Relationship between Oral Contraceptive Therapy and Estrogen Receptor Status in Patients with Breast Cancer*

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Abstract. *Background: Breast cancer (BC) is the most common cancer in women, and the hormone receptor status is one of the most important prognostic factors in patients with BC. The aim of this study was to establish whether a relationship exists between the hormone receptor rate and the main classic risk factors in patients with BC. Patients and Methods: The data regarding a series of 351 consecutive women (median age 57 years, range 26-85 years) who had undergone curative surgery for primary BC was retrospectively reviewed. Eighty-seven (24.8%) patients used oral contraceptives. According to the duration of OC therapy, the patients were dichotomized into two Groups. Group A: less than 22 months (47 patients, 54%) and Group B: 22 months or more (40 patients, 46%). Results: Final pathology showed 15 (4.3%) pT1a, 62 (17.7%) pT1b, 133 (37.9%) pT1c, 125 (35.6%) pT2, and 16 (4.5%) pT3 BC. There were 286 (81.5%) infiltrating ductal, and 24 (6.8%) infiltrating lobular breast carcinomas. The average estrogen receptor (ER) and progesterone receptor (PgR) rate was 59.7±32.8 and 54.2±33.9, respectively. There was no relationship (p=NS) between either ER or PgR and the age of the patients, age at menarche and menopause, number of pregnancies, age at first pregnancy, number of spontaneous abortions, months of breastfeeding and the use of estrogen replacement therapy. As expected, ER and PgR rates correlated significantly (R=0.78, p<0.01). The ER rates of groups A and B were 51.7±35.6% and 68.2±23.6%, respectively (p=0.014). No other differences (p=NS) between the groups were found. Conclusion: The prolonged use of oral contraceptives may increase the ER rate within the tumor tissue, and thus such therapy should be considered an indirect positive prognostic factor in patients with BC.*

Breast cancer (BC) is the most common cancer in women and the hormone receptor status is one of the most important prognostic factors in patients with BC (1, 2). Several risk factors for BC have been reported and in several randomized studies a relationship between hormone replacement therapy and BC onset have been shown (3). However, the correlation between estrogen receptor (ER) and progesterone receptor (PgR) rate and preoperative risk factors is unclear. The aim of this study was to establish whether a relationship exists between the hormone receptor rate and the main classic risk factors in patients with BC.

Patients and Methods

The data regarding a series of 351 consecutive women (median age 57 years, range 26-85 years) who had undergone curative surgery for primary BC was retrospectively reviewed. Eighty-seven (24.8%) patients used oral contraceptives, from 6 to 120 months (median 22 months) prior to surgery.

According to the duration of therapy, patients were dichotomized into two Groups: Group A: less than 22 months (47 patients, 54%) and Group B: 22 months or more (40 patients, 46%).

The following parameters were also considered: age at menarche; age at menopause; number of pregnancies; age at first pregnancy; number of spontaneous abortions; months of breastfeeding; months of use of hormone replacement therapy (Table I).

The immunostaining was obtained for both ER and PgR in all patients. The imunohistochemical assay (IHA) was performed on 4 μm sections cut from the blocks; retrieving the antigen; blocking the endogenous peroxidase and non-specific proteins; binding with primary mouse monoclonal antibody against the ER and PgR; and linking with biotinylated rabbit antibody against mouse immunoglobulin G (4, 5). The specimens were stained manually.

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Key Words: Breast cancer, risk factors, oral contraceptives, estrogen receptor, progesterone receptor.

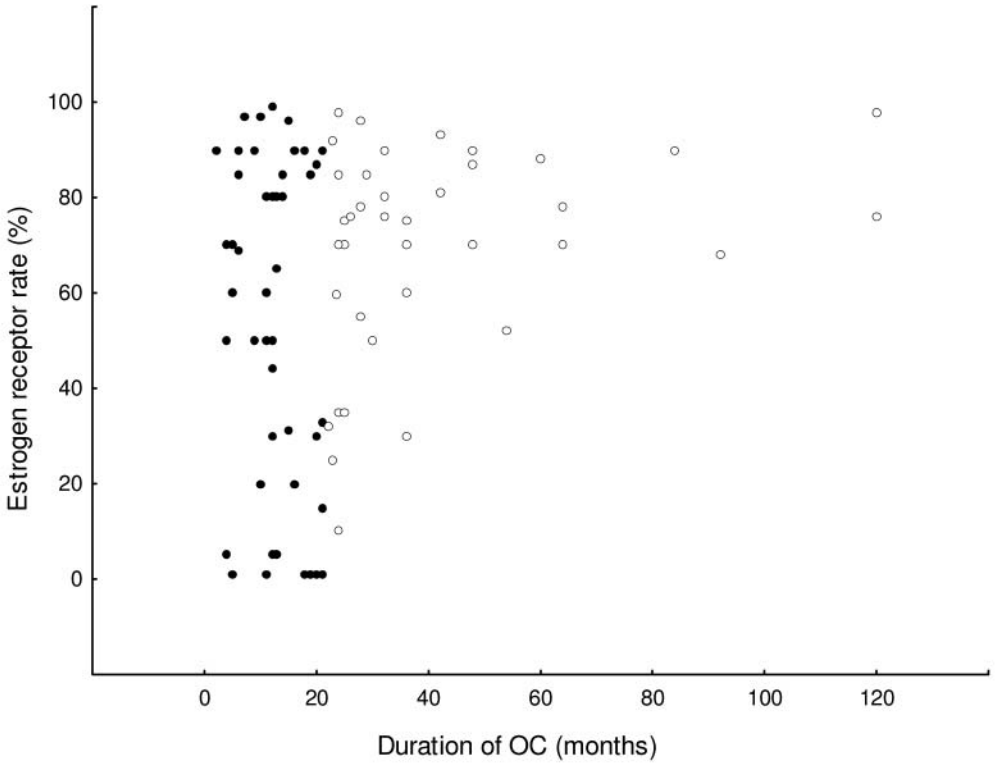

Figure 1. *Relationship between duration of oral contraceptive (OCO) therapy (months) and estrogen receptor rate in patients with breast cancer (● = Group A patients, ○ = Group B patients).*

The reported data are expressed as mean±standard deviation (SD). Differences between means were tested by Student's *t*-test. The Pearson's correlation coefficient (R) calculation was also used to evaluate the linear relationship between pairs of variables. The differences were considered significant at a *p*-value <0.05.

Results

Final pathology showed 15 (4.3%) pT1a, 62 (17.7%) pT1b, 133 (37.9%) pT1c, 125 (35.6%) pT2, and 16 (4.5%) pT3 BC. There were 286 (81.5%) infiltrating ductal, and 24 (6.8%) infiltrating lobular breast carcinomas. The average ER and PgR rate was 59.7±32.8 and 54.2±33.9, respectively.

As reported in Table II, there was no relationship (p=NS) between either ER or PgR and the age of the patients, age at menarche and menopause, number of pregnancies, age at first pregnancy, number of abortions, months of breastfeeding, number of spontaneous abortions and use of estrogen replacement therapy. As expected, ER and PgR rates significantly correlated (R=0.78, p<0.01). A mild (R=0.22, p=0.038) relationship between ER rate and use of oral contraceptives was also found. The ER rates of Groups A and B were 51.7±35.6% and 68.2±23.6%, respectively (p=0.014). No other differences (p=NS) between the Groups were found. Figure 1 shows the relationship between ER rate and duration of oral contraceptive therapy.

Table I. *Patient characteristics (mean±standard deviation).*

Parameter	Mean±SD
Age (year)	57.3±12.4
Age at menarche	12.3±1.6
Age at menopause	49.1±4.1
Number of pregnancies	1.3±1.0
Age at first pregnancy	25.3±4.3
Number of spontaneous abortions	0.2±0.5
Months of breast-feeding	9.5±8.3
Months of contraceptive therapy	26.6±22.5
Months of hormone replacement therapy	30.9±23.5

Discussion

BC is a major public problem in all the developed countries, and currently about 1,400,000 new cancer cases are expected each year in the United States (6). The relationship between BC and estrogen replacement therapy has long been reported, and an increased risk of invasive ductal or lobular carcinoma has been shown (7, 8).

A recent study found that current users of hormone replacement therapy were more likely to develop ER- and PgR-positive tumors than they were to develop ER- and PgR-

Table II. *Relationship between parameters and estrogen and progesterone receptor rate.*

	Estrogen receptor		Progesterone receptor	
Parameter	R	*p*-value	R	*p*-value
Age of the patients	–0.06	0.24	–0.03	0.61
Estrogen receptor	-	-	0.78	<0.01
Progesterone receptor	0.78	<0.01	-	-
Age at menarche	–0.05	0.38	–0.03	0.61
Age at menopause	–0.02	0.72	–0.01	0.92
Number of pregnancies	–0.04	0.45	0.01	0.96
Age at first pregnancy	–0.01	0.96	–0.03	0.67
Number of abortions	0.02	0.54	–0.05	0.31
Months of breast-feeding	–0.03	0.76	–0.01	0.98
Months of oral contraceptives	0.22	0.04	0.21	0.13
Months of hormone replacement therapy	–0.06	0.24	–0.03	0.61

negative ones, suggesting that BC characteristics may be influenced by both endogenous and exogenous hormonal factors (9). However, other non-hormonal risk factors (*i.e.* early age at menarche and nulliparity, late age at first birth, body mass index >25) have more pronounced effects on ER and PgR positive BC than on hormone-negative tumors (9-12).

On the other hand, no relationship has been found between serum tumor markers (*i.e.* CEA and CA 15-3) and ER or PgR status (13-16). Lower *et al.* (17) comparing levels of ER and PgR in pre- and postmenopausal patients with primary BC found that significantly more ER were detected in patients receiving some estrogen therapy compared to those who had never used it. However, although the use of exogenous estrogens may mask the ER by binding all the estrogen sites, IHA may reveal the true ER status.

In conclusion, patients who have undergone prolonged oral contraceptive therapy may have a higher ER rate within the tumor tissue, and thus such therapy should be considered an indirect positive prognostic factor in patients with BC.

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