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CHANGES IN MAMMOGRAPHIC AND ULTRASOUND IMAGE OF THE BREAST OF WOMEN UNDERGOING ESTROGEN REPLACEMENT THERAPY

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Key words: Estrogenous replacement therapy / Density of mammographic image / Tabár's typology / Ultrasound examination

Objective: Evaluation of changes in mammographic and ultrasound image of the breast in female patients undergoing estrogen hormonal replacement therapy (ERT).

Material and methods: 126 women with surgical menopause in case of benign disease using ERT and a control group of 100 women in menopause with no hormonal replacement therapy were selected for the study. Changes in the mammographic image were monitored in relation to individual types of breast according to Tabár's typology and with regard to the type of ERT application. In 38 women, changes in ultrasound image were also monitored together with ERT.

Results: In 17 women (13 %) undergoing ERT, an increase in mammographic image density was found. This data was statistically significant in comparison with the control group without ERT ($\chi^2 = 21.566$, $p < 0.0001$). In 103 (82 %) women there was no change in mammographic density and in 6 women (5 %) decreased density despite using of ERT was found. In the group of patients undergoing ERT in peroral form, we found a greater percentage of women with an increased mammographic density (17 %) in comparison with the group of women with intradermally applied ERT (9 %). Increased density of mammographic image was more frequent in women with a prevalence of adipose tissue in their breasts (type II according to Tabár).

In 8 patients (21 %) of 38 women with ultrasound examination an enlargement or development of new benign formations in the breast was found; this data was statistically insignificant in comparison with the control group.

Conclusion: In women with surgical menopause undergoing ERT, a statistically significant increase in the density of mammographic image was found ($\chi^2 = 21.566$, $p < 0.0001$). Increase in density of mammographic image was most frequent in women with a predominance of adipose tissue in breasts (a type II according to Tabár) and in women undergoing ERT in the peroral form. These data were statistically insignificant in 21 % of women with supplementary ultrasound examination enlargement and development of new benign lesions in the breasts were found.

Abbreviations: ERT – estrogen replacement therapy, HRT – hormonal replacement therapy.

INTRODUCTION

In the Czech Republic, hormonal replacement therapy (HRT) is normally prescribed for women during menopause as a therapy for climacteric, organic and metabolic syndromes. Use of hormonal replacement lowers the risk of development of osteoporosis, colorectal carcinoma and ovarian carcinoma. Beneficial effects of HRT on the urogenital system and on prevention, as well as on the progress, of Alzheimer's disease are well known. A disadvantage of HRT can be temporary mastodynia and the risk of development of venous thrombosis. Epidemiological studies indicate that long term HRT (more than 10 years) slightly increases the relative risk of the development of breast carcinoma. Short term HRT has no influence on the development of breast carcinoma. HRT may increase the density of the mammographic image and, because of this, may slightly decrease the specificity and sensitivity of the mammography. With estrogen replacement therapy, more frequent development or enlargement of benign breast tumors are reported. The objective of this project was the evaluation of the change in mammographic and ultrasound images of the breast in patients with surgical menopause undergoing estrogen hormonal replacement therapy.

MATERIAL AND METHODS

Our group consisted of 126 women aged 34–65 (average age was 52) undergoing estrogen hormonal therapy after hysterectomy for benign diseases. The ERT duration for our group of women was 2–10 years, 4–5 years average.

The control group consisted of 100 women in menopause without hormonal replacement. In 126 women, we retrospectively compared the mammographic image before commencement and after 1–2 years of use of the

hormonal replacement. 69 women used estrogens in a peroral form – Estrofem 2 mg and Premarin 0.625 mg preparations. In 57 women, the estrogens were applied intradermally, in an adhesive plaster form – Estraderm 25, Estraderm 50, Dermestril 25 and Systen 50.

We also evaluated mammographic image changes with regard to the manner of administration of ERT (peroral or intradermal) and in relation to the individual types of breast according to Tabár's typology. The mamographs were produced by the Senographe DR^+ apparatus manufactured by General Electric co. We compared images of both breasts produced by standard projections – craniocaudal and mediolateral. The change of the mammographic image density during ERT administration was evaluated on the basis of an increase in nodular or merging breast densities. This was our modification of an evaluation used in the Özdemira et al., 1999 (Table 1) study. An increase or decrease of up to 25 % of the original volume was considered moderate (1st degree), medium-from 25 to 50 % (2nd degree) and significant-over 50 % (3rd degree).

In 38 women, a supplementary ultrasound examination was carried out on the Logic 500 apparatus manufactured by General Electric co. or the Aspen apparatus from Acuson co. The examination was carried out by a linear probe with 9–12 MHz frequency. In these women, ultrasound findings before the commencement of the therapy and after 1–2 years of ERT administration were evaluated. The results were compared with the ultrasound results from the control group of 30 menopause women without hormonal replacement therapy.

A χ^2 was used for an analysis of statistical results.

RESULTS

From the group of 126 women patients undergoing ERT, in 103 (82 %) there was no change in the mammographic image during hormonal replacement therapy.

An increase in mammographic image density was found in 17 women (13 %) and a decreased density in 6 women (5 %). The increased mammographic image density was moderate (1st degree) in 14 patients and medium (2nd degree) in 3 patients. We found no significant (3rd degree) increase in any case. There was a 1st degree decrease in density of breast parenchyma during ERT administration in 4 patients and a 2nd degree in 2 patients (Table 2). During monitoring there was no increase in mammographic image density in any of the patients from the control group of 100 women; in 32 %, we found a decrease in mammographic image density with physiological involution of the breast in progress in menopause.

An increase in mammographic density in women undergoing ERT was statistically significant in relation to the control group ($\chi^2 = 21.566$, $p < 0.0001$).

In a group of women using estrogen replacement in a peroral form, there was a higher incidence of increased mammographic image density (17 %) in comparison with a group of women with intradermal estrogen application (9 %) (Table 3 and 4). This difference was not statistically significant. Evaluation of mammographic image changes with regard to the breast typology according to Tabár showed that the highest number of patients with an increased mammographic density was a type II according to Tabár (18 %) (Table 5, 6 and 7). With regard to an increase in mammographic density for other breast types acording to Tabár, no statistical significance was found.

In 38 women from the group of 126 patients undergoing ERT, a supplementary ultrasound examination of breasts was carried out. In 30 women (79 %), there was no ultrasound diagnosis change in comparison with an earlier check-up. In 8 women (21 %), an enlargement or development of new benign formations in the breast was found (Table 8). In these women, at the same time, there was no apparent increase in mammographic density. Development of simple cysts was also found in 4 (10 %) patients from the control group of 30 menopause women with no hormonal replacement therapy. The difference was not statistically significant.

During ERT, in our group of patients, no incidence of breast carcinoma was registered.

Table 1. Evaluation of increase of mammography density.

• No change		(0)
• Moderate change	up to 25 %	(±1)
• Medium change	25–50 %	(±2)
• Significant change	over 50 %	(±3)

Table 2. Mammographic image changes in 126 women with ERT.

126 women			
No change od density	103 (82 %)		
Increase in density	17 (13 %)	+1	14
		+2	3
		+3	0
Decrease in density	6 (5 %)	–1	4
		–2	2
		–3	0

Table 3. Mammographic image changes in 69 women with peroral application of ERT.

69 women with peroral application of ERT	
No change in density	55 (80 %)
Increase in density	12 (17 %)
Decrease in density	2 (3 %)

Table 4. Mammographic image changes in 57 women with intradermal application of ERT.

57 women with intradermal application of ERT	
No change of density	48 (84 %)
Increase in density	5 (9 %)
Decrease in density	4 (7 %)

Table 5. The percentual representation of individual breast types according to Tabár in 126 women with ERT.

Tabár I	Tabár II	Tabár III	Tabár IV	Tabár V
37 (29 %)	38 (30 %)	30 (24 %)	14 (11 %)	7 (6 %)

Table 6. Mammographic image changes with regard to individual types of breast according to Tabár.

	Increase in density	No change of density	Decrease in density
TABÁR I (37 women)	6 (16 %)	28 (75 %)	3 (9 %)
TABÁR II (38 women)	7 (18 %)	31 (82 %)	0
TABÁR III (30 women)	3 (10 %)	25 (83 %)	2 (7 %)
TABÁR IV (14 women)	1 (7 %)	12 (86 %)	1 (7 %)
TABÁR V (7 women)	0	7 (100 %)	0

Table 7. Evaluation of mammographic image changes with regard to individual types of breast according to Tabár.

Density / Type of breast	+2	+1	0	–1	–2
TABÁR I 37 (29 %)	1	5	28	2	1
TABÁR II 38 (30 %)	2	5	31	0	0
TABÁR III 30 (24 %)	0	3	25	2	0
TABÁR IV 14 (11 %)	0	1	12	1	0
TABÁR V 7 (6 %)	0	0	7	0	0

Table 8. Ultrasound image changes in 38 patients with ERT.

<table>
<tr><td colspan="4">Ultrasound image changes in 38 women with ERT</td></tr>
<tr><td rowspan="2">Normal finding
20</td><td colspan="3">Benign lesions
18</td></tr>
<tr><td>No change
10</td><td>Enlargement
4</td><td>New lesions
4</td></tr>
<tr><td></td><td>Cysts < 1 cm
6
Cysts >1 cm
2
Fibroadenomas
2</td><td>Cysts 3
Fibroadenoma
1</td><td>Cysts 3
Fibroadenoma
1</td></tr>
<tr><td colspan="2">30 women without change in ultrasound (79 %)</td><td colspan="2">8 women with change in ultrasound (21 %)</td></tr>
</table>

DISCUSSION

At present, in developed countries, 30–50 % women in menopause are undergoing HRT in some form. Since the early nineties, in the Czech Republic, the number of users of hormonal replacement therapy has increased considerably.

Currently 90 % of women reach menopause age and spend one third of their lives in this phase. Hormonal replacement therapy therefore has greater and greater impact on health and quality of life of the postmenopausal female population. HRT alleviates the symptoms of menopause and is a therapy for the prevention of osteoporosis for postmenopausal women. It is reported that HRT reduces the relative risk of colorectal carcinoma by 30–50 %. A beneficial effect of HRT on the central nervous and urogenital system is also known. These advantages outweigh the negative HRT effects which include temporary mastodynia and a certain risk of venous thrombosis. Estrogen replacement therapy increases the risk of development of endometrial carcinoma and estrogen monotherapy is thus for women with hysterectomy. A higher risk of endometrial carcinoma in women with a uterus is eliminated by adding progestogen[1].

The question, which is discussed most frequently, is whether HRT increases the risk of development of breast carcinoma. The main reason for controversial opinions related to these problems is the fact that we do not know the exact cause of breast carcinoma development nor the precise contribution of endogenous and especially exogenous sex hormones. Extensive studies report a moderate increase of the relative risk of breast carcinoma development in women with a long term use of HRT[2, 3].

It is apparent from studies, that the relative risk is higher with users of combined hormonal replacement in comparison with users of estrogen hormonal replacement[4,5]. Short term hormonal therapy does not have any influence on development of breast carcinoma[6,7].

Use of hormonal replacement before diagnosis of breast carcinoma does not influence negatively the prognosis and biological behaviour of tumors[1,8]. Women with breast carcinoma diagnosed during HRT, on the contrary, have a longer survival time, explained not only by a smaller size of carcinoma with regular checkups of HRT users, but also by the biologically more favourable characteristics of tumors[9-11].

HRT increases, by a certain percentage, the density of mammographic image[12-14]. Increased mammographic density is caused by vasodilatation with edema, proliferation of breast fibrous stroma and to a lesser degree also proliferation of epithelium. The conclusions of various studies are in agreement; an increase in the density of mammographic image is more significantly influenced by combined, that is estrogen – progestogen therapy (a density increase is reported in about 35–55 % of women) than by estrogen monotherapy (a density increase is reported in 12–20 % of women)[15-17]. In 17 women (13 %) from our group of 126 women undergoing ERT an increase in mammographic image density was found.

With combined hormonal replacement, a more significant density increase in the breast is reported with continual administration of estrogens and progestogens than with estrogen therapy in cyclic combination with progestogens[6,16].

A less obvious density increase and at a lower percentage level is reported with intradermal application of hormonal replacement therapy in comparison with peroral application[15]. In our group of women using ERT in a peroral form, there was also a higher incidence of increased mammographic image density (17 %) in comparison with intradermal estrogen application (9 %).

It is reported that density increases in relation to type of breast and namely in breasts with a predominance of adipose tissue[16] (a type II and III according to Tabár). In our group of 126 women using ERT the highest number of patients (18 %) with an increased mammographic density was a type II according to Tabár.

On the mammogram, a density increase is apparent very early after commencement of hormonal therapy, after a few weeks or months, and thus decreases equally quickly after termination of HRT. A density increase is usually symmetrical and diffuse, but it can also be asymmetrical and can have a focal or multi-focal character. The Tibolon's study even reports a decrease in density of mammography with the use of this hormonal replacement[18]. In 6 women (5 %) we found a decreased density in breast despite using of ERT.

Some studies report enlargement or development of new benign lesions in the breast (cysts and fibroadenomas) resulting from HRT and this is more significant with estrogen monotherapy than with combined hormonal replacement therapy and has no relationship with a breast density increase as a whole[14]. An enlargement or development of new benign formations in the breast were found in 21 % of women from our group.

To interpret mammographic images of women with HRT correctly, it is necessary that the radiologist have certain knowledge of hormonal replacement therapy. Women in the Czech Republic, who are undergoing HRT, are being monitored within a screening system and the data related to HRT are part of a special questionnaire. Before commencement of hormonal replacement therapy, a mammographic examination is required. Further mammographic check-ups are indicated for asymptomatic women who are undergoing HRT at one-year intervals.

HRT reduces mammographic specificity and sensitivity for carcinoma in the mammographic screening system by about 1–4 %[12]. These results in a moderate increase of the number of women called for a post-mammography supplementary examination, meaning an ultrasound examination or completion of special mammograms or interventionist diagnostic performance (so called "recall rate" in the screening system is increased).

Studies report that despite a certain decrease in mammographic sensitivity, no statistically significant difference in the number of mammographically diagnosed carcinoma, their stages or in the number of negative falsely interpreted mammograms have been proven with HRT users and non-users of hormonal replacement therapy[2,9].

CONCLUSION

1. In women with surgical menopause undergoing ERT, a statistically significant increase in the density of mammographic image was found ($\chi^2 = 21.566$, $p < 0.0001$).
2. Increase in density of mammographic image was most frequent in women with a predominance of adipose tissue in breasts (a type II according to Tabár). This data was statistically insignificant.
3. In a group of patients undergoing ERT in the peroral form, a greater percentage of women with increased mammography density was found in comparison with a group of women with the intradermally applied ERT. This data was of no statistical significance.
4. In 21 % of women with supplementary ultrasound examination enlargement and development of new benign lesions in the breasts were found. It was statistically insignificant in comparison with a group of non-users of ERT.

Fig. 1. 42-year old woman undergoing ERT (Premarin, 0.625 mg) after hysterectomy for two years. Mammographic images of both breasts in oblique view, on the left before undergoing ERT. Mammograms of both breasts in oblique view, on the right after undergoing ERT for two years. Diffuse increase in breast density (1st degree). Breast type I according to Tabár.

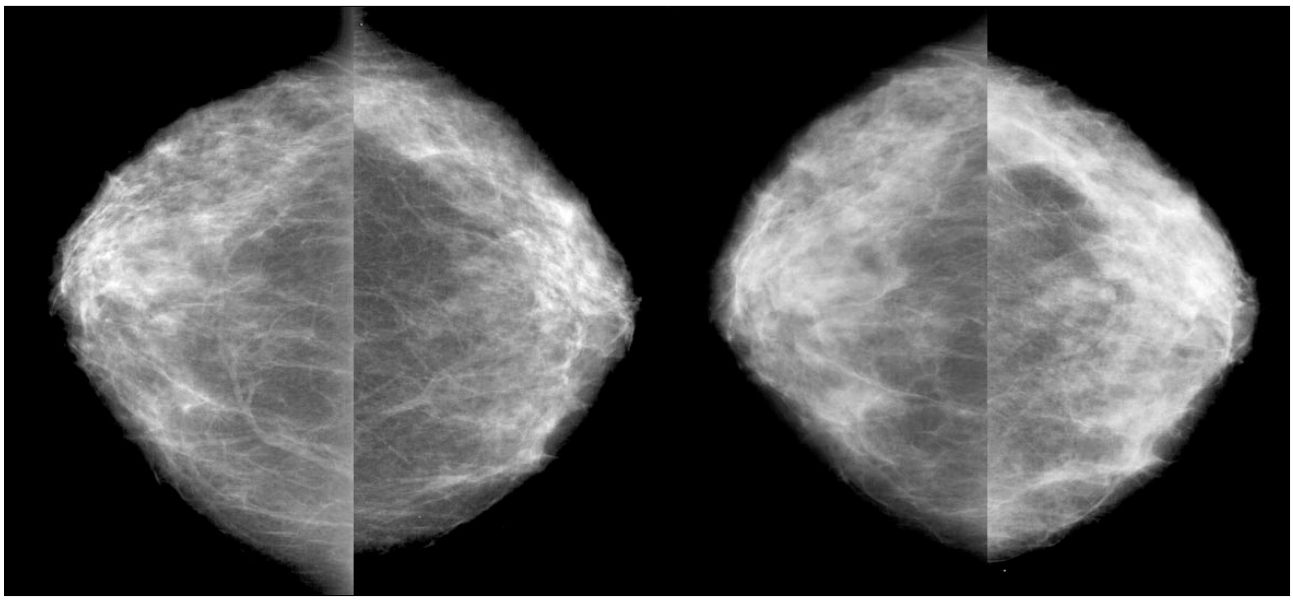

Fig. 2. Mammographic images of the same woman in craniocaudal view- on the left before undergoing ERT and on the right after two years of using ERT. Moderate increase in breast density mainly in outer parts of both breasts.

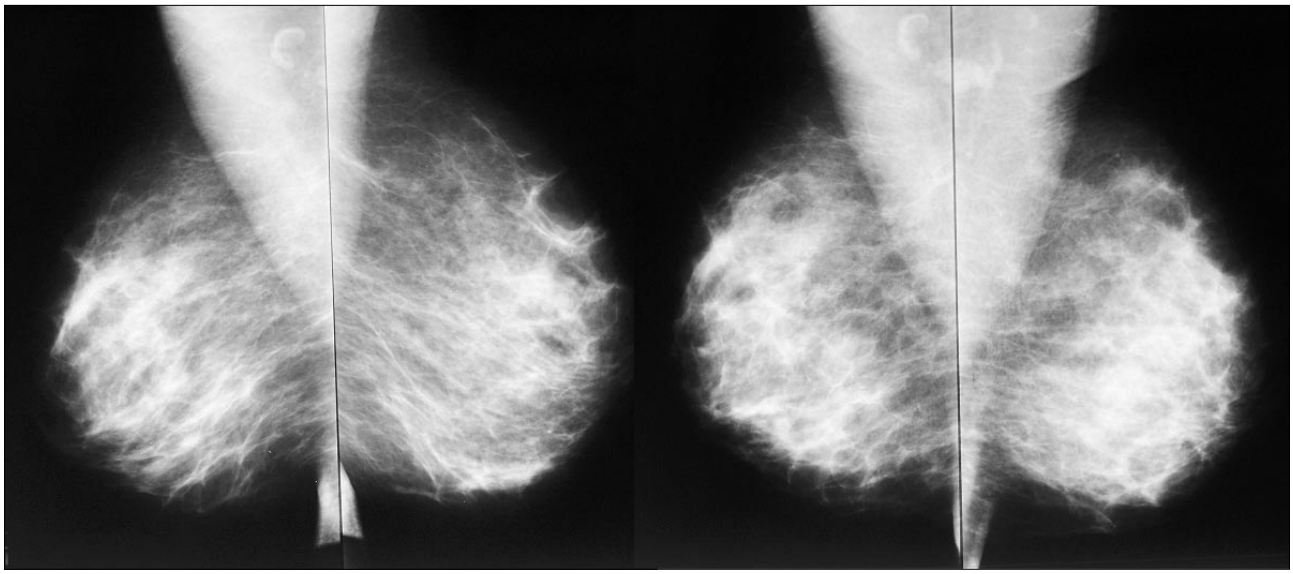

Fig. 3. 49-year old woman in surgical menopause undergoing ERT (Estraderm 50, plaster) for one year. Mammograms of both dense breasts in oblique view before (on the left) and after (on the right) undergoing ERT. Moderate (1st degree) increase in breast density in upper outer quadrant of both breasts. Breast type IV according to Tabár.

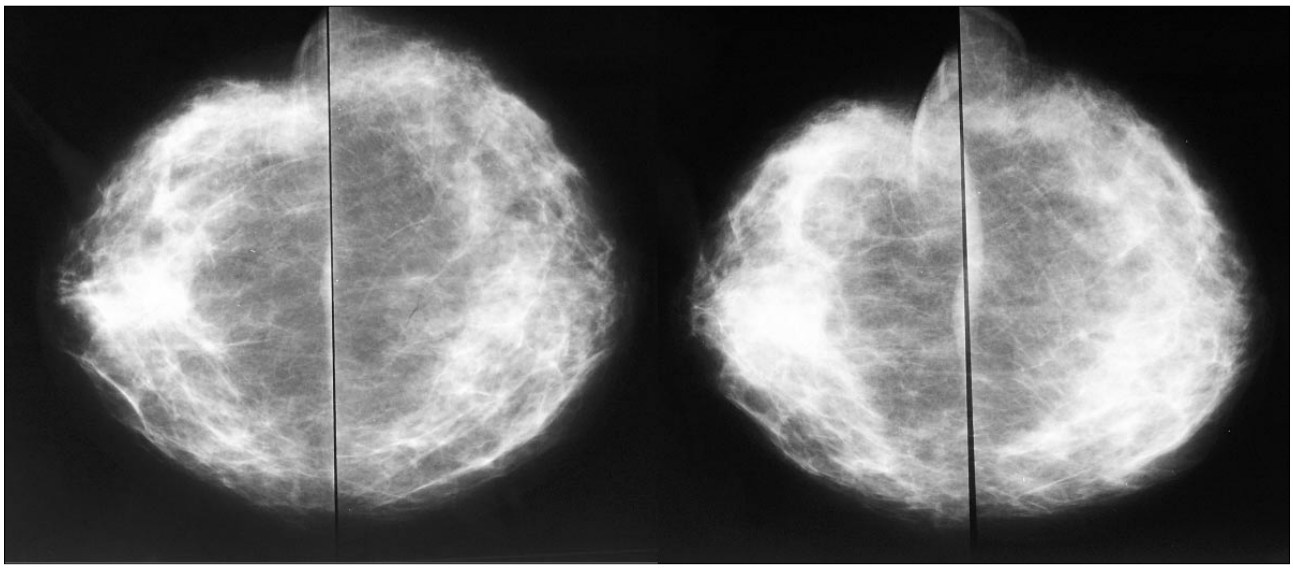

Fig. 4. Mammograms of the same woman, both breasts in craniocaudal view before undergoing Estraderm and one year after.

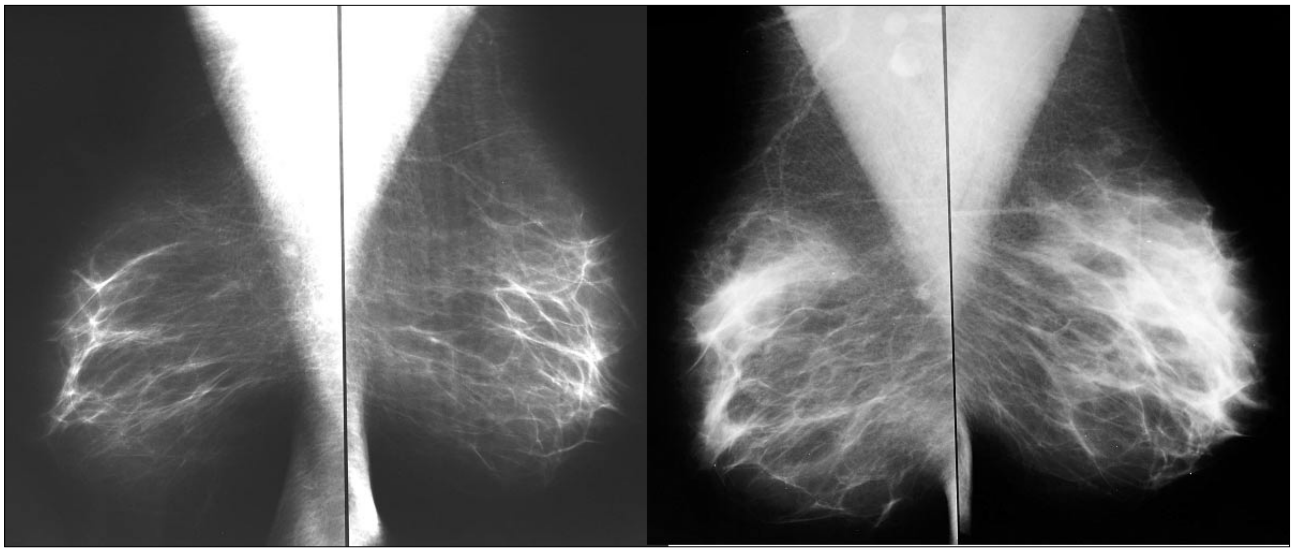

Fig. 5. 53-year old woman in menopause after hysterectomy undergoing Estrofem for two years. Mammograms of both breasts in oblique view- on the left before undergoing ERT and on the right after two years of ERT use. Diffuse medium increase in breast density of 2nd degree is notable. Breast type II according to Tabár.

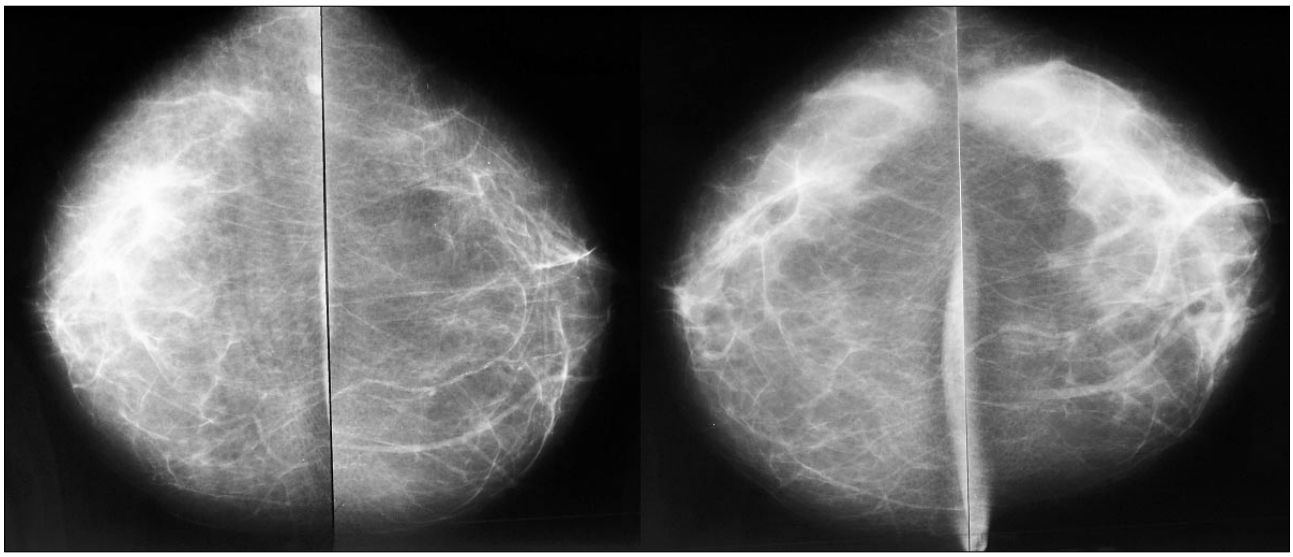

Fig. 6. Mammograms of the same woman in craniocaudal view. On the right medium increase in breast density after undergoing Estrofem for two years.

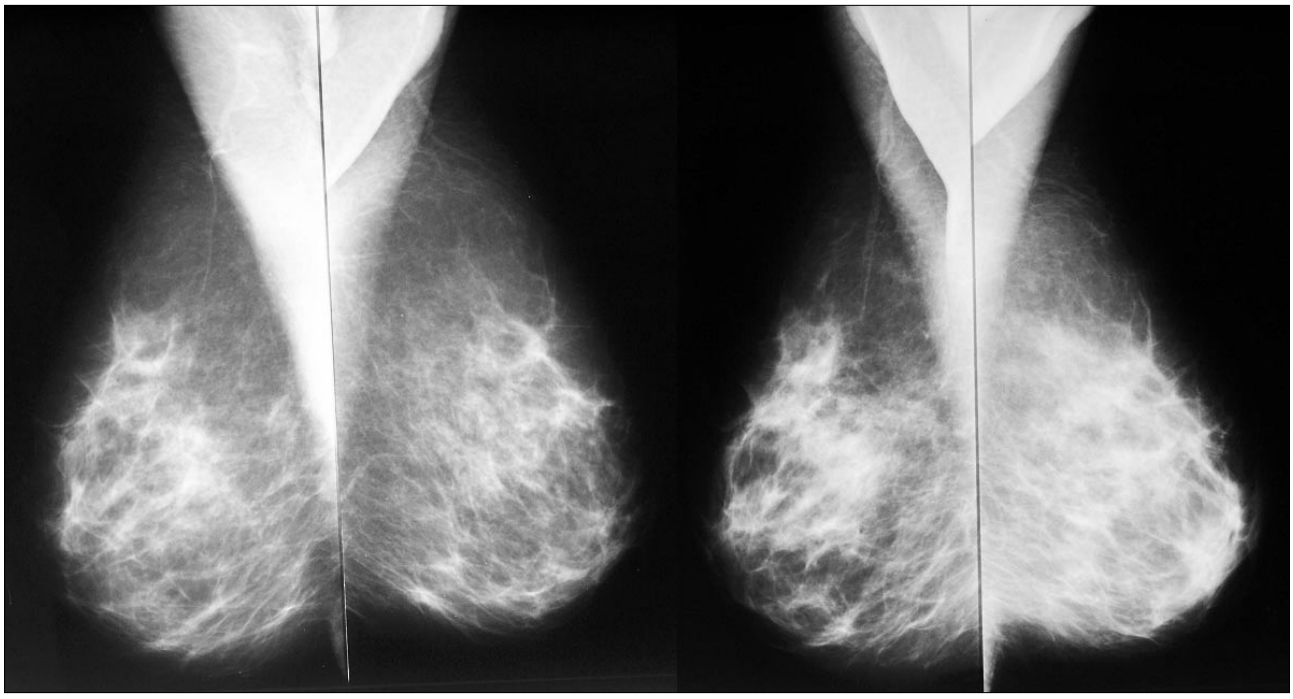

Fig. 7. 36 year old woman undergoing Estraderm 50 after hysterectomy and bilateral oophorectomy for two years. Mammographic images of both breasts in mediolateral view. Moderate increase (1st degree) in breast density after undergoing ERT for two years is notable on the right. Breast type IV according to Tabár.

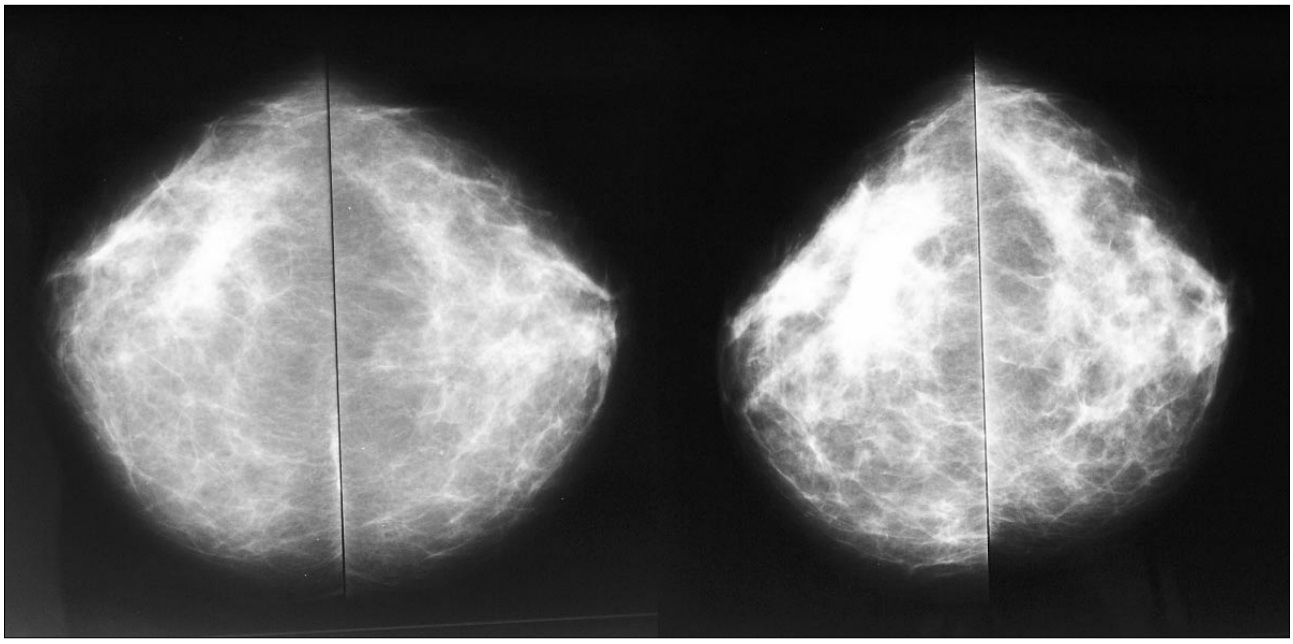

Fig. 8. Mammograms of the same 36-year old patient in craniocaudal view. On the right increase in breast density after undergoing Estraderm 50.

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