Acta Oncologica 28 (1989) Fasc. 6

FROM RADIUMHEMMET, AND THE DEPARTMENT OF TUMOUR PATHOLOGY, DIVISION OF CYTOLOGY, KAROLINSKA HOSPITAL, STOCKHOLM, AND THE DEPARTMENT OF ONCOLOGY, UNIVERSITY OF LINKÖPING, LINKÖPING, SWEDEN.

STEROID RECEPTOR LEVELS IN BREAST CANCER

Relationships with age and menopausal status

N. WILKING, L. E. RUTQVIST, B. NORDENSKJÖLD and L. SKOOG

Abstract

The paper presents descriptive data concerning relationships between age, menopausal status and steroid receptor content in primary breast carcinoma. The study was based on 2329 women with primary breast carcinoma diagnosed in Stockholm county during 1980–1983. Oestrogen (ER) and progesterone receptor (PgR) content was determined using the isoelectric focusing technique. All analyses were done in one laboratory. There was a gradual increase in mean ER values with age. Premenopausal patients had lower mean ER values than peri- and postmenopausal patients of the same age. In contrast, PgR levels were similar in different age-groups. This could be a result of an insufficient stimulation of the tumour cells via the ER pathway. It is also possible that the PgR stimulation is maximal already at ER values below those found in old patients. It is concluded that steroid receptor content measured with commonly used ligand assays may reflect both biological properties of the tumour cells as well as influences by nontumoural factors, e.g. the endogenous levels of sex hormones.

Key words: Breast cancer, steroid receptors, age, menopausal status.

During recent years steroid receptor determinations in breast carcinoma have become a routine procedure. A high oestrogen receptor (ER) content in the primary tumour is associated with a prolonged disease-free survival and a high probability of response to endocrine therapy in case of recurrent disease (1–4). The progesterone receptor (PgR) has also been shown to be a good predictor of both disease-free survival and response to hormonal manipulation (5).

Since the receptor is a prerequisite for hormonal growth control it can be assumed that variations in receptor content reflect differences in the hormonal dependency of the tumours. However, the receptor levels may be underestimated due to endogenous steroids masking the receptor. It is well known that receptor levels vary between pre-, peri- and postmenopausal patients. This may be due to receptor blockade related to the levels of endogenous steroids (6), i.e. high levels of circulating oestrogens may block the receptor making it undetectable with the commonly used ligand-binding assays. Another possibility is that high levels of oestrogens interact with the receptor synthesis. It has also been shown that age of the patient influences the receptor level (7, 8). ER levels increase with age whereas no such correlation appears to exist for PgR (7, 9). If the correlation between ER and age is independent of menopausal status remains controversial.

In this report we present receptor data on 2329 women with breast carcinoma diagnosed in the Stockholm county during 1980–1983. We analysed the relationship between the receptor levels, age and menopausal status.

Material and Methods

The studied group consisted of breast carcinoma patients diagnosed in the Stockholm county during 1980 through 1983. Cancer cases in the county (population 1.6 million) are reported to a population-based, regional cancer registry according to medical statutes. Previous studies have shown that the registry receives reports on about 98% of all new breast cancer cases in the catchment area (10). During 1980–1983 the total number of breast cancer cases reported to the registry was 3455. ER data were available on 2761 cases (80%). Data on both ER and PgR were available on 2329 cases (67%). The age distribution

Accepted for publication 2 January 1989.

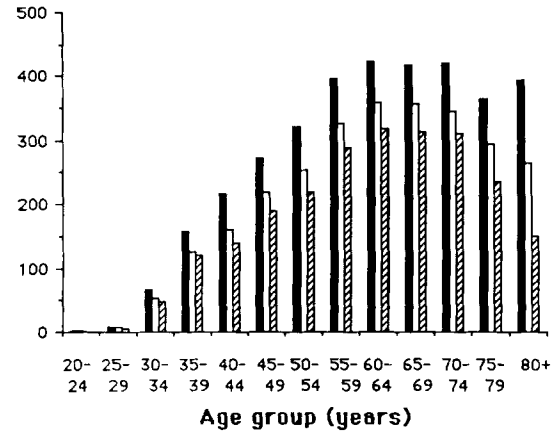

Fig. 1. The number of primary breast cancer cases reported to the Stockholm Cancer Registry during 1980–1983, the number of cases with ER data and the number with both ER and PgR data by age group. ■, Total No. (n=3455); □, No. with ER (n=2761); ▨, No. with ER and PgR (n=2329).

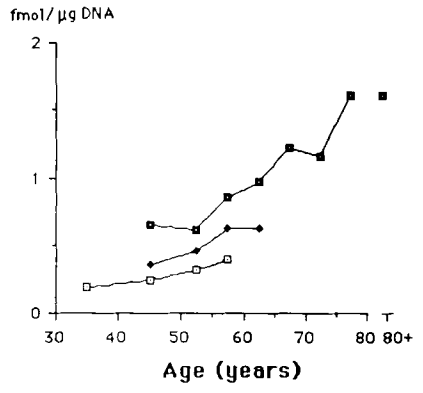

Fig. 2. Mean values of ER by age and menopausal status. —□—, Pre (n=626); —◆—, Post 0–5 yrs (n=198); —■—, Post >5 yrs (n=1937).

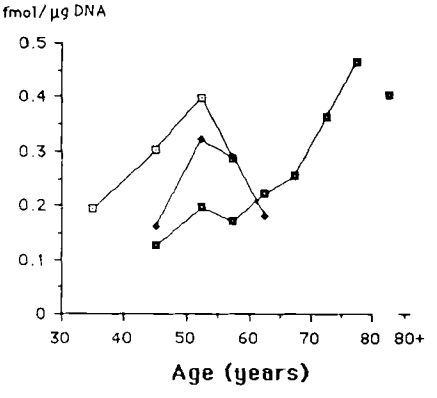

Fig. 3. Mean values of PgR by age and menopausal status. —□—, Pre (n=556); —◆—, Post 0–5 yrs (n=169); —■—, Post >5 yrs (n=1604).

of all recorded cases and those with receptor data is shown in Fig. 1. The percentage without receptor data was higher in older patients. At ages above 80 years, ER data were missing in 33% compared with 10–15% in younger patients. A previous study showed that receptor data were more often unavailable in patients with small than with large tumours (unpublished data). This reflects the fact that there is more often insufficient tumour material for receptor determination in small than in large tumours.

Data on menopausal status were obtained from clinical records. A woman was considered to be postmenopausal if more than 6 months had elapsed since her last menstrual period. Data on menopausal status were available in about 97% of all receptor-measured patients. The remaining patients were recorded as postmenopausal if they were aged above 49 years.

All receptor assays were performed in one laboratory on thawed tumour specimens which had been excised immediately after surgery and stored in the vapour phase of liquid nitrogen for 2 weeks or less. The assay technique was isoelectric focusing on polyacrylamide gel. This technique is sensitive and well-suited for measuring steroid receptors in breast cancer: results correlate well with those obtained using other ligand biding methods as well as techniques based on monoclonal antibodies (11–13).

The receptor values were normalized to DNA content and expressed as fmol of ER/PgR per µg of DNA. Values of less than 0.05 fmol/µg DNA were classified as receptor negative since the assay cannot reliably distinguish between tumours that are completely negative and those with very low values. Tumours with a receptor content of 0.05 fmol/µg DNA or more are reproducibly recognised as receptor positive. With the mentioned cut-off level, 25% of the tumours were classified as ER negative (ER−) and 56% as PgR negative (PgR−).

Results

Fig. 2 shows the mean ER value in 5-year age groups by menstrual status: pre, post 0–5 years and post >5 years. Patients of the same age but different menstrual status had different mean values. The premenopausal women had the lowest ER content, the perimenopausal women intermediate values and the postmenopausal women the highest mean content. There was also a gradual increase of the ER with increasing age in all three subgroups.

Fig. 3 shows the variation of PgR in relation to menstrual status and age. Within the different menstrual groups there was an increase of the receptor values with age. However, in contrast to ER, there was only a minor overall increase of PgR with age when menstrual status was ignored.

The percentage of ER negative patients is shown in Fig. 4. There was a gradual decrease with age in the percentage of ER-tumours. A similar age dependent decrease was noted for the proportion of PgR− tumours in premenopausal and 0–5 years postmenopausal patients, but not in >5 years postmenopausal patients (Fig. 5).

Fig. 6 shows the combined ER and PgR data by age.

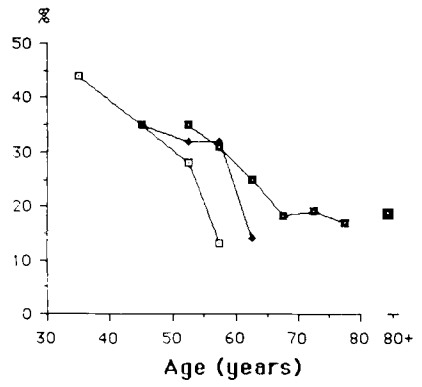

Fig. 4. Percentage ER− by age and menopausal status. −□−, Pre: −◆−, Post 0–5 yrs; −■−, Post >5 yrs.

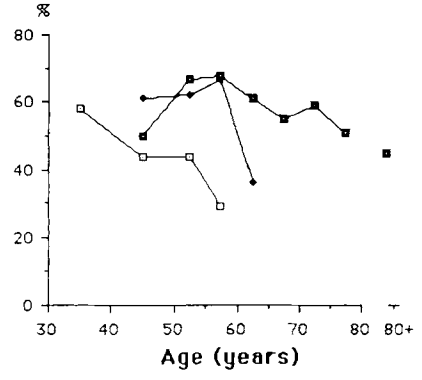

Fig. 5. Percentage PgR− by age and menopausal status. −□−, Pre; −◆−, Post 0–5 yrs; −■−, Post >5 yrs.

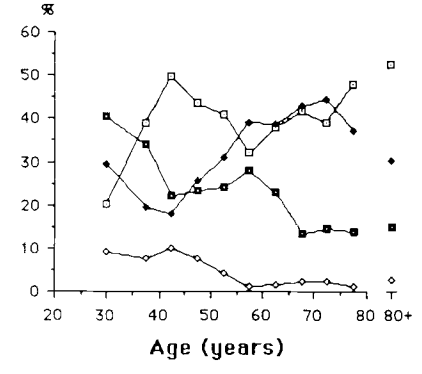

Fig. 6. The relative frequency of receptor subgroups by age. −□−, ER+Pgr+ (n=951); −◆−, ER+PgR− (n=813); −■−, ER−PgR− (n=485); −◇−, ER−PgR+ (n=80).

The lowest percentage of receptor positive tumours (20%) was observed in the 25–29-year subgroup. Above 29 years the percentage varied between 30–50% and showed no apparent correlation with age. There was a gradual increase of the proportion ER+/PgR− patients with age as well as a gradual decrease of ER−/PgR− patients. The proportion of ER−/PgR+ patients decreased from about 10% before the menopause to less than 5% at ages above 55 years.

Discussion

In agreement with several investigators we found that ER levels were higher among postmenopausal than premenopausal women (7, 8). Several explanations have been proposed for this observation. The low ER values in premenopausal patients may represent a true lack of the receptor protein. However, it is also possible that the high levels of endogenous oestrogens in premenopausal women may block the ER, making it undetectable with ligand assays. This theory accords with results indicating an inverse correlation between plasma estradiol level and ER level N (6).

Among women who were 0–5 years postmenopausal the mean ER values were lower than for women who were >5 years postmenopausal. This may reflect that the oestrogen level in patients with a recent menopause is high enough to block the ER, thus making it undetectable with the current assay. An alternative possibility is that ER+ tumours are delayed in their clinical presentation due to the menopause. This would result in a higher proportion of ER− primary tumours among perimenopausal women.

Age-related differences in ER status may also reflect true differences in the biological properties of the tumours. It has been speculated that subsets of tumours are influenced by different growth promoting factors. Some tumours may be regulated mainly by steroid hormones. The steroid receptor status would in such tumours reflect the regulatory mechanism. Other tumours may be regulated by growth factors, e.g. epidermal growth factor (EGF) or transforming growth factor (TGF) (14–16). There are indications that such tumours are more common among premenopausal women while those regulated by steroid hormones are more common in older patients (17).

The receptor status may also reflect the degree of tumour cell differentiation. It is well known that tumours among elderly women tend to be more highly differentiated than those among younger women (18).

Several other explanations have been proposed for the relationship between hormone receptors and age, e.g. an increased proliferative activity of tumours found in premenopausal women compared to that of postmenopausal patients of the same age (19). Decrease of ER synthesis due to the cyclic progesterone increase in the premenopausal women has also been suggested (20).

The continuous increase with age of ER values in both pre- and postmenopausal women might result from changes in the intratumoural oestrogen levels. It is well known that the adrenal androgen production decreases in the decade after the menopause. This may lead to a deficit in available substrate for aromatisation both in peripheral tissues and the tumour itself. We have previously described the sulphatase pathway as a major source of oestrogen synthesis in breast tumours (21). This pathway was

age dependent, i.e. the oestrogen production decreased with age. At present we do not know if this observation may help to explain the correlation between ER content and age.

A lack of correlation between PgR-level and age has been observed by several authors (7, 9). It is possible that the low levels of circulating oestrogens in postmenopausal women are insufficient to stimulate synthesis of PgR. Accordingly it has been shown that ER+/PgR− tumours in postmenopausal women may be converted to ER+/PgR+ after administration of exogenous oestrogen (22). Our results showed that the mean level of PgR increased with age within different menopausal subgroups. To our knowledge this has not been described by others. This increase may result from mechanisms similar to those described for ER. Thus the PgR may be 'demasked' when the endogenous level of progesterone falls at the menopause. The increase in mean ER content may also result in an increase of the mean PgR content.

We found that only few patients were classified as ER−/PgR+. The percentage of such patients decreased with age. Several authors have described the ER−/PgR+ subgroup as a laboratory artifact, i.e. a false negative ER assay. The current age dependent decrease of such patients may also reflect an endogenous blockade of the ER in young patients which is not present in postmenopausal women who have lower levels of circulating oestrogens.

About 25% of the premenopausal women were ER+/PgR+. The proportion rapidly increased to 50% at the menopause. During the following decade the proportion of ER+/PgR+ patients decreased but after 60 years of age, i.e. after both the menopause and the adrenopause, there was an increase to 50% again. This observation accords with reports on the response to endocrine therapy of recurrent breast cancer in different age groups. It is possible that the proportion of ER+/PgR+ patients more accurately reflects the hormonal dependency of breast carcinoma than the ER status or PgR status alone. Thus, the age related increase in mean ER values may be spurious and probably does not represent a true increase in the hormonal dependency of breast carcinomas.

REFERENCES

1. Hawkins RA, Roberts MM, Forrest APM. Oestrogen receptors in breast cancer: Current status. Br J Surg 1980; 67: 153–69.
2. Jensen EV, Block GE, Smith S, DeSombre E. Estrogen receptors and breast cancer response to adrenalectomy. Natl Cancer Inst Monograph 1971; 34: 55–70.
3. Knight WA, Livingston RB, Gregory EJ, McGuire WL. Estrogen receptor as an independent prognostic factor for early recurrence in breast cancer. Cancer Res 1977; 37: 4669–73.
4. McGuire WL. Hormone receptors: Their role in predicting prognosis and response to endocrine therapy. Semin Oncol 1978; 5: 428–33.
5. Clark GM, McGuire WL. Progesterone receptors and human breast cancer. Breast Cancer Res Treat 1983; 3: 157–63.
6. Theve NO, Carlström K, Gustafsson JÅ, et al. Oestrogen receptors and peripheral serum levels of oestradiol-17β in patients with mammary carcinoma. Eur J Cancer 1978; 14: 1337–40.
7. Clark GM, Osborne CK, McGuire WL. Correlations between estrogen receptor, progesterone receptor, and patient characteristics in human breast cancer. J Clin Oncol 1984; 2: 1102–9.
8. McCarty KS Jr, Silva JS, Edwin BC, Leight GS, Wells SA, McCarty KS Sr. Relationship of age and menopausal status to estrogen receptor content in primary carcinoma of the breast. Ann Surg 1983; 197: 123–7.
9. Fisher B, Wickerman DL, Brown A, Redmond CK, et al. Breast cancer estrogen and progesterone values: Their distribution, degree of concordance, and relation to number of positive axillary nodes. J Clin Oncol 1983; 1: 349–58.
10. Mattsson B, Rutqvist LE, Wallgren A. Undernotification of diagnosed cancer cases to the Stockholm Cancer Registry. Int J Epidemiol 1985; 14: 64–9.
11. Fernö M, Borg Å, Sellberg G. Enzyme immuno assay of estrogen receptor in breast cancer biopsy samples. A comparison with isoelectric focusing. Acta Radiol Oncol 1986; 25: 171–6.
12. Wrange Ö, Nordenskjöld B, Gustafsson J-Å. Cytosol estradiol receptor in human mammary carcinoma. An assay based on isoelectric focusing in polyacrylamide gel. Anal Biochem 1978; 85: 416–21.
13. Wrange Ö, Humla S, Ramberg I, et al. Progestin-receptor analysis in human breast cancer cytosol by isoelectric focusing in slabs of polyacrylamide gel. J Steroid Biochem 1981; 14: 141–8.
14. Macias A, Perez R, Hägerström T, Skoog L. Identification of transforming growth factor alfa in human primary breast carcinomas. Anticancer Res 1987; 7: 1271–6.
15. Perez R, Pascual MR, Macais A, Lage A. Epidermal growth factor receptors in human breast cancer. Breast Cancer Res Treat 1984; 4: 189–93.
16. Salmon ED, Zwiebel AJ, Bano MM, Losonczy IL, Fehnel P, Kidwell WR. Presence of transforming growth factors in human breast scanner cells. Cancer Res 1984; 44: 4069–77.
17. Skoog L, Macias A, Azavedo E, Lombardero J, Klintenberg C. Receptors for EGF and estradiol and thymidine kinase activity in different histological subgroups of human mammary carcinomas. Br J Cancer 1986; 54: 271–6.
18. Fallenius AG, Skoog LK, Svane GE, Auer GU. Cytophotometrical and biochemical characterization of nonpalpable, mammographically detected mammary adenocarcinomas. Cytometry 1984; 5: 426–9.
19. Bertuzzi A, Daidone MG, DiFronzo G, Silvestrini R. Relationship among estrogen receptors, proliferative activity and menopausal status in breast cancer. Breast Cancer Res Treat 1981; 1: 253–62.
20. Saez S, Martin PM, Chouvet CD. Estradiol and progesterone levels in human breast adenocarcinoma in relation to plasma estrogen and progesterone levels. Cancer Res 1978; 38: 3468–73.
21. Wilking N, Carlström K, Gustafsson SA, Sköldefors H, Tollbom Ö. Oestrogen receptors and metabolism of oestrone sulphate in human mammary carcinoma. Eur J Cancer 1980; 16: 1339–44.
22. Degenshein GA, Bloom N, Tobin E. The value of progesterone receptor assays in the management of advanced breast cancer. Cancer 1976; 46: 2789–93.