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Levels of Estrogen and Progesterone in postmenopausal Breast cancer patients

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Abstract

This study was performed with an objective to compare the levels of estrogen and progesterone in postmenopausal breast cancer patient with age matched healthy controls. We performed a cross-sectional comparative study of two age matched groups of postmenopausal participants: 25 participants (cases) had carcinoma of breast and the other 25 participants (controls) were heathy females. The women with breast cancer had a mean age of 53.6 years and the heathy women had a mean age of 52.2 years. Blood samples were collected from all participants and assayed for serum estrogen and serum progesterone. The estrogen and progesterone levels in cases were significantly high as controls ($p = <0.001$ and $p = <0.05$ respectively). Estrogen levels were also significantly correlated with progesterone levels ($r = 0.540$, $p < 0.05$). In conclusion, study suggest that estrogen and progesterone should be routinely estimated in breast cancer patients for better treatment approaches as well as monitoring of disease progression.

Keywords: Postmenopausal, Estrogen, Progesterone, Breast cancer, Women

Introduction

Worldwide, breast cancer is a most common invasive cancer in women, India also, 27% (2012) among all diagnosed cancer in females.[1]It occurs more commonly in the developed countries, accounting for 3-5% of deaths while its incidence is 1-3% in developing countries. Carcinoma of breast is extremely rare below 20 years of age but thereafter the incidence steadily rises. At the age of 30 years the incidence is 1:622 females, at the age of 60 it is 1:24 females and by the age of 90, the incidence is 1:8 females.[2] Incidence- according to Breast Cancer India, globally the incidence and mortality of breast cancer risin from 13,84,000 cases and 4,58,000 deaths(2008) to 16,77,000 cases and 5,22,000 deaths(2012). In India also increased from 1,34,420 cases (2008) to 1,44,937 cases(2012).[1] Primary risk factors - female sex and older age.[3] Other risk factors - delayed childbearing, no breastfeeding, higher hormone levels, obesity and diet.[4-6] Postmenopausal > pre-menopausal females. The ratio of female to male breast cancer incidence is approximates 100:1.[2]

Epidemiologic data now provide strong evidence for an influence of plasma steroid hormones on the risk of breast cancer in postmenopausal women.[7] The associations between the risk of breast cancer and the level of estrogens and androgens (with relative risks [RRs] for breast cancer ranging from 2.0 to 2.5 when comparing the top 20% with the bottom 20% of hormone levels) are strong compared with those of most other breast cancer risk factors. However, few studies have investigated these associations as stratified by tumor receptor status or by invasive versus *in situ* disease. In addition, studies of the effect of postmenopausal hormone use suggest that formulations containing estrogen and progestin are associated with a greater increase in breast cancer risk than those with estrogen only.[8-11] Multiple lines of evidence support a central role of hormones in the etiology of breast, endometrial and ovarian cancers. Evidence of an association between circulating hormones and these cancers varies by both hormone and cancer site, with the most consistent associations observed for sex steroid

hormones and breast cancer risk among postmenopausal women.[12] Various endogenous and exogenous sex hormones play a role in the etiology of breast cancer. Excess endogenous or exogenous estrogens can enhance risk by stimulating proliferation of epithelial cells of breast that have undergone partial malignant transformation.[13] Correlation of ovarian function with estrogen production and the isolation of the estrogen receptor protein, combined with the observed greater incidence of estrogen receptor positive tumors in postmenopausal women, led to the identification of a strong association of estrogen dose and length of exposure with increased breast cancer risk.[14-27] The importance of ovarian steroidogenesis in normal breast development and in the genesis of breast cancer is highlighted by the facts that early menarche and late menopause are associated with greater breast cancer risk, whereas late menarche and early menopause, that occurring before 40 years of age, result in a significant reduction of the same.[28-31] Breast development at puberty and during sexual maturity is stimulated by 17β-estradiol (E_2), which is the predominant circulating ovarian steroid and the most biologically active hormone in breast tissue.[32,33] At menopause E_2 plasma levels decrease by 90%.[28-30] But in postmenopausal women, estrogen formed by peripheral aromatization of ovarian and adrenal androgens, which plays a more significant role.[34,35]

Estrogens are considered to play a major role in promoting the proliferation of both the normal and the neoplastic breast epithelium. Their role as breast carcinogens has long been suspected and recently confirmed by epidemiological studies. Three major mechanisms are postulated to be involved in their carcinogenic effects: stimulation of cellular proliferation through their receptor-mediated hormonal activity, direct genotoxic effects by increasing mutation rates through a cytochrome P450-mediated metabolic activation, and induction of aneuploidy.[36] Progesterone has strong influences on breast physiology and has been hypothesized to both decrease and increase breast cancer risk.[37] Progesterone's effect on breast can be proliferative or anti-proliferative depending upon the type, dosage and duration of exposure. Clarke and Sutherland showed that progesterone and progestin's impact on breast tissue is mediated by PR and alters local breast estrogen activity (e.g. via local aromatase), ER activity and local peptide growth factor function.[38]

It has been found that progesterone increases DNA synthesis in normal breast epithelium in organ culture.[39] However, other studies show that progesterone either decreases or has no effect on the proliferation of normal mammary epithelium explanted into nude mice.[40] Using normal epithelial cells of human breast, it was demonstrated that the progestin, promegestone (R-5020) decreases cell proliferation .[41]

Materials and Methods

This study was conducted in the Department of Biochemistry in collaboration with the Department of Oncology, PGIMS, Rohtak between March 2014 and October 2014. All participating women gave written informed consent before beginning the study. The study population comprised of 25 female patients with breast cancer confirmed by biopsy (Cases) and 25 age matched healthy females (Controls) with postmenopausal status.

Inclusion criteria - Women had to be in the postmenopausal stage (no menstrual cycle from last 12 month) with breast cancer diagnosed with in last 6 month.

Exclusion criteria - Premenopausal, currently on chemotherapy or hormonal therapy or drugs that may affect hormone levels, hysterectomy, oophorectomy and had disease which affect hormonal levels.

Blood samples were withdrawn from the antecubital vein and allow to clot for 30-45 minutes. Serum was separated from venous blood after centrifugation at 3000 rpm for 10 minutes, stored at -20^0C until assayed.

Levels of estrogen and progesterone were estimated in serum of study population by competitive immunoassay using direct chemiluminescence technique on ADVIA-CENTAUR CP.

Results

The 25 women with breast cancer (cases) had a mean Estrogen (71.56±68.13 pg/mL) and Progesterone (4.32±4.19 ng/mL), with a range of 206.6 to 3.85 pg/mL and 13.39 to 0.02 ng/mL respectively. The healthy women had a Estrogen (1.38±1.04 pg/mL) and Progesterone (3.14±2.65 ng/mL) with a range of 4.2 to 0.03 pg/mL and 10.05 to 0.13 ng/mL respectively. The mean age in the cases was 53.6 years with a range of 43 to 76 years. The mean age in the controls was 52.2 years with a range of 45 to 74 years. There was no significant difference between the two groups regarding age. The mean levels of estrogen and progesterone were significantly higher (71.56±68.13 pg/mL; p=<0.001 and 4.32±4.19 ng/mL; p<0.05 respectively) in cases than controls (1.38±1.04 pg/mL and 3.14±2.65 ng/mL respectively). These data are shown in the table 1.

Table 1: Estrogen and Progesterone levels

	Cases (n=25)	**Controls (n=25)**	**P Value**
Estrogen (pg/mL)	71.56±68.13	1.38±1.04	<0.001
Progesterone (ng/mL)	4.32±4.19	3.14±2.65	<0.05
Age (years)	53.6±8.4	52.2±6.7	>0.05

Estrogen is also significantly correlated with Progesterone (r= 0.540, p< 0.05).

Fig. 1 demonstrates the correlation between serum estrogen and progesterone.

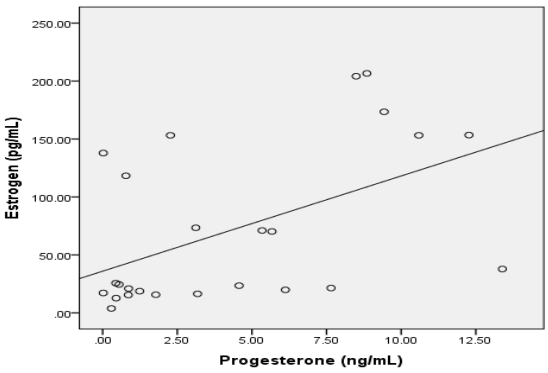

Fig. 1: Correlation between serum Estrogen and Progesterone

Discussion

Our study was designed to explore the estrogen and progesterone levels to see the risk of breast cancer in postmenopausal women because in postmenopausal period significant changes occurs in reproductive hormones than premenopausal period and these changes adversely affect reproductive organs. Our study resulted that significant changes in estrogen and progesterone levels for a very long period had association with development of breast cancer. Many studies also similar results. In postmenopausal women the ovaries cease the production of estrogens as a result of the complete loss of primordial follicles. Estrogen, however, continue to be synthesized by the peripheral aromatization from androgens that reach in circulation from both the adrenals and ovaries. Peripheral aromatase activity increases with age.[36,21] Estrogen have a proliferative effect on breast tissue. The y are related to increased mitotic activity and believed to influence rather than an initiating effect. The proliferation of cells is essential for carcinogenesis because the risk of errors during DNA replication is increased during cell division.[7,17,21,28] Exogenous progestins have been shown to induce growth factors

(EGF, TGF-β), to stimulate the expression of the growth factors and growth factor receptors (EGFR) protein and it's mRNA.[42,37]

Conclusion

Our results indicate that estrogen and progesterone should be routinely estimated in breast cancer patients for better treatment approaches as well as monitoring of disease progression since estrogen and progesterone receptors are correlated with severity and response to treatment in certain studies.

References

1. Global Comparison of breast Cancer from Breast Cancer India [Internet]. 2012 [Cited 2014 Oct 5] Available from: http:// http://www.breastcancerindia.net/bc/statistics/ stat_global.htm
2. Braun M. The Breast. In: Russel RCG, Williams NS, Bulstrode CJK, editors. Bailey and Love's Short Practice of Surgery. 24th ed. London: Hooldev Arnold Oxfort; 2004.p.835-9.
3. Reeder JG, Vogel VG. Breast cancer prevention. Cancer treat Res 2008;141:149–64.
4. Beral V, Bull D, Doll R, Peto R, Reeves G. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. Lancet 2002;360(9328):187–95.
5. Yager JD, Davidson NE. Estrogen carcinogenesis in breast cancer. N Engl J Med 2006;354(3):270–82.
6. Santoro E, DeSoto M, Hong Lee J. Hormone Therapy and Menopause. National Research Center for Women & Families 2009.
7. Key T, Appleby P, Barnes I, Reeves G. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. J Natl Cancer Inst 2002;94:606–16.
8. Colditz GA, Hankinson SE, Hunter DJ, Willett WC, Manson JE, Stampfer MJ, et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. N Engl J Med 1995;332:1589–93.
9. Beral V. Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet 2003;362:419–27.
10. Magnusson C, Baron JA, Correia N, Bergstrom R, Adami HO, Persson I. Breast-cancer risk following long-term oestrogen- and oestrogen-progestin-replacement therapy. Int J Cancer 1999;81:339–44.
11. Greendale GA, Reboussin BA, Sie A, Singh HR, Olson LK, Gatewood O, et al. Effects of estrogen and estrogen-progestin on mammographic parenchymal density. Postmenopausal Estrogen/Progestin Interventions (PEPI) Investigators. Ann Intern Med 1999;130:262–9.
12. Eliassen AH, Hankinson SE. Endogenous hormone levels and risk of breast, endometrial and ovarian cancers: prospective studies. Adv Exp Med Biol 2008;630:148-65.
13. Devid BT. Do hormones causes breast cancer? Cancer 1984;53:595-604.
14. Block G. Estrogen excretion following operative and irradiation castration in cases of mammary cancer. Surgery 1958;43:415–22.
15. Toft D, Shyamala G, Gorski J. A receptor molecule for estrogens: Studies using a cell free system. Proc Natl Acad Sci 1967;57:1740–3.
16. Green S, Walter P, Greene G, Krust A, Goffin C, Jensen E, et al. Cloning of the human estrogen receptor cDNA. J Steroid Biochem 1986;24:77–83.
17. Dorgan JF, Longcope C, Stephenson HEJr, Falk RT, Miller R, Franz C, et al. Relation of prediagnostic serum estrogen and androgen levels to breast cancer risk.Cancer Epidemiol Biomarkers Prev 1996;5:533–9.
18. Dorgan JF, Stanczyk FZ, Longcope C, Stephenson HEJr, Chang L, Miller R, et al. Relationship of serum dehydroepiandrosterone (DHEA), DHEA sulfate, and 5-androstate-3β, 17β-diol to risk of breast cancer in postmenopausal women. Cancer Epidemiol Biomarkers Prev 1997;6:177–81.
19. Thomas HV, Key TJ, Allen DS, Moore JW, Dowsett M, Fentiman IS, et al. A prospective study of endogenous serum hormone concentrations and breast cancer risk in postmenopausal women on the island of Guernsey. Br J Cancer 1997;76:401–5.
20. Hankinson SE, Willett WC, Manson JE, Colditz GA, Hunter DJ, Spiegelman D, Barbieri RL, Speizer FE. Plasma sex steroid hormone levels and risk of breast cancer in postmenopausal women. J. Natl. Cancer Inst.1998;90:1292–9.
21. Toniolo PG, Levitz M, Zeleniuch-Jacquotte A, Banerjee S, Koenig KL, Shore RE, et al. A prospective study of endogenous estrogens and breast cancer in postmenopausal women. J Natl Cancer Inst 1995;87:190–7.
22. Berrino F, Muti P, Micheli A, Bolelli G, Krogh V, Sciajno R, et al. Serum sex hormone levels after menopause and subsequent breast cancer. J Natl Cancer Inst 1996;88:291–6.

23. Garland CF, Friedlander NJ, Barrett-Connor E, Khaw K-T. Sex hormones and postmenopausal breast cancer: a prospective study in an adult community. Am J Epidemiol 1992;135:1220–30.
24. Kabuto M, Akiba S, Stevens RG, Neriiski K, Land CE. A prospective study of estradiol and breast cancer in Japanese women. Cancer Epidemiol Biomarkers Prev 2000;9:575–9.
25. Cauley JA, Lucas FL, Kuller LH, Stone K, Browner W, Cummings SR. for the Study of Osteoporotic Fractures Research Group Elevated serum estradiol and testosterone concentrations are associated with a high risk for breast cancer Ann Intern Med 1999;130:270–7.
26. Helzlsouer KJ, Alberg AJ, Bush TL, Longcope C, Gordon GB, Comstock GW. A prospective study of endogenous hormones and breast cancer. Cancer Detect Prev 1994;18:79–85.
27. Key T, Appleby P, Barnes I, Reeves G. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. J Natl Cancer Inst 2002;94:606–16.
28. Henderson BE, Ross R, Bernstein L. Estrogens as a cause of human cancer: the Richard and Hinda Rosenthal Foundation award lecture. Cancer Res 1988;48:246–53.
29. Pike MC, Spicer DV, Dahmoush L, Press MF. Estrogens, progestagens, normal breast cell proliferation, and breast cancer risk. Epidemiol Rev 1993;15:17–35.
30. Kelsey JL, Gammon MD, John EM. Reproductive factors and breast cancer. Epidemiol Rev 1993;15:36–47.
31. Bernstein L, Ross RK. Endogenous hormones and breast cancer risk. Epidemiol Rev 1993;15:48–65.
32. Russo J, Ao X, Grill C, Russo IH. Pattern of distribution of cells positive for estrogen receptor alpha and progesterone receptor in relation to proliferating cells in the mammary gland. Breast Cancer Res Treat 1999;53:217–27.
33. Russo IH, Russo J. The role of estrogen in breast cancer. In: Russo J, Russo IH, editors. Molecular Basis of Breast Cancer Prevention and Treatment. Springer-Verlag; Heidelberg: 2005. p. 89–136.
34. Miller WR, O'Neill J. The importance of local synthesis of estrogen within the breast. Steroids 1987;50:537–48.
35. Russo J, Hu YF, Russo IH. Estrogens and breast cancer in humans. In: Metzler M, editor. Endocrine disrupters of the Environment. Springer-Verlag; Heidelberg: 2000. p. 1–26.
36. Russo J, Russo IH. The role of estrogen in the initiation of breast cancer. J Steroid Biochem Mol Biol 2006;102:89-96.
37. Susan E. Hankinson and A. Heather Eliassen. Endogenous estrogen, testosterone, and progesterone levels in relation to breast cancer risk. J Steroid Biochem Mol Biol 2007; 106(1-5): 24–30.
38. Clare CL, Sutherland RL. Progestin regulation of cellular proliferation. Endocr 1990;11:266-301.
39. van Bogart LJ. Effect of hormone on human mammary duct in vivo. Hormone Metab Res 1978;10:337-40.
40. McManus MJ, Welsch CW. The effect of estrogen, progesterone, thyroxine, and human placental lactogen on DNA synthesis of human breast ductal epithelium maintained in athymic nude mice. Cancer. 1984;54:1920-7.
41. Gompel A, Malet C, Spritzer P, Lalardrie JP, Kuttenn F, Mauvais-Jarvis P. Progestin effect on cell proliferation and 17β-hydroxysteroid dehydrogenase activity in normal human breast cells in culture. J Clin Endocrinol Metab 1986;63:1174-80.
42. Pasqualini JR. Progestines in the menopause in healthy women and breast cancer patients. Maturitas 2009;62:343-8.