appropriate to increase the precision of the overall result. By the law of large numbers, the larger the sample size, the closer the conclusions can be considered more accurate and reliable.

Inclusion criteria

Studies which have a comparison group to unopposed Estrogen only HRT:

- **Population:** Peri-menopausal or menopausal women.
- **Intervention:** Estrogen only HRT as tablets or gel or patches versus placebo or non-user controls.
- **Study designs:** Quantitative Studies which are prospective cohort studies, retrospective cohort studies, case-control studies and randomized controlled trials.
- **Outcome:** Risk of Breast cancer measured with incidence rate, prevalence rate, odds ratio, hazards ratio or relative risk.
- **Time Limits:** There were no time limits.
- **Hierarchy of evidence:** The order of hierarchy of studies is as follows:

i. Randomized controlled studies;

ii. Prospective cohort studies; o Retrospective cohort studies such as Case-control studies or cross-sectional studies.

Exclusion criteria: This systematic review excluded studies where the risk of Breast cancer was estimated in comparisons between perimenopausal or post-menopausal women on combined Estrogen + Progestogen HRT. and search terms. The Medline database (OVID) was used to identify studies that were eligible. Google Scholar was also used to retrieve studies that were eligible.

Search engines

The following databases were searched. The Cochrane database was used to identify or exclude previous systematic review on the same subject. A systematic review that is less complete was used to guide the scoping review for the search keywords and search terms. The Medline database (OVID) was used to identify studies that were eligible. Google Scholar was alsoused to retrieve studies that were eligible.

This systematic review screened topic specific review articles, systematic reviews, reference lists of pertinent studies, editorials, supplements, conference proceedings, and abstract books in English to potentially identify further studies.

Finally, this Systematic review hand searched for any articles that were not available electronically and other bibliographies.

Data extraction strategy

The full texts of all studies that met the inclusion criteria were retrieved. A data collection form was used to extract data from the eligible reports.

Quality appraisal strategy

Critical appraisal: This systematic review examined the publications that are included in the final list for methodological weakness and strengths. Each publication abstract was scrutinized for clarity and specification of the study design, for example, whether it is an observational study (prospective cohort, retrospective cohort, cross-sectional or case-control study) or a randomized controlled study or a systematic review. When this is not clear cut stated, we scrutinized the methods section to ensure that the study was clearly specified. When

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this was still not possible, then we planned to exclude the study and record the reason for exclusion.

Analysis strategy

Tabulation of data

i. Author and Date

ii. Study Design

iii. Sample size, age range and Country

iv. Intervention

v. Results

vi. Limitations and Comments

Categorical classification of the quantitative results expressed, incidence risk or prevalence rate for prospective cohort study, odds ratio for retrospective cohort study and case control studies, and relative risks or hazards ratio for randomized controlled studies of breast cancer with unopposed Estrogen from the different study designs as:

a) Significantly increased risk [relative risk or incidence rate/ratio or odds ratio greater than 1.0 but where the 95% confidence interval does not include 1.0].

b) Non-significant increased risk [relative risk or incidence rate/ratio or odds ratio greater than 1.0 but where the 95% confidence interval includes 1.0].

c) Significantly decreased risk [relative risk, incidence rate/ratio or odds ratio lesser than 1.0 but where the 95% confidence interval does not include 1.0].

d) Non-significant decreased risk [relative risk, incidence rate/ratio or odds ratio lesser than 1.0 but where the 95% confidence interval does not include 1.0].

Meta-analysis

There was no meta-analysis from this systematic review for the following reasons:

i. It would not be valid to look at different study types (prospective and retrospective studies) which cannot be combined to reach more precise estimates of the risk of Breast cancer from ERT;

ii. The benefits that a meta-analysis can achieve if all the studies were randomized controlled studies but there was only one suitable study.

iii. It will not be valid to combine different measures of effect such a hazards ratio, incidence rate, prevalence rates, odds ratio and relative risks.

iv. The scoping review had shown that there are not enough randomized controlled studies which are the only studies that can be meta-analyzed on the measurement of effect, the relative risk.

Results

Case-control studies

The majority of studies that had examined the relationship between unopposed Estrogen HRT and Breast cancer have been retrospective studies. Of the 16 retrospective studies in Table 1, eleven studies correctly used the appropriate measure of effect – that is, an odds ratio [14,15,19,24-29].

However all eleven studies incorrectly interpreted the results. Firstly, since case-control studies start from disease (the outcome we are interested to measure) such as the risk of Breast cancer, the reported odds ratio are all measuring the odds of exposure to Estrogen only HRT. In Ross, et al. 2000 [14] (OR 1.06, 95% CI 0.97-1.15 per 5 years); Lytinnen, et al. 2000 (OR 1.06, 95% CI 0.97-1.15 per 5 years); Yang, et al. 1992 [25] (OR 1.00, 95% CI, 0.80-1.30 for at least 10 years); Stanford, et al. 1995 [24] (OR 0.9 95% CI 0.7-1.3); Li, et al. 2003 (OR 1.0 95% CI, 0.70-1.4 for greater than 25 years); Magnasson, et al. 1999 [26] (OR 1.48 95% CI, 0.89-2.47); Moorman, et al. 2000 [27] (OR 0.8 95% CI, 0.5-1.2); Kirsh & Kreiger, 2002 [28] (OR 1.74 95% CI, 0.93-3.24 for greater than 10 years), Persson, et al. 1997 [3] (OR 0.5 95% CI 0.3 -1.0 for 1-10 years and OR 1.3 95% CI 0.5-3.7 for more than 11 years; Henrich, et al. 1998 [29] (OR 1.48 95% CI, 0.89-2.47).These results from case control studies show no reliable epidemiological increase in the risk of Breast cancer in women who use Estrogen alone HRT because the risk of Breast cancer was never measured.

Five studies used the relative risk as the measure of effect. However as this is reserved in the way they are calculated for randomized controlled studies, the interpretation of these results is incorrect [13,17,19,31,32]. These additional results from case control studies show no reliable epidemiological increase in the risk of Breast cancer in women who use Estrogen alone HRT because the risk of Breast cancer was never measured.

Prospective cohort studies

Five studies, reported as 'prospective studies', were supposed to have examined the relationship between unopposed Estrogen HRT and Breast cancer (Table 2). One study (Zang, et al. 2006) used the odds ratio as a measure of effect, as if the study was a retrospective study when it should have been the incidence rate or the risk ratio for the number of new cases following exposure to unopposed Estrogen. This result from the prospective cohort study by Zang, et al. (2006) was wrongly summarized and reported.

In Lytinnen, et al. [16], a valid prospective cohort of 110,984 women population, 2171 developed Breast cancer while on unopposed Estrogen only HRT. They estimated that under 5 years use, the incidence ratio was 0.93 (95% CI 0.80-1.04) which was not statistically significant. For women who used Estrogen only HRT for greater than 5 years, the incidence ratio was 1.44 (95% CI 1.29-1.59), which was a statistically significant difference between users of Estrogen only HRT and nonusers for greater than 5 years.

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Table 1: Case-control Studies.

	Study Name Year	Study type Size	Results 95%CI Relative risk (RR) Odds ratio (OR)	Comment
I	Brinton & Hoover, USA 1981 [1973-1977] 35-74 years	Case-Control Cases 881 Controls 863	(RR) of 1.24 (95% C.I. 1.0-1.5)	RR was incorrect measure of effect Interpretation was incorrect
II	Ross, et al. USA 2000 [1980-1990] 55-72 years	Case-Control Cases 1897 Controls 1637	OR 1.06 [0.97-1.15] Per 5 years	OR was correct measure Wrong interpretation
III	Lytinnen, et al. USA 2000 [1980-1990] 55-72 years	Case-Control Cases 1897 Controls 1637	OR 1.06 [0.97-1.15] Per 5 years	OR was correct measure Wrong interpretation
IV	Casagrande et al 1976 Natural Menopause	Case-Control Cases 90 Controls 83	-	No relationship shown
V	Kaufman, et al. 1991 US + Canada [1980-1986] Years	Case-Control Cases 1686 Controls 2077	RR: 1.2 [1.0-1.4 RR: 0.9 [0.4-1.9] At least 15 years	RR was incorrect measure of effect Interpretation was incorrect The results of this large study provide no evidence that the use of unopposed conjugated Estrogens increases the risk of Breast cancer, even after long durations of
				use or long latent intervals, but the possibility of a modest increase (less than a doubling) could not be excluded.
VI	Palmer, et al. Toronto 1991 Years	Case-Control Cases 607 Controls 1214	RR: 0.9 [0.6 - 1.2] RR: 1.5 [0.6-3.8] At least 15 years	RR was incorrect measure of effect Interpretation was incorrect1, 1a The results provide evidence against an increase in risk among women who used unopposed conjugated estrogens for less than 15 years and for recent users; for women with durations of at least 15 years, an increase could not be ruled out.
VII	Yang, et al. B Columbia 1992 [1988-1989] <75 years	Case-Control Cases 699 Controls: 685	OR: 1.0 [0.8 - 1.3]	OR correct measure of effect. Interpretation was incorrect1, 1a Our results suggest that everuse of estrogen, with or without progestogen, does not appreciably increase the risk of Breast cancer. However, longterm and recent use of unopposed estrogen may be associated with a moderately increased risk.
VIII	Newcombe, et al. USA 1995 [1989-1991] years	Case-Control Cases: 3130 Controls: 3698	RR: 1.05 [0.93 - 1.18] RR: 1.11 [0.87-31.43] At least 15 years	RR was incorrect measure of effect Interpretation was incorrect1, 1a
IX	Stanford, et al. USA 1995 [1998-1990] 50-64 Years	Case-Control Cases: 537 Controls: 492	OR: 0.9 [0.7 - 1.3]	OR was correct measure of effect Interpretation was incorrect1, 1a
X	Persson, et al. USA 1997 [1998-1990] 40-74 Years	Case-Control Cases: 435 Controls: 1740	OR: 0.5 [0.3 - 1.0] 1-10 years OR: 1.3 [0.5 – 3.7] 11+ years	OR was correct measure of effect Interpretation was incorrect1, 1a
XI	Henrich, et al. USA 1998 >45 years	Case-Control Cases: 109 Controls: 545	OR: 1.48 [0.89 – 2.47]	OR was correct measure of effect Interpretation was incorrect1, 1a The positive association between ERT use and invasive Breast cancer we observed"
XII	Magnasson, et al. USA 1999 50-74years	Case-Control Cases: 3345 Controls: 3454	OR: 1.48 [0.89 – 2.47]	OR was correct measure of effect Interpretation was incorrect1, 1a The positive association between ERT use and invasive Breast cancer we observed"
XIII	Moorman, et al. USA 2000 [1993-1996] Cases: 20-74 years Controls: 65-74 Years	Case-Control Cases: 397 Controls: 425	OR: 0.8 [0.5 – 1.2]	OR was correct measure of effect Interpretation was incorrect1, 1a
X1V	Kirsh, et al. USA 2002 [1995-1996] 20-74 years	Case-Control Cases: 404 Controls: 403	OR: 1.74 [0.93 – 3.24] >10 years	OR was correct measure of effect Interpretation was incorrect1, 1a
XV	Newcomb, et al. USA 2002 50-79 years	Case-Control Cases: 5298 Controls: 5571	RR: 1.39 [1.17 – 1.65]	RR was incorrect measure of effect Interpretation was incorrect1, 1a
XVI	Li, et al. USA 2003 [1997-1999]	Case-Control Cases: 975 Controls: 1007	OR: 1.0 [0.7 – 1.4] >25 years	OR was correct measure of effect Interpretation was incorrect1, 1a
	65-79 years			Women using unopposed estrogen replacement therapy (ERT) (exclusive ERT use), even for 25 years or longer, had no appreciable increase in risk of Breast cancer, although the associated odds ratios were not inconsistent with a possible small effect

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Table 2: Cohort Studies.

Study Name Year	Study type Size	Time Frame	
Zang, et al. USA, 2006 [1980-1990] 55-72 years	Prospective Cohort of WHI	OR 1.06 [0.97-1.15] Per 5 year	Should be risk ratio, or incidence Rate Ratio. Incorrectly summarized.
Lyytinen, et al. Finland, 2006 [1994-2001]	Prospective Cohort 110, 984 population 2171 cases	Incidence ratio: < 5 years: 0.93 [0.80 – 1.04] No extra cases > 5 years: 1.44 [1.29 – 1.59] 2-3 extra cases per 1000 women	No significant increase in risk within 5 years Significant increase in risk after 5 years use
Shairer, et al. USA 1994 [1980-1989]	Prospective Cohort 49017 population 276 cases	Rate ratio: < 5 years: 1.0 [0.90 – 1.2]	No increase in risk even after 20 years use
		> 20 years: 1.2 [0.8 – 1.6] 2-3 extra cases per 1000 women	
Collaborative Group on Hormonal Factors in Breast Cancer 1997 [1980-1989]	Re-analysis of individual data from 51 epidemiological studies of 52,705 premenopausal and postmenopausal women with Breast cancer and 108,411 women without Breast cancer	Re-analysis focuses on HRT. It does not report on Estrogen only HRT	The comparisons are invalid, even for HRT and Breast cancer risk since cohort studies were recasted as nested case control studies.
Million Women Study 2003	1,129,025 women 65% response by 2 years 15,759 invasive and in situ diagnosed	The results are not valid	Relative risk and incidence of Breast cancer were confused measures and therefore inappropriate. P-value used to show difference.

Shairer, et al. (1994) showed that for a valid prospective cohort of 49,017 women population, 276 developed Breast cancer while on unopposed Estrogen only HRT. They estimated that under 5 years use, the rate ratio was 1.0 (95% CI 0.9 0-1.20) which was not a statistically significant result. Even after more than 20 years, when there were 2-3 extra cases of Breast cancer in women per 1000 women, the rate ratio 1.2 (95% CI 0.80-1.60) was still not statistically significant.

The Collaborative Group on Hormonal Factors in Breast Cancer (CS study, 1997) centrally re-analyzed 90% of the worldwide epidemiological evidence from 51 studies in 21 countries. The investigators sought to examine the relationship between the risk of Breast cancer based on the use of hormone replacement therapy based on individual data on 52,705 women population of Breast cancer and 108,114 women without Breast cancer.

The CR study was neither suitable to assess the prospective relationship between individual data on 51 studies, as neither a retrospective or prospective study. There was an unusual mixed observational study which contributes little.

Indeed, Shapiro, et al. [11] critically summarized that the findings in the CR study 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. They concluded that HRT may or may not increase the risk of Breast cancer, but the collaborative reanalysis did not establish that it does. These criticisms apply equally to unopposed Estrogen and risk of Breast cancer.

The MWS investigators claim that Estrogen alone HRT also increases the risk, although to a lesser degree than does combined Estrogen and Progesterone. However, Shapiro [21] was critical again in stating that apart from size, this study was scientifically deficient in contributions to cause and effect of even HRT and risk of Breast cancer because of overwhelming biases [33].

Randomized controlled studies

There have been two studies in this classification which have the ability to strongly contribute to the "cause and effect relationship" between unopposed ERT or Estrogen only HRT and the incidence of Breast cancer (Table 3). The Women's Health Initiative randomized controlled trial of unopposed Estrogen versus placebo showed a risk reduction for Breast cancer (WHI, 2004 [10]: RR 0.77; 95% CI: 0.59–1.01) which was not-statistically significant. The WHI prospective follow-up study of 5310 women randomized to either unopposed Estrogen HRT, compared to 5429 women who used placebo, the relative risks on an intention to treat basis in the randomized groups showed a non-significant reduction in the risk of Breast cancer after 7.1 years (Relative risk 0.77, 95% CI 0.59-1.01). However after 10.7 years in the 'as treated groups', there was a significant reduction in the risk of Breast cancer in Estrogen only users of HRT compared to placebo (RR 0.67, 95% CI 0.47-0.97: Chlebowski, et al. 2019) [23].

Conclusions

Pirhadi, et al. [34] fortified the importance of correct terminology, clearly marking the difference between HRT as a combined Estrogen and Progesterone, especially in women with a womb and Estrogen alone HRT, at least with regards to the evidence for the future with regard to benefits and harms. While there is almost universal agreement that HRT as defined by Pirhadi, et al. [34] can cause Breast cancer, there has not

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Table 3: Randomised controlled studies.

WHI*	Study Type	Results	Interpretation
WHI 2004	Randomized Controlled Trial	RR 0.77; 95%; CI: 0.59–1.01	Correct interpretation
WHI 2019	WHI + Observational Prospective Follow-up for 10 years	RR 0.67; 95%; CI: 0.47–0.97	Correct interpretation

WHI* Women's Health Initiative

been consistent or in fact, no reliable evidence of the cause and effect relationship between unopposed ERT or Estrogen only HRT and Breast cancer. Secondly, Manyonda, et al. [35] make a plausible case that Progestogens of HRT are the difference between HRT and Estrogen only HRT with regards to the risks associated with Breast cancer. Lastly, Manyonda, et al. [36] made a strong theoretical argument that unopposed ERT can actually protect the breasts against cancer [37-42].

The theoretical basis that unopposed Estrogen alone in women might actually protect against Breast cancer has not previously been explored in its own right. This systematic review assessed the evidence underlying the long-standing theory that Estrogens cause Breast cancer which might deter older women from accepting Estrogen as part of HRT.

The purest form of evidence arises from studies that estimate the cause and effect relationship between the use of unopposed Estrogens and the increase risk of Breast cancer. The most available evidence on this relationship are observational case control, prospective or retrospective cohort studies or combined studies to make nested case control studies, that cannot estimate a cause and effect relationship. Basically there is no evidence. Although it is universally accepted, especially, following the Collaborative Studies [4] and Million Women's study [6], that HRT causes Breast cancer, the challenges by Shapiro, et al. [11,23], by showing the deficiencies in these observational studies as epidemiological spoofs are not widely disseminated. Their critical group analysis have not given any strong support to the standard criteria for cause and effect relationships to make the CR and the MWS results valid because apart from the size of trial, other relevant factors, singly or in combination such as time order of the association, information bias, detection bias, confounding, statistical stability and strength of association, dose/duration-response, dose response, duration-response, internal consistency, external consistency, biologic consistency and biologic plausibility were absent.

Moreover, apart from the CR study and the MWS, all of the other observational studies did not directly investigate the effects of unopposed Estrogens and the risk of Breast cancer.

The first conclusion from this systematic review is that there is no acceptable evidence that unopposed ERT has a valid association with Breast cancer. All evidence is based on case control studies which are inadequate to examine the relationship between using unopposed ERT and risk of Breast cancer. The second conclusion is that there is little acceptable evidence that unopposed ERT has a valid association with Breast cancer. Apart from Lyytinen et at 2006 [16], all prospective cohort evidence is based on studies which are inadequate to examine the relationship between using unopposed ERT and risk of Breast cancer..

The randomized control studies report differently and consistently. This best evidence shows that that there is no evidence that Estrogen alone HRT carries a higher risk of Breast cancer. They also support that unopposed Estrogen might protect against Breast cancer.

This systematic review does not support that unopposed Estrogens increased the risk of Breast cancer in older women which is consistent with the knowledge in younger girls, women young enough to be using the combined contraceptive pill, and pregnant women.

This evidence will buttress the findings that unopposed Estrogens might reduce the risk of Breast cancer and not to harm the breasts.

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