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ORIGINAL ARTICLE

Endocrine therapy for primary prevention of breast cancer: Systematic review and updated meta-analysis

Terapia endocrina para la prevención primaria del cáncer de seno: Revisión sistemática y metaanálisis actualizado

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Abstract

Introduction. Because breast cancer is a disease associated with a significant morbidity and mortality rate when diagnosed in the symptomatic period, enormous efforts have been made towards the primary prevention of this disease.

Methods. A search was conducted for all randomized clinical trials evaluating the efficacy of endocrine therapy in reducing the risk of developing breast cancer. The methodological quality of the selected studies was assessed using the Cochrane Collaboration tool to assess risk of bias in randomized trials. Heterogeneity of eligible primary studies was assessed using the T^2, I^2, H^2 statistics. Publication bias was evaluated using the Harbord test and the funnel plot. The effect measure used in this meta-analysis was the relative risk (RR) with the calculation of the 95% confidence intervals (CI).

Results. We found twelve randomized clinical trials that recruited 68,180 women who were randomly assigned to receive some type of endocrine therapy to reduce the risk of developing breast cancer or placebo. Endocrine therapy as a whole reduced the proportional risk of breast cancer (invasive plus in situ) by 42%, a statistically significant result RR 0.58 (95% CI 0.50 - 0.69).

Conclusions. Endocrine therapy is the standard preventive management in healthy women at risk of developing non-hereditary breast cancer.

Keywords: meta-analysis; breast neoplasms; primary prevention; selective estrogen receptor modulators; aromatase inhibitors.

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Resumen

Introducción. Debido a que el cáncer de seno es una enfermedad asociada a una significativa tasa de morbilidad y mortalidad cuando se diagnostica en el período sintomático, se han hecho enormes esfuerzos orientados hacia la prevención primaria de esta enfermedad.

Métodos. Se realizó una búsqueda de todos los experimentos clínicos aleatorizados que evaluaran la eficacia de la terapia endocrina para la reducción del riesgo de desarrollar cáncer de seno. La calidad metodológica de los estudios seleccionados fue valorada utilizando la herramienta de la Colaboración Cochrane para medir el riesgo de sesgo en ensayos aleatorizados. Se evaluó la heterogeneidad de los estudios primarios elegibles utilizando los estadísticos T^2, I^2, H^2. El sesgo de publicación fue evaluado mediante el test de Harbord y mediante la gráfica de *funnel plot*. La medida de efecto utilizada en este metaanálisis fue el riesgo relativo (RR) con el cálculo de los intervalos de confianza (IC) del 95%.

Resultados. Encontramos doce experimentos clínicos aleatorizados que reclutaron a 68.180 mujeres, las cuales fueron asignadas al azar para recibir algún tipo terapia endocrina para reducir el riesgo de desarrollar cáncer de seno o placebo. La terapia endocrina en conjunto redujo el riesgo proporcional de cáncer de seno (invasivo más in situ) en un 42 %, resultado estadísticamente significativo RR 0,58 ($IC_{95\%}$ 0,50 – 0,69).

Conclusiones. La terapia endocrina es el manejo estándar de prevención en mujeres sanas con riesgo de desarrollar cáncer de seno no hereditario.

Palabras claves: metaanálisis; neoplasias de la mama; prevención primaria; moduladores selectivos de los receptores de estrógeno; inhibidores de la aromatasa.

Introduction

Because breast cancer is a disease associated with a significant rate of morbidity and mortality when diagnosed in the symptomatic period, enormous efforts have been made towards the primary prevention of this disease.

Based on the concept that estrogens are immediate breast cancer promoters [1], two endocrine pharmacological strategies have been proposed to reduce the risk of developing breast cancer. The first strategy by intracellular blockade of estrogen receptors at the mammary level using selective estrogen receptor modulators, with the aim of avoiding the proliferative effect of estrogens at the level of mammary cells. The second strategy by blocking estrogen synthesis with peripheral aromatase enzyme blockers, with the aim of reducing estrogen levels.

Selective estrogen receptor modulators (SERMs) are antiestrogens at the mammary cell level and act by binding to the estrogen receptor, interfering with the transcription of estrogen-induced genes involved in the regulation of cell proliferation. Some SERMs, in addition to having an antiestrogenic effect at the mammary level, have stimulating estrogenic activity on the uterine endometrium, bones and liver, as is the case with tamoxifen.

Because of the ability of SERMs to have alternative effects on various estrogen-regulated tissues, the term "selective estrogen receptor modulators" has been used to describe this class of drugs. Selective estrogen modulators include tamoxifen, raloxifene, lasofoxifene, and arzoxifene.

The second great endocrine pharmacological strategy to reduce the risk of developing breast cancer is the blockade of estrogen synthesis at the level of the terminal stage, through the aromatase enzyme. Aromatase is an enzyme that catalyzes the rate-limiting step in estrogen biosynthesis, that is, the conversion of androgens to estrogens. Two major androgens, androstenedione and testosterone, serve as active substrates for the aromatase enzyme [2].

There are two types of agents that block the aromatase enzyme: steroidal aromatase-inactivating compounds, whose prototype is exemestane, and non-steroidal aromatase-inhibiting com-

pounds, whose prototype is anastrozole and letrozole [3].

This systematic review and meta-analysis has two primary objectives. The first is to assess the efficacy of endocrine therapy on the overall incidence of breast cancer (invasive plus carcinoma in situ), estrogen receptor-positive invasive breast carcinoma, estrogen receptor-negative invasive breast carcinoma, and ductal carcinoma in situ. The second objective is to evaluate the side effects of endocrine therapy, such as endometrial cancer, thromboembolic events, and bone fractures.

Methods

Selection criteria

According to the so-called PICOST checklist [4,5], the eligibility criteria were the following: 1) Population: pre- and post-menopausal women without previous breast cancer, with normal or increased risk of developing breast cancer; 2) Intervention: endocrine therapy with genuine activity for the reduction of the risk of developing breast cancer; 3) Control: placebo; 4) Outcomes: incident cases of breast cancer and serious adverse events; 5) Type of study: only phase III, randomized, controlled, double-blind clinical trials whose results expressed the intention-to-treat principle when evaluating TERCS versus placebo were eligible; 6) Follow-up: women were to be treated with TERCS and followed up over time to record the occurrence of breast cancer and adverse events. On the other hand, in case of finding a clinical experiment published several times, the one with the longest follow-up period was selected.

Exclusion criteria

Clinical trials comparing one endocrine therapy with another endocrine therapy were excluded. Similarly, clinical trials using pharmacological compounds other than endocrine therapy for breast cancer risk reduction were excluded. In addition, clinical trials comparing vitamin compounds for this same purpose were excluded.

Duplicate primary clinical trials were excluded, as were randomized clinical trials with $2^{x}2$ design and those with factorial design.

Information sources

For the search, the Medline (Pubmed) and Embase databases were included. In addition, the search was intensified using the list of references in the selected articles.

Search

The review authors searched for studies published until July 1, 2021. The search for this meta-analysis was conducted between April 1, 2021 and July 1, 2021.

The search filter proposed by Cochrane for clinical trials was used as search criteria: ("breast neoplasms"[MeSH Terms] OR ("breast"[All Fields] AND "neoplasms"[All Fields]) OR "breast neoplasms" [All Fields] OR ("breast"[All Fields] AND "cancer"[All Fields]) OR "breast cancer"[All Fields]) AND ("chemoprevention"[MeSH Terms] OR "chemoprevention"[All Fields]) AND ("clinical trial"[All Fields] OR "clinical trials as topic"[MeSH Terms] OR "clinical trials"[All Fields]). No time or language restrictions were made.

Screening of studies

Titles and abstracts were screened independently by two reviewers (ET and JPT) to select potentially relevant studies based on the above eligibility criteria. After excluding duplicate and non-relevant studies, the remaining articles were read in full text. Any disagreement was resolved by discussion and consensus (ET and JPT).

Data extraction

Data forms were developed and used to extract information from each identified clinical trial that met the inclusion criteria. Two reviewers independently abstracted the data for each article. Main data and outcome measures for efficacy of endocrine therapy and adverse events were extracted.

Information and statistical analysis

For each of the studies, the frequency of occurrence of any type of breast carcinoma, ie, invasive breast carcinoma plus carcinoma in situ, was tabulated for both the active treatment group and the

control treatment group. In addition, the frequency of estrogen receptor-positive invasive breast cancer, estrogen receptor-negative invasive breast cancer, and ductal carcinoma in situ was tabulated separately for both the active treatment group and the control group.

For serious adverse event outcomes, the frequency of endometrial cancer, thromboembolic events, and vertebral and non-vertebral fractures, taken together for both the active treatment group and the active treatment group, was tabulated separately for each of the studies. of control.

The percentage for the parameters in each treatment group was calculated. The epidemiological measure to express the effect of endocrine therapy on the incidence of breast cancer was the relative risk (RR), which is the ratio between the incidence of breast cancer in the experimental and in the control arms. Similarly, the RR was used to express the effect of endocrine therapy on the adverse effects of each class of them.

First, the overall impact of all drugs used as endocrine therapy in the primary studies on breast cancer incidence (invasive breast carcinoma and ductal carcinoma in situ) was assessed. Second, a subgroup analysis was performed according to the type of endocrine therapy used in the primary studies, to assess the impact of each of these drug groups on the incidence of breast cancer (invasive breast cancer and ductal carcinoma in situ). Third, the impact of endocrine therapy on the main adverse effects of each class of them was evaluated.

Evaluation of the methodological quality of the studies

The methodological quality of the selected clinical trials was assessed using "the Cochrane Collaboration tool for assessing risk of bias in randomized trials" [6]. The tool is composed of seven domains: random sequence generation RSG (selection bias), allocation concealment AC (selection bias), blinding of participants and staff BP (performance bias), blinding of outcome assessment BOA (detection bias), incomplete outcome data IOD (attrition bias), selective reporting SR (reporting bias) and other sources of bias PIA (eg, per protocol analysis rather than intention-to-treat analysis). Based on the results obtained with this tool, the included studies were classified into one of the following categories: low (-), high (+) or unclear (?) risk of bias.

Two reviewers independently assessed the methodological quality of the studies (ET and JPT). Any disagreement was resolved through iteration, discussion, and consensus.

Evaluation of the heterogeneity of the studies

Heterogeneity of primary studies was calculated using the T^2, I^2, H^2 statistics [7]. The I^2 statistic examines the percentage of total variation between studies due to heterogeneity rather than chance [7]. It was anticipated that I^2 values greater than 70% would lead to not combining the results of the primary clinical trials and performing only the systematic review. Similarly, it was anticipated that, in the absence of heterogeneity, given by I^2 values equal to zero, a fixed effects model would be chosen to pool the results of the primary clinical trials.

It was planned to use the DerSimonian–Laird random effects model to combine the results of the primary clinical experiments for I^2 values between 51% and 70%, and to use the Mantel-Haenszel common effect model to combine the results. results of primary clinical experiments in case of I^2 values between 1% up to 50%. Additionally, the heterogeneity of the studies was evaluated, using the Galbraith [8] and the L'Abbé plots [9].

Assessment of publication bias

Publication bias was evaluated using the Harbord test [10] and the funnel plot [11,12].

Statistical program used in the meta-analysis

The statistical program STATA 17.0, BE—Basic Edition (Copyright 1985-2021 StataCorp LLC / StataCorp; College Station, Texas, USA) was used with the metacommand to perform the statistical analysis. STATA 17.0 was also used to perform all the graphics required for this review.

Results

Studies' selection

Figure 1 summarizes our study selection process according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flowchart [13]. 1,876 records were obtained from the Medline database and 680 records from Embase, in addition to 4 records using the reference list in the selected articles.

After checking the title and abstract, four systematic reviews of primary prevention in breast cancer were excluded [14-17]. In total, 23 clinical trials for the primary prevention of breast cancer were excluded for the following reasons: a clinical trial called the "Study of Tamoxifen and Raloxifene" (STAR) [18,19] comparing tamoxifen versus raloxifene in postmenopausal women and a clinical trial comparing tamoxifen versus phenretidine [20]; three clinical trials comparing alendronate, zoledronate, tibolone versus placebo [21-23]; two clinical trials comparing aspirin versus placebo [24,25]; eight clinical trials comparing some type of vitamin supplement versus placebo [26-33]; seven clinical trials comparing some type of statin versus placebo [34-40], and one clinical trial evaluating anastrozole versus tamoxifen in women with ductal carcinoma in situ, the IBIS II DCIS study [41].

Finally, 12 double-blind randomized clinical trials were selected and included, and their results expressed the intention-to-treat principle for the present study [42-53]. It is noted that some included

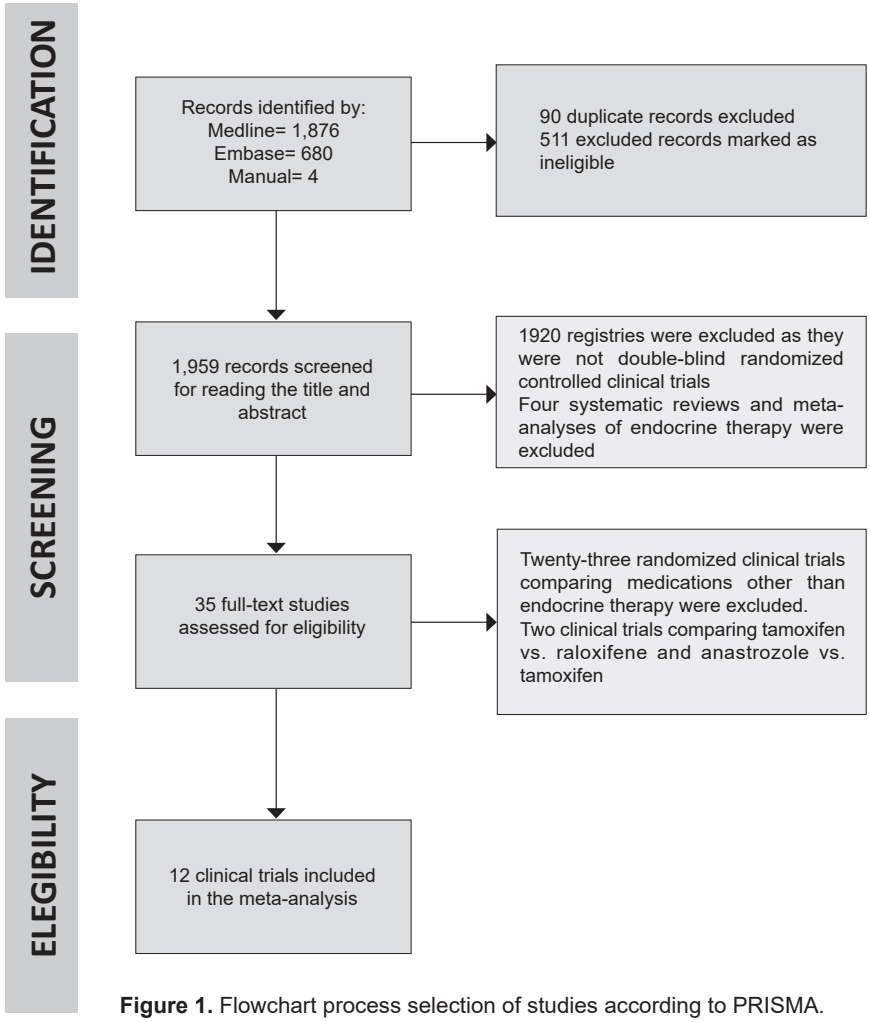

Figure 1. Flowchart process selection of studies according to PRISMA.

Source: elaborated by the authors.

randomized clinical trials were published multiple times with different follow-up periods; however, only those studies with the longest follow-up period are selected for analysis.

The twelve included clinical trials analyzed recruited a total of 68,180 women, with a total incidence of invasive breast cancer plus carcinoma in situ of 3.2%, and spanned a period of time from 1998 (the first clinical trial of prevention carried out with endocrine therapy) until the year 2019 (the last experiment).

Characteristics of the primary clinical trials included in the analysis for primary prevention of breast cancer

Four randomized clinical trials compared tamoxifen at a dose of 20 mg daily versus placebo in reducing the risk of developing breast cancer [42-45]. Two randomized clinical trials compared raloxifene at a dose of 60 mg daily versus placebo for the same purpose [46,47] and two other randomized clinical trials compared lasofoxifene, arzoxifene versus placebo [48,49].

Two randomized clinical trials compared exemestane, anastrozole versus placebo in women at high risk of developing breast cancer for the primary prevention of breast cancer [50,51]. Two randomized clinical trials compared 5 mg tamoxifen versus placebo in women with breast intraepithelial neoplasia and in women taking hormone replacement therapy for breast cancer risk reduction [52,53].

Details of the characteristics of the included randomized clinical trials are presented in table 1.

Evaluation of the methodological quality of the primary studies

According to "the Cochrane Collaboration tool to assess the risk of bias in randomized trials", the risk of bias for the 12 double-blind randomized clinical trials was low (Table 2).

Assessment of heterogeneity of primary clinical trials

The heterogeneity values of the studies using the T^2, I^2, H^2 statistics were 0.04, 61.14% and 2.57, respectively. The evaluation of the heterogeneity of the studies, using the Galbraith and L'Abbé plots, is illustrated in figures 2 and 3.

Assessment of publication bias

There was no publication bias in the present review according to the Harbord test, with a result of p=0.09. The inverted funnel plot to assess publication bias is shown in figure 4.

Overall efficacy of endocrine therapy for the primary prevention of breast cancer

Endocrine therapy as a whole reduced the proportional risk of breast cancer (invasive plus in situ) by 42%, a statistically significant result, with a RR value of 0.58 (95% CI 0.50-0.69; p=0.00). The number needed to treat (NNT) with endocrine therapy for primary prevention of breast cancer is 66; that is, 66 healthy women at risk of developing breast cancer need to be treated with an endocrine therapy agent to prevent breast cancer.

The forest plot in figure 5 shows two important findings to highlight: the Italian ITPS study did not demonstrate a preventive effect of endocrine therapy with tamoxifen at a dose of 20 mg/day in women undergoing oophorectomy. In the same sense, the HOT TRIAL study did not demonstrate a preventive effect of endocrine therapy with tamoxifen at a dose of 5 mg/day in women who take hormone replacement therapy concomitantly.

Endocrine therapy reduced the proportional risk of estrogen receptor-positive invasive breast cancer by 56%, with a statistically significant difference (RR 0.44; 95% CI 0.34-0.56). However, endocrine therapy did not significantly reduce the proportional risk of estrogen receptor-negative invasive breast cancer (RR 1.11; 95% CI 0.91-1.36).

Efficacy of selective estrogen receptor modulators for the primary prevention of breast cancer

SERMs taken together reduce the proportional risk of breast cancer (invasive plus in situ) by 39%, with a statistically significant difference (RR

Table 1. Characteristics of the included clinical experiments.

Comparative therapies (n)				Duration	Risk
RMHT (Tamoxifene 20 mg)	2471	Tamoxifene Placebo	(1238) (1233)	5-8 years	High
IBIS I (Tamoxifene 20 mg)	7154	Tamoxifene Placebo	(3579) (3575)	5-8 years	High
NSABP-P-1 (Tamoxifene 20 mg)	13.388	Tamoxifene Placebo	(6681) (6707)	5-8 years	High
ITPS (Tamoxifene 20 mg)	5408	Tamoxifene Placebo	(2700) (2708)	5-8 years	Normal Low
MORE / CORE (Raloxifene 60 mg)	4011	Raloxifene Placebo	(2725) (1286)	4-8 years	Normal
RUTH (Raloxifene 60 mg)	10.101	Raloxifene Placebo	(5044) (5057)	5 years	Normal
PEARL (Lasofoxifene 0.5 mg)	5585	Lasofoxifene Placebo	(2745) (2740)	5 years	Normal
GENERATIONS (Arzoxifene 20 mg)	9354	Arzoxifene Placebo	(4676) (4678)	4 years	Normal
MAP3 (Exemestane 25 mg)	4560	Exemestane Placebo	(2285) (2275)	5 years	High
IBIS II (Anastrozole 1 mg)	3864	Anastrozole Placebo	(1920) (1944)	5 years	High
TAM01 (Tamoxifene 5 mg)	500	Tamoxifene Placebo	(253) (247)	3 years	High
HOT TRIAL (Tamoxifene 5 mg)	1884	Tamoxifene Placebo	(938) (946)	5 years	High

Table 2. Risk of bias assessment of clinical trials.

Name of the clinical experiment	RSG	AC	BP	BOA	IOD	SR	PIA
RMHT	+	+	+	+	+	+	+
IBIS I	+	+	+	+	+	+	+
NSABP-P-1	+	+	+	+	+	+	+
ITPS	+	+	+	+	+	+	+
MORE / CORE	+	+	+	+	+	+	+
RUTH	+	+	+	+	+	+	+
PEARL	+	+	+	+	+	+	+
GENERATIONS	+	+	+	+	+	+	+
MAP3	+	+	+	+	+	+	+
IBIS II	+	+	+	+	+	+	+
TAM01	+	+	+	+	+	+	+
HOT TRIAL	+	+	+	+	+	+	+

Source: elaborated by the authors.

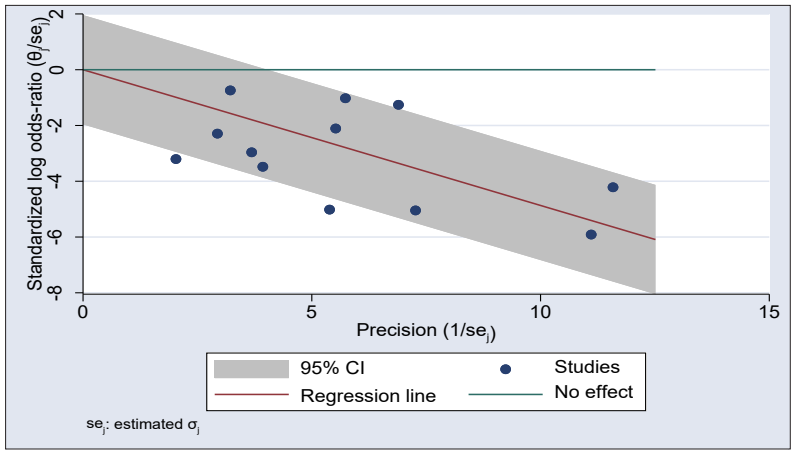

Figure 2. Galbraith plot to assess the heterogeneity of the studies.

* Source: prepared by the authors using STATA 17.

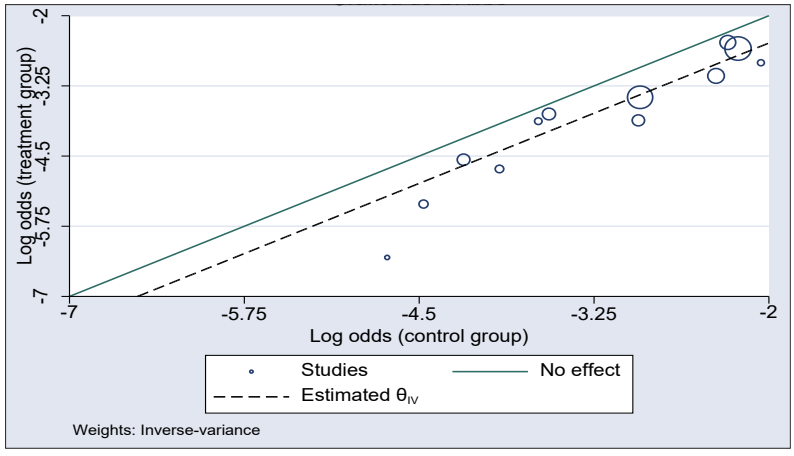

Figure 3. L'Abbé plot to assess the heterogeneity of the studies.

* Source: prepared by the authors using STATA 17.

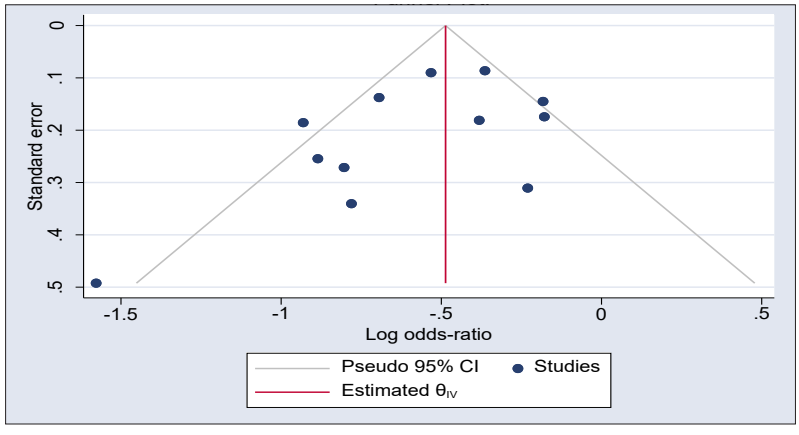

Figure 4. Inverted funnel plot to assess publication bias.

* Source: prepared by the authors using STATA 17.

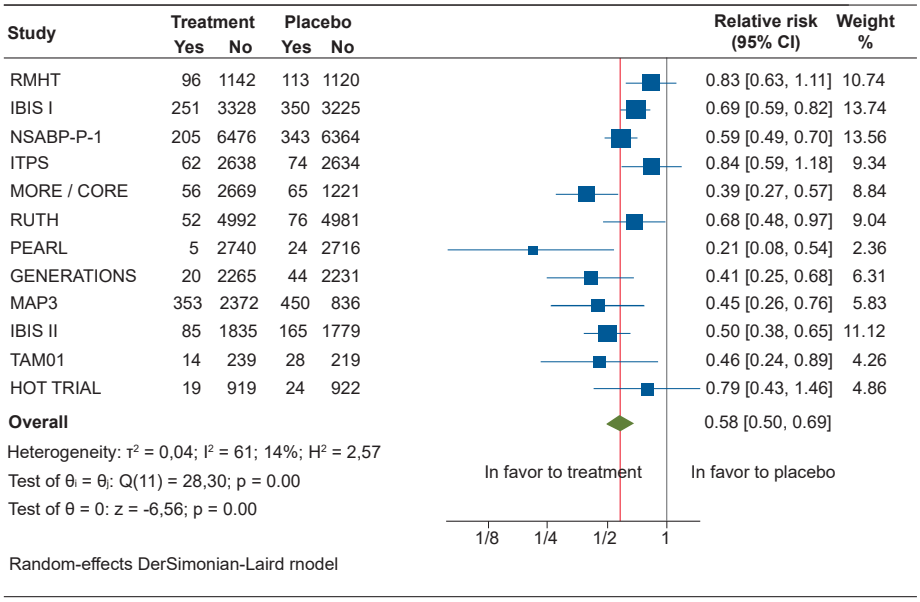

Figure 5. Efficacy of endocrine therapy for the primary prevention of nonhereditary breast cancer.

* Source: prepared by the authors using STATA 17.

0.61; 95% CI 0.51-0.73; p=0.001) (figure 6). The number needed to treat (NNT) with SERMs for primary prevention of breast cancer is 72; that is, it is necessary to treat 72 healthy women at risk of developing breast cancer with an agent of the SERMs to prevent breast cancer.

Tamoxifen at a dose of 20 mg reduces the proportional risk of breast cancer by 30% (RR 0.70; 95% CI 0.60-0.83), while raloxifene reduces the proportional risk of breast cancer by 48% (RR 0.52; 95% CI 0.30-0.89), and the drugs lasofoxifene / arzoxifene taken together reduce the proportional risk of breast cancer by 67% (RR 0.33; 95% CI 0.18 -0.62), all with statistically significant results.

It is pointed out that the TAM01 study found that tamoxifen at a dose of 5 mg per day prevents the risk of developing breast cancer by 54% in women with breast intraepithelial neoplasia (RR 0.46; CI 95% 0.24-0, 89); however, the HOT TRIAL study shows that tamoxifen at a dose of 5 mg is not effective in reducing the risk of developing breast cancer in women taking concomitant hormone replacement therapy (RR 0.79; 95% CI 0.43-1.46).

Estimation of the effect of SERMs on the risk of developing endometrial cancer

Tamoxifen at a dose of 20 mg per day significantly increased the proportional risk of developing endometrial cancer by 53.7% (RR 2.16; 95% CI 1.41-3.31) (Figure 7). In contrast, neither raloxifene (RR 0.71; 95% CI 0.21-2.42), lasofoxifene or arzoxifene (RR 1.49; 95% CI 0.48-4.62) significantly increased the proportional risk of developing endometrial cancer.

Estimation of the effect of SERMs on the risk of producing thromboembolic events

Together, selective estrogen receptor modulators increased the proportional risk of thromboembolic events by 38%, with a statistically significant result (RR 1.62; 95% CI 1.24-2.12; p=0.03) (Figure 8).

Tamoxifen increased the proportional risk of thromboembolic events by 37.5% (RR 1.60; 95% CI 1.21-2.12). Similarly, lasofoxifen and arzoxifen increased the proportional risk of thromboembolic events by 61.8% (RR 2.62; 95% CI 1.77-3.87). Raloxifen increased the proportional risk of producing thromboembolic events by 15.2%, but it

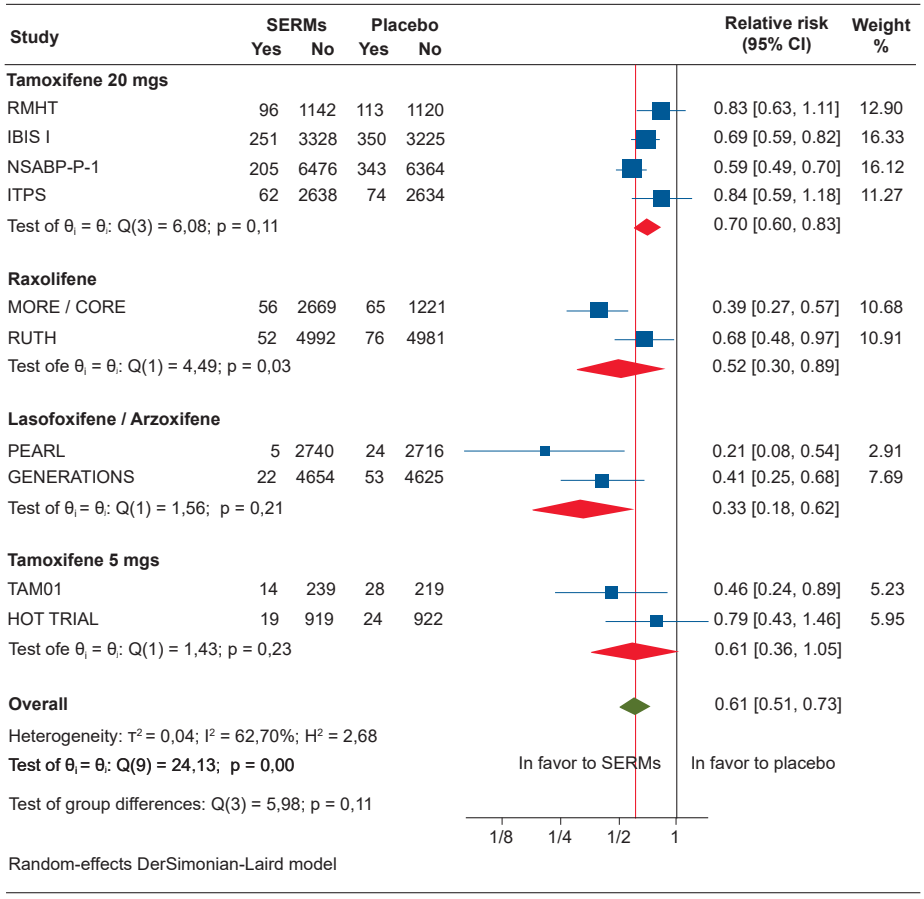

Figure 6. Efficacy of SERMs on the global incidence of breast cancer.

* Source: prepared by the authors using STATA 17.

did not reach a statistically significant result (RR 1.18; 95% CI 0.73-1.93).

Efficacy of SERMs in reducing the risk of fractures

SERMs reduced the proportional risk of fractures by 31%, with a statistically significant result (RR 0.69; 95% CI 0.49-0.98; p=0.04) (Figure 9).

Efficacy of aromatase blockers on the overall incidence of breast cancer (invasive breast cancer plus in situ)

Aromatase blockers taken together reduce the proportional risk of breast cancer (invasive plus in situ) by 51%, with a statistically significant difference (RR 0.49; 95% CI 0.38-0.62; p=0.001). The NNT with aromatase blockers for primary prevention of breast cancer is 41; that is, 41 healthy women at risk of developing breast cancer need to be treated with an aromatase blocker to prevent breast cancer.

Discussion

The only hormone therapy drug that can be given to both pre- and post-menopausal women is tamoxifen. Raloxifene, lasofoxifene, arzoxifene, exemestane, and anastrozole are used only in postmenopausal women. Endocrine therapy with tamoxifen is not indicated in women with prior oophorectomy or in women using concomitant hormone replacement therapy.

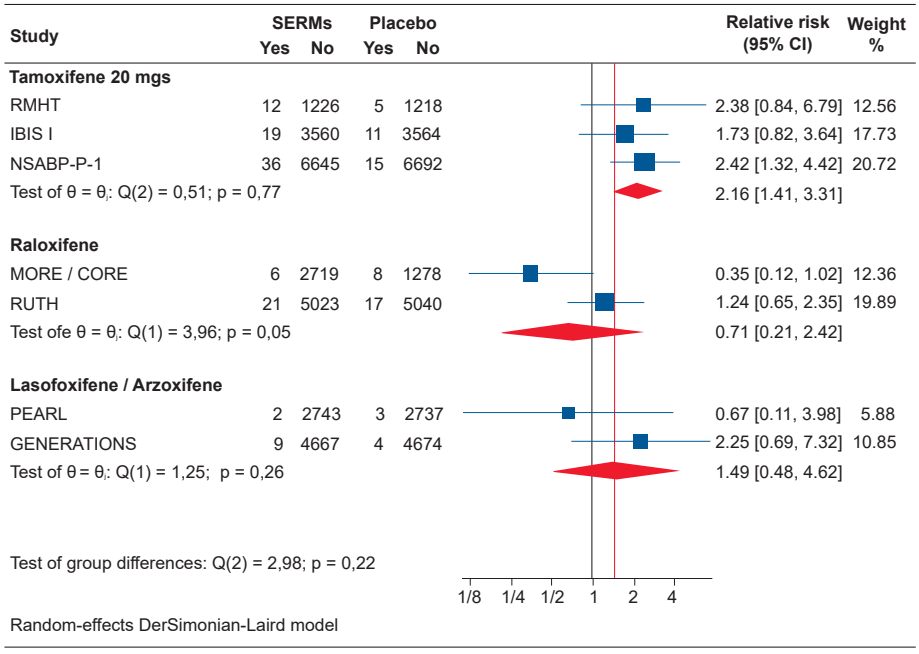

Figure 7. Effect of SERMs on the incidence of endometrial cancer.

* Source: prepared by the authors using STATA 17.

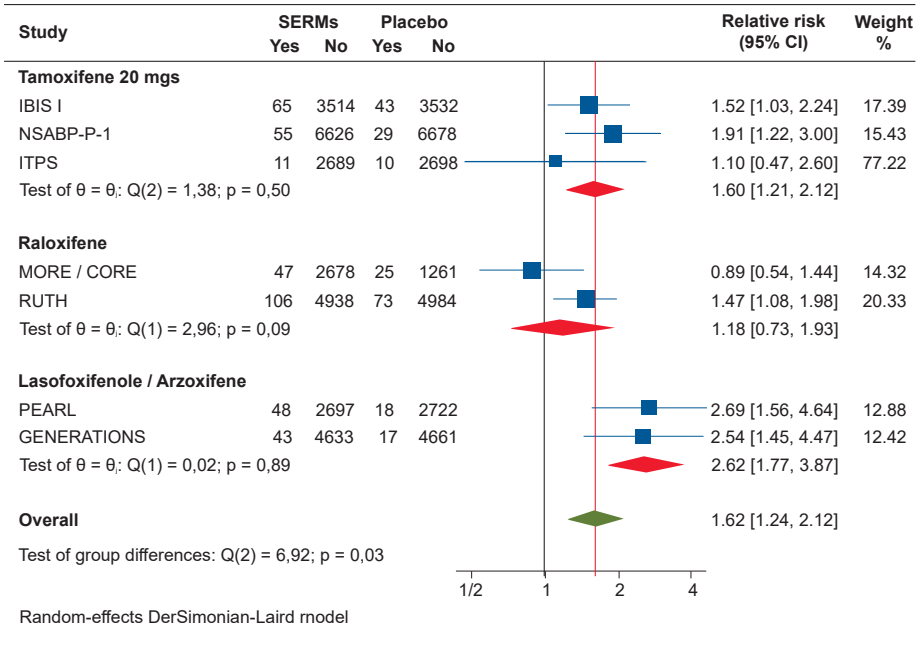

Figure 8. Effect of SERMs on the incidence of thromboembolic events.

* Source: prepared by the authors using STATA 17.

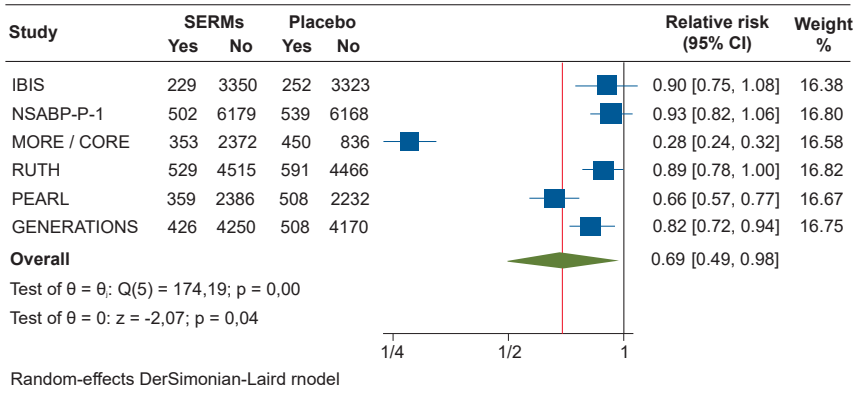

Figure 9. Effect of SERMs in reducing the risk of fractures.

* Source: prepared by the authors using STATA 17.

SERMs reduced the incidence of breast cancer primarily due to the reduction in the incidence of estrogen receptor-positive invasive breast cancer. Tamoxifen at a dose of 20 mg daily for 5 years or at a dose of 5 mg daily for 3 years is the drug of choice to reduce the risk of developing breast cancer in pre- and post-menopausal women diagnosed with breast intraepithelial neoplasia.

Raloxifene is the drug of choice to reduce the risk of developing breast cancer in post-menopausal women with an intact uterus and no history of thrombotic events. Raloxifene is the only SERM that can be used continuously for up to 8 years to treat osteoporosis, and therefore these women will secondarily benefit from this strategy in reducing their risk of developing breast cancer. Women with osteoporosis treated with third-generation SERMs with properties similar to lasofoxifen or arzoxifen will also reduce their risk of developing breast cancer as a secondary gain.

Neither SERM is indicated for breast cancer prevention therapy in women who are actively taking hormone replacement therapy.

Exemestane at a dose of 25 mg daily for 5 years and anastrozole at a dose of 1 mg daily for 5 years can be considered as effective therapy to reduce the risk of breast cancer in healthy post-menopausal women at high risk of develop breast cancer. Exemestane and anastrozole are the drugs of choice to reduce the risk of developing breast cancer in postmenopausal women with a history of thrombotic events, in whom tamoxifen and raloxifen are contraindicated.

Anastrozole and exemestane, along with tamoxifen and raloxifene, are the drugs of choice to reduce the risk of developing breast cancer in post-menopausal women diagnosed with breast intraepithelial neoplasia. Neither anastrozole nor exemestane is indicated as primary prevention therapy in pre-menopausal women.

All post-menopausal women taking aromatase blockers should receive calcium and vitamin D supplements, since these cause loss of bone mineralization. Aromatase blockers, like selective estrogen receptor modulators, are not indicated as primary prevention therapy in breast cancer in women who are actively taking hormone replacement therapy.

Conclusions

Endocrine therapy is the standard preventive management in healthy women at risk of developing non-hereditary breast cancer, specifically women who meet the following conditions:

1. Women between the ages of 35 and 59 with a projected risk of developing breast cancer greater than 1.66% at 5 years, determined by the Gail model

2. Women with a previous diagnosis of atypical ductal hiperplasia
3. Women with a previous diagnosis of atypical lobular hiperplasia
4. Women with a previous diagnosis of lobular carcinoma in situ
5. Women with ductal carcinoma in situ treated with mastectomy
6. Women older than 60 years with any of the risk factors listed above.

Compliance with ethical standards

Informed consent: This study is a systematic review of the literature, and as such there is no need for informed consent or approval from the Institutional Ethics Committee.

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