

Is Hormone Replacement Therapy-Related Breast: A Case-Control Study

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Citation

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Abstract

Aim: HRT-related breast cancer may carry a better prognosis since there is no increase in breast cancer deaths. We looked at the prognostic risk factors and outcome in patients who had ever taken HRT compared to those who had not, in a case control study. Subgroups of recent users and those using HRT for greater than 5 years were also compared to controls.

Method: Tumour size, grade, vascular invasion, lymph node and oestrogen receptor status as well as median Nottingham Prognostic Indicator (NPI) were compared between cases and controls. Absolute survival between ever-users and never-users was compared by life table analysis.

Results: There was no difference between all the cases and their controls for the 5 prognostic factors. NPI in each group was also similar. Absolute survival between ever-users and never-users was not significantly different either ($p=0.450$).

Conclusion: There was no evidence that HRT-related breast cancer has a more favourable outcome.

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer in women and accounts for up to 20% of all cancers. It is therefore one of the leading causes of cancer related deaths in women. Hormone Replacement Therapy (HRT) is currently used in the treatment of vasomotor symptoms of the menopause and may have beneficial effects in the prevention of coronary artery disease, as well as an increase in bone matrix density, which reduces the risk of fractures secondary to osteoporosis. HRT may be oestrogen alone or be combined with progestins and may be given in various doses and cycles. Duration rather than dosage appears to be the more important factor in its beneficial effects₁.

However continued HRT use for 5 years or more is associated with an increased risk of breast cancer (relative risk 1.35) and the longer the duration of HRT the greater the relative risk. This risk equates to a delay in the onset of the menopause₂. Although any preparation of HRT may result in this increased risk, the addition of progestins appears to significantly enhance it₃. The association of breast cancer and HRT use is however restricted to the 10 – 15 years after its last use₄.

Several recent studies have however questioned the precise nature of this relationship. One report₅ noted that the relative risk of developing an invasive breast tumour with favourable histology was 4.42 amongst current users of HRT compared to non-users, even when adjusted for age and other breast cancer risks. The duration of HRT use seems to determine the strength of this association. Furthermore, others have shown that after adjustment for T, N and M stage of breast cancer, this increase in favourable breast tumours amongst HRT users is significantly associated with overall longer survival when compared with those who had never used HRT (Relative Risk of death is 0.78)₆.

The present study therefore aimed to examine the relationship between the known prognostic variables of breast tumours and HRT use and whether absolute survival of those diagnosed with breast cancer is significantly improved by HRT use prior to diagnosis.

PATIENTS AND METHODS

A retrospective case-control study was taken from a validated database of all women with primary operable breast cancer presenting to a district general hospital between January 1960 and December 1999.

Each patient on the database had completed a detailed questionnaire indicating the duration and timing of HRT use prior to diagnosis. Specific preparations or doses of HRT were not recorded. The data included both screen-detected and symptomatic cases.

Where available, the database contained the tumour size, grade, lymph nodes status, oestrogen receptor status, vascular invasion and Nottingham Prognostic Index (NPI) 7. Details of whether patient had survived or died due to breast cancer or other causes at the study date were extracted from the database.

The study population included all breast cancer patients on the database who had ever taken any preparation of HRT for any period of time prior to diagnosis. Each case was matched with a control that had never used HRT prior to diagnosis. Controls were matched for age and date of diagnosis.

Five markers of prognosis, were compared between the case and control populations. Mean tumour size was compared by the student's t test. Tumour grade, lymph node status, vascular invasion and oestrogen receptor (ER) status were compared by the chi square test.

The NPI is calculated from 3 separate parameters; tumour size, tumour grade and number of positive lymph nodes,. The median NPI for both populations was calculated and compared. The numbers of cases and controls in each of the 3 prognostic groups,; good, moderate and poor prognostic groups were compared by the chi square test.

Absolute survival between cases and controls in the general population and also in each prognostic group was compared by the Kaplan-Meier method of life table analysis with the log rank test of significance. A subgroup of cases that had been on HRT for 5 years or more were analysed separately, as were those who had used HRT within 1 year of diagnosis (recent users).

RESULTS

1882 patients diagnosed with primary breast cancer from January 1960 to end December 1999 were reviewed. 388 ever-users of HRT were identified and matched with 388 control patients. Table 1 shows the distribution by year of diagnosis for the whole database and case and control populations. Median follow up for cases and controls were 44 and 62 months respectively (ranges 0 - 447 and 0 - 670 months respectively). For both populations, 370 (cases) and

366 (controls) had died or were followed up within 12 months of the study date, 31-Dec-1999. The remainder (18 cases and 21 controls) was followed up within 24 months of the study date. The mean age of both the case and control populations was 63 (standard error of mean 0.534 and 0.544 respectively). The median duration of HRT use was 2 years (range 0 – 23.6). Closeness of match data were as follows: for mean age, 75% of cases and controls were matched within 6 months of their age, whilst only 1% were more than 3 years apart. For date of diagnosis, 64% were matched within 1 year and 11% were greater than 3 years apart. For ever-users of HRT, 39% were on HRT at time of diagnosis. The median time since first use was 6 years and the median time since last use was 0.1 years. One hundred and five women had used HRT for 5 years or more of which only 31 had used it for more than 10 years.

Figure 1

Table 1: Distribution by year of diagnosis for database and case and control populations

	Database	HRT – Ever users	Control
1960s	1%	0.5%	0.5%
1970s	8%	1.5%	6.7%
1980s	29%	18%	32%
1990s	62%	80%	60.6%

Comparison of prognostic markers between cases and controls are shown in Table 2. In the study population (the cases) 2860 lymph nodes were retrieved from 314 patients of which 365 nodes (13%) were positive for tumour metastasis. This compares with 14% positive nodes (396 positive nodes from a total of 2839) from 305 control patients (p = 0.19 (ns)). Only 297 (76%) cases and 290 (75%) controls had grade of tumour recorded. Comparison of tumour types is shown in Table 3.

Figure 2

Table 2: Comparison of prognostic markers in cases and controls.

	HRT users (388)		Controls (388)		P value
		Unknown N (%)		Unknown N (%)	
Median tumour size (cm)	1.9 (0.1 – 10.1)	56 cases	2 (0.1 – 9)	71 cases	
Positive lymph nodes	111 (35%)	74 (19%)	111 (38%)	93 (24%)	0.61
Positive ER status	44 (77%)	331 (85%)	34 (72%)	341 (88%)	0.65
Positive vascular invasion	106 (35%)	87 (22%)	100 (41%)	146 (37%)	0.16
Grade I	92 (31%)	91 (23%)	67 (26%)	130 (33%)	0.22
Grade II	137 (46%)		124 (48%)		0.67
Grade III	68 (23%)		67 (26%)		0.43

Figure 3

Table 3: Comparison of tumour types between cases and controls.

	HRT	users
Control		
DCIS		46
36		
Infiltrating ductal		268
272		
Infiltrating lobular		33
50*		
Medullary	4	5
Mixed IDC/ILC	2	5
Mucinoid		9
2*		
Tubular/cribriform	13	6
Other		8
2		
Unknown		5
10		

* p<0.05

273 (70%) cases and 270 (69%) controls had data to calculate the NPI. The median NPI of cases and controls was 3.54 Vs 3.5. There was no difference in the distribution of cases and controls in any of the prognostic groups (good prognostic group: 43% Vs 42% respectively p = 0.81, moderate: 43% Vs 44% p = 0.77, poor: 14% Vs 14% p = 0.84).

Comparison of absolute survival between cases and controls on the life table analysis showed no difference in survival using the log rank test (p = 0.450) (Figure 1). This was also the case when comparing survival between cases and controls in each prognostic group (Good prognostic group; p = 0.454, Moderate; p = 0.086, Poor; p = 0.268) (Figure 2).

Figure 4

Figure 1: Comparison of the life table analysis of absolute survival between HRT Ever-Users and controls.

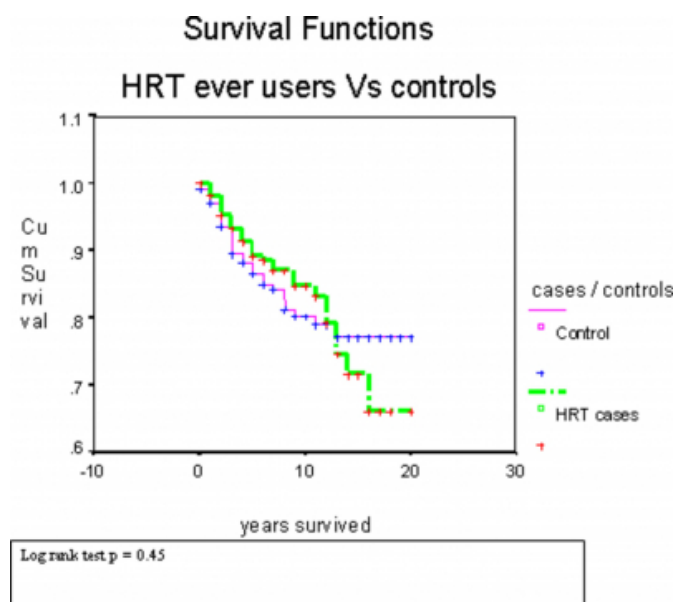
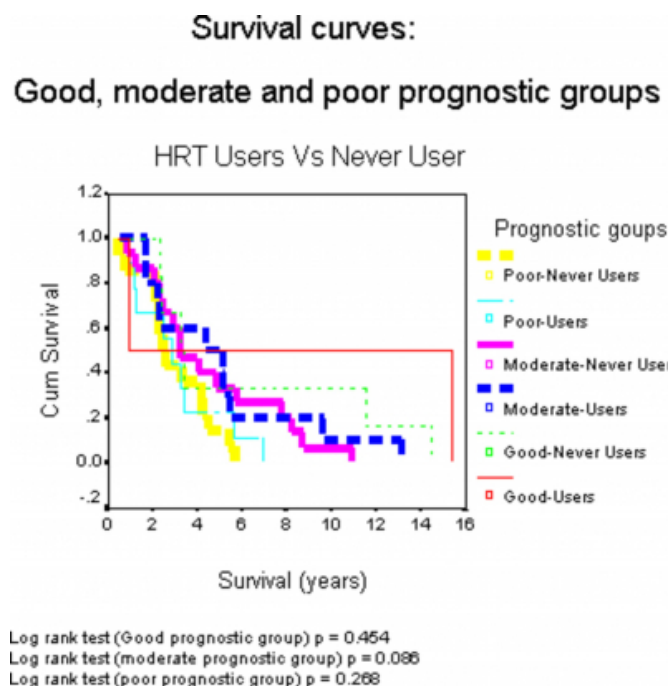


Figure 5

Figure 2: Comparison of absolute survival of HRT users and never users in the good, moderate and poor prognostic groups.



Comparison of prognostic factors for the subgroup of those who have used HRT for 5 years or more is shown in Table 4. There were 207 cases that had used HRT within 1 year of diagnosis (recent-users) and the median NPI of this group (3.5) was the same as the overall control population. The distribution of the prognostic markers in the recent-user

group was not significantly different from the overall control population (Table 5).

Figure 6

Table 4: Comparison of prognostic factors between cases with 5 or more years on HRT and their controls.

	HRT users =>5 yrs N = 105	Control N = 105	P value
Median tumour size (cm)	1.8 (0.14 – 10)	2.0 (0.25 – 4.0)	
Mean tumour size (cm)	2.0 (SEM 0.14)	2.1 (SEM 0.10)	0.85
Positive lymph node	33 / 87 (39%)	25 / 84 (30%)	0.33
Positive ER status	18 / 25 (72%)	11 / 13 (84%)	0.07
Positive vascular invasion	33 / 89 (37%)	28 / 79 (35%)	0.22
Grade III	14 / 87 (16%)	17 / 78 (22%)	0.20

Figure 7

Table 5: Comparison of prognostic factors between recent users and control populations

	Recent-users n = 207	control population n = 388	P value
Median tumour size (cm)	1.9 (0.1 – 10.1)	2.0 (0.1 - 9)	
Mean tumour size (cm)	2.15 (SEM 0.104)	2.27 (SEM 0.070)	0.39
Positive lymph nodes	59 / 170 (34%)	111 / 295 (38%)	0.55
Positive ER status	31 / 40 (77.5%)	34 / 47 (72%)	0.11
Positive vascular invasion	58 / 164 (35%)	100 / 242 (41%)	0.25
Grade III	31 / 164 (19%)	67 / 258 (26%)	0.10

DISCUSSION

The results of this case-control study have shown that ever-use and recent use of HRT before diagnosis of breast cancer did not predict a favourable tumour type except the well-differentiated mucinoid breast tumour, which were more common in the HRT group compared to the control population. Conversely, the data showed that there was a slight but significant increase of infiltrating lobular carcinomas in the control group. These two apparently significant findings may have arisen by the play of chance from multiple comparisons. All other types were distributed non-significantly in both populations. The study failed to detect a significant association between ductal carcinoma in-situ and HRT use but the numbers were small.

None of the markers of prognosis, nor the NPI scores were different between ever-use, recent-use and control populations. Neither did those cases that had used HRT for 5 years or more differ from the controls. The increased risk of developing breast cancer after starting HRT is increased only after continued use for 5 years or more², but this group of 105 patients had similar prognostic markers to controls

(Table 4).

As tumour characteristics were therefore not different in any of the case or control populations (as shown by similar NPIs in the populations) then survival is not expected to be different. This was seen in our data where life table analyses of overall survival showed no significant difference between cases and controls (figure 1) or between these two populations in each of the prognostic groups (figure 2). However Manjer et al¹⁰ found a very different result. Their population-based prospective study showed a greater number of stage 1, well-differentiated tumours as well as lobular and tubular tumours amongst the HRT users compared to non-users. The population consisted of post-menopausal women who were followed up for an average 9 years. As in the present study, there was no differentiation between screen detected and symptomatic patients and the duration of HRT use was not documented.

The results of studies in screen-detected patients are conflicting. Harding et al¹¹ also found that grade 1 and node negative tumours were more common amongst HRT users but a more recent study¹² failed to detect this in a larger study population. The latter study did detect more HRT users in the interval tumour group compared to the screen-detected group (22% vs. 12.3%) but there was no survival advantage for either users or non users.¹³ Women on HRT are more likely to experience reduced sensitivity and specificity of breast cancer screening by mammography compared to women not using HRT¹⁴, which may lead to an increased risk of interval cancer. The cause of this reduced sensitivity is probably due to increased mammographic density¹⁵ secondary to exogenous oestrogens. Different HRT regimens and dosage seem to affect the density differently, with continuous combination therapy having the most potent effect.

The present study population is small and there is no information on the regime and dosage of HRT used by our patients. The median duration of HRT use of 2 years may not be sufficient to detect those tumours that were related to HRT use, but examination of the subgroup with more prolonged HRT exposure failed to detect any difference.

In conclusion the present case-control study failed to show any survival advantage to HRT-related breast cancer. Furthermore it did not provide any evidence that HRT confers a more favourable breast tumour.

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174

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