

# Breast Pathology and Cancer Diagnosis: A Link Between Hormonal Replacement Therapy and Breast Cancer Risk

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## ABSTRACT

**Objective:** The main objective of this study was to investigate the link between the hormonal replacement therapy and the risk of breast cancer.

**Study Design:** Case-control study

**Place and Duration of Study:** This study was conducted at the Department of Pathology, Watin Medical and Dental College, Rawalpindi from January 2019 till January 2020.

**Materials and Methods:** In this study 700 females, aged from 50 to 70 years were included. All of these females were past menopause and recently got diagnosed with the primary invasive breast carcinoma. All the data of patients was collected from Watin medical and dental college hospital's data base. The women included in this study were divided into four groups: the one that did not have history of hormonal replacement therapy, the one with less than 2 years of HRT, the one with 2 to 5 years of HRT and the one with more than 5 years of HRT. These groups were compared using ANOVA test and chi-square test. To measure the hazard ratio of the prevalence of breast cancer in accordance to the time period of hormonal replacement therapy, Cox proportional hazards regression analysis was used. SAS software was used to analyze all of the data. P value less than 0.05 was considered significant.

**Results:** Out of 700 women included in this study, 15.1% had used HRT at some point in their life. 0.7% of the women got diagnosed with the breast cancer newly after almost 5 years of follow up. The hazard ratio was 1.35 (95% CI 1.33, 1.40) of breast cancer risk in hormonal replacement therapy users in comparison to the non-users. The results show that the occurrence of breast cancer increases with the increase in the duration of HRT. The women who got HRT for less than 2 years had hazard ratio of 1.09 (95% CI 1.05, 1.23). The women who got HRT for 2 to 5 years had hazard ratio of 1.42 (95% CI 1.36, 1.50) and the one who got this therapy for more than 5 years had hazard ratio of 1.83 (95% CI interval 1.74, 1.93). This pattern of increase in the breast cancer incidence with the increase in HRT duration was observed in both, the women who had invasive breast carcinoma and the women who had ductal carcinoma in situ. The breast cancer risk associated with HRT was also more in older women and the women with breasts of high density.

**Conclusion:** As the results show, the risk of breast cancer do increase with the use of hormonal replacement therapy. As the duration of HRT increased, so did the risk of breast cancer. Risk factors like old age and higher breast density also increased the risk of breast cancer related to HRT.

**Key Words:** Breast cancer, Hormonal replacement therapy, breast carcinoma.

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## INTRODUCTION

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Hormone Replacement Therapy (HRT), is a therapy done to alleviate the symptoms of menopause. After menopause the women are no longer able to reproduce hence it marks the end of the reproduction.

The use of HRT increased rapidly back in the days when it was approved for the prevention of osteoporosis in postmenopausal women<sup>1</sup>. But later its use decreased due to the publications that reported its (HRT) association with increased risk of breast cancer<sup>1,2</sup>. Since then, many studies have reported the link between HRT and increased breast cancer incidence<sup>3,13</sup>. Nonetheless, whether all postmenstrual women are at increased risk of breast cancer due to HRT or not, is not clear yet.

The symptoms that this therapy alleviate, other than preventing osteoporosis, are night sweats, vaginal dryness, hot flushes, reduced sex drive and mood swings<sup>11</sup>.

Other than increasing the risk of breast cancer, HRT also increases the risk of ovary cancer, stroke, endometrium cancer and thrombus<sup>12</sup>.

Most studies that investigated the link between the hormonal replacement therapy and the risk of breast cancer were conducted in the western countries<sup>4, 13</sup>. But the dynamic of breast cancer is very different in western countries and in Asian countries. The age at which the incidence of breast cancer is highest differs in both regions. In Asian countries this age is between 40 to 50 years while in western countries this age is 60 to 70 years<sup>5, 6</sup>. The type of most common breast cancer are also different in both the regions. For instance the most common type of breast cancer in Korea is estrogen receptor negative<sup>7</sup>.

There are some risk factors contributing to the HRT related breast cancer risk. Obesity is one of those. Postmenstrual women are at increased risk of breast cancer if they are obese. Another one of those risk factor is breast density<sup>8</sup>. The history of breastfeeding and the use of oral contraceptives impacts the prevalence of breast cancer. They also effect the use of HRT<sup>9, 10</sup>.

The decision to use the hormonal replacement therapy depends on its risk to benefit ratio of the individual case. In this study, we investigated the link between the hormonal replacement therapy and the risk of breast cancer.

## MATERIALS AND METHODS

In this study 700 females, aged between 50 to 70 were included. All of these females were post menopause and recently got diagnosed with the primary invasive breast carcinoma. These patients had their cancer diagnosed between Jan 2019 and Jan 2020. All the data of patients included in this study was collected from Watin medical college hospital's database. The women included in this study were divided into four groups: the one that did not have any history of hormonal replacement therapy, the one with less than 2 years of HRT, the one with 2 to 5 years of HRT use and the one with more than 5 years of HRT.

The data collected included age of menopause, history of oral contraceptive, history of hormonal replacement therapy, history of breastfeeding, and diagnosis of any previous benign breast lumps.

The four groups of women based on the duration of hormonal replacement therapy were compared using ANOVA test and chi-square test. To measure the hazard ratio of the prevalence of breast cancer in accordance to the time period of hormonal replacement therapy, Cox proportional hazards regression analysis was used. Age, history of oral contraceptives, breastfeeding history and

breast density were adjusted. SAS software was used to analyze all of the data. P value less than 0.05 was considered significant.

## RESULTS

In this study, out of 700 postmenopausal 15.1% had at some point in their lives used HRT. The results show that out of total, 85% of the participants had no history of HRT. 8.5% off the women used HRT for less than 2 years, 3.6% used it for 2 to 5 years and 3% of the women used HRT for more than 5 years. These results are given in Table 1.

Women who never opted for HRT had more fatty breasts, history of breastfeeding and had no history of benign breast lumps. On the other hand, the women who took oral contraceptives for longer duration and gave no births had linear relation with the duration of HRT.

0.7% of the women got diagnosed with the breast cancer newly after almost 5 years of follow up. 93% of these women had invasive breast carcinoma while the 7% had ductal carcinoma in situ. The hazard ratio was 1.35 (95% CI 1.33, 1.40) of breast cancer risk in hormonal replacement therapy users in comparison to the non-users.

The multivariate analysis of breast cancer incidence according to HRT duration is shown in Table 2. These results show that the occurrence of breast cancer increases with the increase in the duration of HRT. The women who got HRT for less than 2 years had hazard ratio of 1.09 (95% CI 1.05, 1.23). The women who got HRT for 2 to 5 years had hazard ratio of 1.42 (95% CI 1.36, 1.50) and the one who got this therapy for more than 5 years had hazard ratio of 1.83(95% CI 1.74, 1.93). This pattern of increase in the breast cancer incidence with the increase in HRT duration was observed in both the women who had invasive breast carcinoma and the women who had ductal carcinoma in situ.

The link between the risk of breast cancer and HRT according to risk factors of breast cancer is shown in Table 3. The results show that the women of age older than 66 were at higher risk of HRT related breast cancer with the P interaction value being less than 0.0001. The association also varied with the breast density. The women with higher breast density i.e. 51 – 75 % breast density, hazard ratio 1.38 (95 % CI 1.29, 1.52), 76 – 100 % breast density, hazard ratio 1.39 (95 % CI 1.33, 1.43), had a higher breast cancer risk then the women of lesser breast density i.e. 25 – 50 % breast density, hazard ratio 1.21 (95 % CI 1.22, 1.34) ( P interaction value being 0. 0354). The breast cancer risk associated with HRT was not influenced by number of births, oral contraceptive history, personal history of benign breast lumps and breast feeding history.

**Table No.1: Characteristics of participants according to Hormone Replacement Therapy**

		Non- users of HRT%	HRT use <2 years%	HRT use 2<5 years%	HRT use ≥5 years%
Total		85	8.5	3.6	3
Age in years	50	4.3	7	4.1	2.3
	50-59	41.5	52	50	34
	60-69	32	33.5	39	53
	70	20	7.5	7.1	11
Number of births	0	2.2	3	3	4
	>1	91	87.2	87	87.2
Oral contraceptive history	None	84	73.5	71	70.1
	<1 year	8	15	12	11.5
	>1 year	5.3	9	12	13.1
Breastfeeding history	None	8	10.8	11.5	11.3
	<6 months	8	11	10.5	9
	>1 year	70	60	57	64
	No	86	90	90.5	89.3
Breast density	<25%	40	29	25.3	25
	25-50%	32.2	35.4	35.8	36.3
	51-75%	22	29	31	31.2
	76-100%	6.3	8.6	9.2	8.9
Personal history of benign breast lumps	Yes	6	10.2	11	11.3
	No	88	85.2	84.4	84.2

**Table No.2: Hazard ratios and 95% confidence intervals of the risk of breast cancer according to HRT duration and invasive breast carcinoma and ductal carcinoma in situ**

	HRT duration	Total percentage	Breast cancer%	Incidence per person	Hazard ratio (95% CI)
Total	None	85	0.55	1.113	1
	All HRT users	15.1	0.79	1.629	1.35 (1.33, 1.40)
	HRT use <2 years	8.5	0.68	1.397	1.09 (1.05, 1.23)
	HRT use 2-5 years	3.6	0.83	1.738	1.42 (1.36, 1.50)
	HRT use >5 years	3	1.09	2.239	1.83(1.74, 1.93)
Invasive breast carcinoma	None	85	0.51	1.055	1
	All HRT users	15.1	0.73	1.582	1.35 (1.32, 1.40)
	HRT use <2 years	8.5	0.63	1.398	1.09 (1.15, 1.24)
	HRT use 2-5 years	3.6	0.78	1.579	1.41 (1.36, 1.50)
	HRT use >5 years	3	0.99	2.035	1.79 (1.60, 1.89)
Ductal carcinoma in situ	None	85	0.04	0.089	1
	All HRT users	15.1	0.06	0.263	1.45 (1.30, 1.50)
	HRT use <2 years	8.5	0.05	0.089	1.07 (0.93, 1.34)
	HRT use 2-5 years	3.6	0.06	0.239	1.45 (1.22, 1.78)
	HRT use >5 years	3	0.10	0.306	2.33 (1.96, 2.78)

**Table No.3: Link between the risk of breast cancer and Hormone Replacement Therapy according to risk factors of breast cancer**

Subgroup		Hazard ratio (95% CI)	P value for interaction
Age	<55	1.22 (1.26, 1.38)	<0.0001
	>55-65	1.19 (1.24, 1.35)	
	>66	1.34 (1.35, 1.54)	
Number of births	0	1.31 (1.05, 1.49)	0.4725
	>1	1.37 (1.33, 1.47)	
Oral contraceptive history	No	1.30 (1.35, 1.42)	0.7856

	<1 year	1.05 (0.96, 1.25)	
	>1 year	1.43 (1.30, 1.59)	
	Unknown	1.42 (1.26, 1.64)	
Personal history of benign breast lumps	No	1.34 (1.20, 1.39)	0.2124
	Yes	1.08 (1.03, 1.28)	
Breastfeeding history	No	1.44 (1.34, 1.55)	0.2428
	Yes	1.35 (1.30, 1.38)	
Breast density	<25%	1.32 (1.25, 1.42)	0.0354
	25–50%	1.21 (1.22, 1.34)	
	51–75%	1.38 (1.29, 1.52)	
	76–100%	1.39 (1.33, 1.43)	

## DISCUSSION

In our study, the hazard ratio of HRT users was 1.35, with the incidence per person being 1.63. These results are similar to another meta-analysis study published recently<sup>4</sup>. This study showed high risk of breast cancer in both, current and past users of HRT, with the relative risk of 1.17 95% confidence interval 1.10 – 1.26. The results of this study are accordant with our results, the breast cancer risk was almost 7.9% in women who got HRT for less than 2 years and 72.2% in women who used it for more than 5 years. These results correlate with our results that say that the risk of breast cancer increase with the increase in the duration of HRT use.

HRT use increased the risk of invasive breast carcinoma and ductal carcinoma in situ in our study. Even with a small ratio but the risk of DCIS increased consistently with HRT duration. Some other studies show different results regarding DCIS and HRT association<sup>14,15</sup>. One of the study reported that the increase in DCIS risk related to HRT use was not significant<sup>14</sup>.

There are not many studies on the risk of breast cancer related to HRT use and these studies show varying results<sup>16,17</sup>. One of the recent study showed that compared to Caucasians (HR 1.34), the Asian population (HR 1.84) had a higher risk of breast cancer due to HRT use<sup>18</sup>.

In our study, women with dense breasts had a higher risk of HRT related breast cancer. Few studies reported that obesity decreased the link between HRT use and breast cancer risk<sup>4, 19</sup>.

Small sample size is one of the limitation of this study. Another limitation is not separating the effects of estrogen-progesterone replacement therapy and estrogen only replacement therapy. This study also lacks the information about the subtype of cancer.

The results of this study could be helpful while deciding on the hormone replacement therapy. Also, more research should be done on this topic to eliminate the limitations of this study and have more clear views about the relation of breast cancer and HRT use.

## CONCLUSION

As the results show, the risk of breast cancer do increase with the use of hormonal re-placement therapy. As the duration of HRT increased, so did the risk of breast cancer. Risk factors like old age and higher breast density also increased the risk of breast cancer related to HRT.

### Author's Contribution:

Concept & Design of Study: Momina Khadija Abbasi  
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**Conflict of Interest:** The study has no conflict of interest to declare by any author.

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