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What is True Risk of Endometrial Carcinoma from Unopposed Oestrogen Therapy: A Review of the Published Evidence

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1. Abstract

It is generally accepted worldwide that unopposed non-contraceptive Oestrogens can cause endometrial cancer in women with a uterus. This led to a change of practice that reduced the of incidence endometrial cancer by additional Progestogens. However, this addition became associated with breast cancer.

We explored the association between use of unopposed non-contraceptive Oestrogens and endometrial cancer.

Methodology: We interviewed the literature for the association between unopposed non-contraceptive oestrogens and endometrial cancer.

Results: We found 32 reports of case control studies that recruited women with endometrial cancer that had used unopposed non-contraceptive hormones.

Conclusion: We did not find any prospective cause and effect evidence of studies that use of non-contraceptive unopposed Oestrogens can lead to endometrial cancer.

2. Introduction

Most doctors worldwide would be uncomfortable to prescribe unopposed Estrogens to women who still have a uterus. The main reason is the concern about endometrial cancer. The benefits of non-contraceptive estrogen for menopausal symptoms and prevention of osteoporosis are well established and has become standard practice. Prior to 1976 however, these unopposed Estrogens, mainly conjugated estrogens, were prescribed without Progestogens. The risk of breast cancer was not recognized or discussed.

This study was concerned with the evidence about the association between unopposed non-contraceptive Estrogen therapy and the subsequent risk of endometrial cancer.

A cursory look suggested that the majority of evidence is based on case control studies which are methodologically inadequate to show that unopposed Estrogens cause endometrial cancer. A case-control study starts with women with or without endometrial cancer. It then reports on their exposure to unopposed Estrogens. The best from such research is that there is an association between presence of endometrial cancer and the use of unopposed Estrogens.

This association between disease, endometrial cancer and exposure, use of unopposed Estrogens, is far from the inferences that unopposed Estrogens cause endometrial cancer. This type of studies, so far, might be methodologically inadequate to show cause and effect between exposure and disease because they start from disease and measure the risk of exposure.

Manyonda et al. (2021) [1] have argued that Estrogen

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alone protects against breast cancer. Manyonda et al. (2021) [2] have also shown that Progesterone is the plausible cause of breast cancer.

We aim to show the strength of the evidence that led to routine addition of Progestogens to estrogens to prevent endometrial cancer in women who require hormone replacement therapy.

3. Methods

We reviewed all the publications on unopposed Estrogen use and endometrial cancer risk. We hand searched review articles (Table 1) which provided references for further hand searches (Table 2).

Table 1: We hand searched review articles.

		No (%)	Outcome Measure
1	Randomized controlled trials	0	Risk of endometrial cancer after unopposed Estrogens
2	Prospective Cohort study	0	Risk of endometrial cancer after unopposed Estrogens
3	Cross-sectional studies	0	Risk of endometrial cancer after unopposed Estrogens
3	Case-control studies	**32**	Risk of using Estrogens, if you have endometrial cancer
Total		32	

Table 2: Case-control Studies.

X `	Study Name and Year	Study type and Size	Results 95%CI: Relative risk ReR or Risk ratio RiR or Rate ratio RaR	Comments: Measure of Effect and Study Design
1	Smith et al. [7] 1975 [1960-1972]	Case-control; Cases: 317; Controls: 317	ReR: 2.66	Relative Risk was incorrect measure of effect. Interpretation was incorrect.
2	Ziel et al. [8] 1975 [1970-1974]	Case-control; Cases: 94; Controls: 188	RiR: 2.66	Risk Ratio was incorrect measure. Interpretation was incorrect.
3	Mack et al. [9] 1976 [1971-1975]	Case-control; Cases: 63; Controls: 396	RiR: 8.0	Risk Ratio was incorrect measure. Interpretation was incorrect.
4	McDonald et al. [10] 1977 [1945-1974]	Case-control; Cases: 145; Controls: 580	ReR: 0.96	Relative Risk was incorrect measure.
5	Gray et al. [11] 1977 [1947-1976]	Case-Control; Cases: 205; Controls: 205	ReR: 3.1	Relative Risk was incorrect measure. Interpretation was incorrect.
6	Feinstein et al. [12] 1978 [1974-1976]	Case-control; Cases: 149; Controls 149	ReR: 8.8	Relative Risk was incorrect measure. Interpretation was incorrect.
7	Hoogerland et al. [13] 1978 [1960-1974]	Case-control; Cases: 587; Controls: 587	ReR: 2.0	Relative Risk was incorrect measure. Interpretation was incorrect.
8	Wigle et al. [14] 1978 Canada [1971-1973]	Case-control; Cases: 202; Controls: 1243	ReR: 2.2	Relative Risk was incorrect measure. Interpretation was incorrect.
9	Antunes et al. [15] 1979 USA	Case-control; Cases: 451; Controls: 888	ReR: 6-15	Relative risk was incorrect measure. Interpretation was incorrect.
10	Völker et al. [16] 1980, Germany	Case-control; Cases: 130; Controls: 130	-	Relative risk was incorrect measure. Interpretation was incorrect.
11	Jick et al. [17] 1979, USA [1972-1977]	Case-control; Cases: 67; Controls: 74	ReR: 2.1	Relative Risk was incorrect measure. Interpretation was incorrect.
12	Weiss et al. [18] 1980 [1975-1976]	Case-control; Cases: 322; Controls: 289	ReR: 2.4	Relative Risk was incorrect measure. Interpretation was incorrect.
13	Jelovsek et al. [19] 1980 [1940-1975]	Case-control; Cases: 431; Controls: 431	ReR: 2.38	Relative Risk was incorrect measure. Interpretation was incorrect.

14	Salmi et al. [20] 1980, Finland [1970-1976]	Case-control; Cases: 318; Controls: 282	ReR: 0.76	Relative Risk was incorrect measure. Interpretation was incorrect.
15	Shapiro et al. [21] 1980, USA	Case-control; Cases: 149; Controls: 402	RaR: 3.3	Rate Ratio was incorrect measure. Interpretation was incorrect.
16	Hulka et al. [22] 1980a, USA [1970-1976]	Case-control; Cases: 256; Controls: 224	ReR: 5.2 after 3.5 years	Relative Risk was incorrect measure. Interpretation was incorrect.
17	Obrink et al. [23] 1981, Sweden [1974-1977]	Case-control; Cases: 622; Controls 1866	ReR: 5	Relative Risk was incorrect measure. Interpretation was incorrect.
18	Spengler et al. [24] 1981 Toronto [1977] 40-74 years	Case-control; Cases: 88; Controls: 177	Odds Ratio: 2.9	Odds Ratio was correct measure. Study design was incorrect.
19	Kelsey et al. [25] 1982, USA [1977-1979] 45-74 years	Case-control; Cases: 167; Controls: 903	-	Odds Ratio was correct measure. Study design was incorrect.
20	Henderson et al. [26] 1983 [1972-1979] <=45 years	Case-control; Cases: 127; Controls: 127	ReR: 1.7	Relative Risk was incorrect measure. Interpretation was incorrect.
21	La Vecchia et al. [27] 1984 Italy [1979-1983] 33-74 years	Case-control; Cases: 283; Controls: 566	ReR: 5.1 greater than 2 years of use	Relative Risk was incorrect measure. Interpretation was incorrect.
22	Shapiro et al. [28] 1985, USA [1976-1982] 50-69 years	Case-control; Cases: 425; Controls: 792	RaR: 2.1	Rate Ratio was incorrect measure. Interpretation was incorrect.
23	Buring et al. [29] 1986	Case-control; Cases: 188; Controls: 482	ReR: 3.8	Relative Risk was incorrect measure. Interpretation was incorrect.
24	Pettersson et al. [30] 1986 Sweden [1980-1981]	Case-control; Cases: 254; Controls: 254	ReR: 4.2	Relative Risk was incorrect measure. Interpretation was incorrect.
25	Ewertz et al. [31] 1988, Sweden [1977-1978] 44-89 years	Case-control; Cases: 149; Controls: 154	ReR: 10	Relative Risk was incorrect measure. Interpretation was incorrect.
26	Lawrence et al. [32] 1989 Newyork [1979-1981] 40-69 years	Case-control; Cases: 84; Controls: 168	ERT contributed very little to risk of advanced stage disease.	Study design was incorrect.
27	Rubin et al. [33] 1990 USA [1980-1982] 40-54 years	Case-control; Cases: 196; Controls: 986	ReR: 2.8	Relative Risk was incorrect measure. Interpretation was incorrect.
28	Voight et al. [34] 1991, USA [1985-1987] 40-64 years	Case-control; Cases: 158; Controls: 182	ReR: 5.7	Relative Risk was incorrect measure. Interpretation was incorrect.
29	Jick et al. [35] 1993, USA [1979-1989] 50-64 years	Case-control; Cases: 172; Controls: 172	ReR: 1.9	Relative Risk was incorrect measure. Interpretation was incorrect.
30	Brinton et al. [36] 1993, USA [1987-1990] 20-74 years	Case-control; Cases: 300; Controls: 207	ReR: 3.0	Relative Risk was incorrect measure. Interpretation was incorrect.
31	Levi et al. [37] 1993, Swiss [1988-1992] 50-64 years	Case-control; Cases: 158; Controls: 468	ReR: 2.7	Relative Risk was incorrect measure. Interpretation was incorrect.
32	Weiderpass et al. [38] 1999	Case-control; Cases: 709; Controls 3368	ReR: 6.2	Relative Risk was incorrect measure. Interpretation was incorrect.

4. Results

We identified 35 eligible studies that looked at the association between unopposed estrogens and breast cancer. There were no randomized controlled trials.

There were no clean prospective cohort studies or cross-sectional studies. One study by Gambrell et al., 1979[39] combined a prospective study and a retrospective study. It was excluded because the results could not be differentiated between the prospective incidence rate and the retrospective odds ratio.

5. Discussion

There are significant benefits of using estrogens as Estrogen Replacement Therapy (ERT) in peri-menopausal and menopausal women, including prevention of Alzheimer's Dementia [3], depression, osteoporosis and migraines. It is generally accepted that provided oral estrogens are avoided, the risks associated with thrombotic events like deep vein thrombosis, pulmonary embolism and thrombotic strokes are not elevated. Moreover, the risks associated with breast cancer are not elevated with unopposed estrogens in the short-term [4] and after long term use [5]. When Hormone Replacement Therapy (HRT) is used because of endometrial protection in women with a uterus, the risk profile changes, especially for breast cancer where there are confirmed extra risks [5,6]. The benefits of Estrogen Replacement Therapy (ERT) on the prevention of Alzheimer's dementia are also diminished [3].

The practice of avoiding unopposed estrogens for women with a uterus because of the risk of endometrial cancer changed in the 1970's. However, it is not certain that this was supported by cogent evidence-based medicine.

The standard evidence for a 'cause and effect' relationship that ERT use causes endometrial cancer can be derived from prospective cohort studies and randomized controlled studies because they start with women without endometrial cancer but develop these after exposure to unopposed Estrogen. A successful randomized controlled study has additional benefits which include elimination of bias, minimization of known and unknown confounding factors. There are no randomized studies of the 'cause and effect' relationship between unopposed estrogen use and the risk of endometrial cancer. Therefore, there is no direct relevant 'cause and effect' study to support the practice of stopping unopposed estrogens because of the risk of endometrial cancer. Similarly, there are no prospective cohort studies of the relationship between unopposed estrogen use and the risk of endometrial cancer.

The majority of evidence underpinning the relationship between unopposed Estrogen and endometrial cancer is from retrospective case control studies. These start from women with or without endometrial cancer and measure their relative exposure to ERT or not. These exposures, either as ever versus never users or users over a duration compared to never users or users over a shorter duration of time. The important point of this evidence is that it measures exposure (use of unopposed Estrogen) and not disease (development of endometrial cancer). Therefore, while these reports measure the association between unopposed Estrogen and endometrial cancer, they cannot inform on the 'cause and effect' relationship between prior unopposed Estrogen use and subsequent endometrial cancer.

This review has shown that there are no RCT's. Similarly, there were no prospective cohort studies. The majority of the evidence of association between unopposed ERT use and endometrial cancer is from retrospective studies.

There are other limitations of these case-control reports of association. Their measure of effect is an odds ratio. Any measure like a relative risk or risk difference, which are measures of randomized controlled studies are clearly wrong.

Our starting point is that unopposed ERT could protect the breast in terms of development of cancer [1]. Secondly, it is not unopposed estrogens that cause breast cancer but the combined Estrogen and Progestogens (WHI 2009), the commonest cancer in women. It is the fear of bleeding from the womb that

led to fear of endometrial cancer. BUT there was never credible evidence for this.

The choice is between the development of endometrial cancer which shows itself quickly with irregular vaginal bleeding and prompts early investigation, with lower mortality and breast cancer when unopposed estrogens are used. There is the option of using a Mirena coil to prevent cancer in the womb without exposure to breast cancer from addition Progestogens.

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