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FACTORS OF RISK FOR BREAST CANCER INFLUENCING POST-MENOPAUSAL LONG-TERM HORMONE REPLACEMENT THERAPY

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The advantages of hormone replacement therapy (HRT) are well documented in contrasting the symptomatology of climacterium and in reducing morbidity and mortality associated with coronary heart disease and osteoporotic fractures of postmenopausal age. However, growing evidence points to increased breast cancer risk in HRT long-term users, and the adverse effect would, obviously, overwhelm any other benefit. At present, the risk/benefit ratio of HRT is an object of hot debate, and we feel it necessary and urgent to select women who can safely benefit from HRT and women whose risk of breast cancer can be perilously increased by the raised hormonal levels related to HRT. We have reviewed studies on the breast cancer risk in HRT users and data on the interaction between steroid hormones and breast cancer. Reasoning that the outcome of mammary cancer can be increased by hormonal overstimulation of the breast, we have focused on those factors of risk that could be further enhanced by the exogenous hormonal stimulus of HRT, so as to cause a further significant increase in the risk of breast cancer. We conclude that some biologic and clinical markers, namely android obesity, bone density, mammographic density, androgen and estrogen circulating levels, alcohol consumption, benign breast disease, and familiarity, should be carefully considered before prescribing long-term HRT. Our analysis suggests that HRT could increase the risk of breast cancer and useless in preventing coronary heart disease and osteoporotic fractures when administered in women with positivity for one or more of these markers.

Key words: breast cancer, hormone replacement therapy, menopause.

Background

It is largely accepted that hormone replacement therapy (HRT) decreases the risk of coronary heart disease and osteoporotic fractures in postmenopausal women[25], thus reducing mortality among women taking hormones[19,21,28]. On the basis of such findings, HRT has been increasingly prescribed and, according to some physicians, the treatment should be proposed to all perimenopausal women and possibly prolonged until the oldest age. However, in the last few years, circumstantial evidence has indicated a causal relationship between HRT and breast cancer development in long-term users[10,12], and, at present, the risk/benefit ratio of HRT is an object of hot debate.

To overcome the gap, an approach for calculating the risk of coronary heart disease, osteoporotic fractures and breast cancer in the individual subject has been proposed[24]. The authors[24] suggested individualizing the choice of HRT on the basis of risks, reasoning that the benefits of the therapy grow with increasing risk for these diseases, whereas women at low risk of coronary heart disease and osteoporotic fractures receive mainly the adverse effect of the therapy[24]. We completely agree with the analysis. The present study is aimed at selecting a subgroup of women at increased risk for breast cancer if submitted to HRT. In these women, the adverse effect of the therapy would largely exceed any other benefit, whereas women at low risk for breast cancer could benefit from HRT in preventing or treating coronary heart disease and osteoporotic fractures.

HRT for all women?

The American College of Physicians recommended that "All women, regardless of race, should consider preventive hormone therapy"[1] and supported the view that the maximum benefit in the prevention of coronary heart disease and osteoporotic fractures can be obtained with long-term therapy for 10-20 years or more.

There is some concern about the attitude in prescribing HRT for a long time, if not for all life, also to asymptomatic women without evident factors of risk for coronary heart disease and osteoporotic fractures, and the matter is much debated. Analyzing the issue from a hormonal point of view, not all postmenopausal women need HRT. Possibly, women with elevated levels of endogenous hormones, who are at increased risk for breast cancer, are at low risk of coronary heart disease and osteoporotic fractures and therefore do not require the therapy.

In this review, we will discuss the possibility that HRT could favor a higher incidence of breast cancer in those women with evidence of anomalous endogenous hormonal stimulation, as in the case of women with increased circulating levels of sex steroids, elevated bone

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density and elevated mammographic density. For our purpose, we will consider, among the numerous factor of risk for breast cancer, only those factors that could be further worsened by the additive effect of increased circulating levels of estradiol induced by HRT.

Factors of risk for breast cancer for women intending to assume HRT

Among the numerous factors of risk for breast cancer we will consider the following: android obesity, bone density, mammographic density, estrogen and androgen levels, alcohol consumption, benign breast disease and familiarity. Other factors of risk will not be examined, because the potential additive effect of increased estrogen levels by HRT is questionable (as in the case of age at first term pregnancy, age at menarche, age at menopause, abortions, nulliparity, profession and school degree), because they are not easy to recall in the anamnesis or to quantify (such as menstrual abnormalities, use of oral contraceptives, anovulatory cycles, sterility and associated treatments), or because they represent by themselves an absolute contraindication to the use of HRT. Paradigmatic, in this respect, is a previous history of breast cancer.

Android obesity. Obesity is positively associated with increased risk of postmenopausal breast cancer, and the risk seems mainly linked to the typically elevated endogenous hormonal levels of the women. Postmenopausal women with a body mass index (BMI) ≥29 kg/m^2 have a mean value of circulating estradiol of 10 pg/mL compared with a value of 4 pg/mL in women with a BMI <21 kg/m^2 [26]. An abnormal biosynthetic activity occurs in the adipose tissue of obese subjects; insulin resistance is frequently present and may play a role in the pathogenesis of hyperandrogenic syndromes in women[39]. In addition, obesity is associated with the increased aromatization of androgens and decreased levels of SHBG, resulting in an increase in free, biologically active, sex steroid concentrations. However, general obesity does not seem to affect breast cancer in women taking HRT[12]. The risk of breast cancer in postmenopausal obese women[16] is mainly associated to the upper body type (android) obesity[20,44], and such subjects are characterized by higher levels of circulating testosterone and estradiol and lower levels of SHBG compared to women with lower body type (gynoid) obesity[37].

Bone density. Bone density is directly associated to a higher incidence of breast cancer[7,53], with a relative risk (RR) between extreme quartiles of 3.5[53]. Bone density might represent a biologic marker of estrogen action.

Mammographic density. The increased risk of cancer has been reported for breasts dense to mammography, with a fivefold risk for a density equal to or greater than 75%[4,40]. Evaluation of mammographic density is more objective than Wolfe's classification[51], which is based on the mammographic parenchymal features (N1, P1, P2 and DY). The mammographic picture of the breast depends on the relative abundance of the adipose, connectival and epithelial tissues. A dense pattern indicates the prevalence of the last two components over the adipose tissue and roughly reflects the response of the connective and epithelial cells to hormone stimulation[35]. It should be noted that the epithelial and stromal cells of the breast interact with each other, and the communication is critical for the normal and pathologic growth of the mammary gland[41]. Findings in the literature suggest that an increase in the percentage of breast density is associated with increased breast cancer risk[34], in premenopausal and in postmenopausal women[6], and in women on HRT[35]. The mammographic pattern has been included in the eligibility criteria of breast cancer prevention trials[14].

Estrogens. A positive relationship between the levels of estradiol and breast cancer risk has been found in several studies[3,17,27,46-48,52]. Such findings confirm that endogenous estrogen levels affect breast cancer development and support the current outlook that the proliferation of susceptible, or already transformed cells is an important determinant of risk. We would suggest that the measurement of circulating estrogen levels may be employed to predict the possible quantitative effect of added exogenous hormones on the risk of breast cancer. HRT, at doses relieving menopausal symptoms, gives rise to circulating estradiol levels similar to those observed in the medium-follicular phase of normal cycling premenopausal women and 5 times higher than in untreated postmenopausal women. In study of Toniolo *et al.*[48], doubling estradiol levels is associated to a threefold increase in breast cancer risk. The increased risk of breast cancer has also been reported for high levels of estrone[46].

Androgens. Numerous case-control studies have indicated that androgen excess is the endocrine abnormality which characterizes breast cancer patients[43]. Recently published prospective studies[3,17,52,46,47] have confirmed that high levels of testosterone are associated with a significant increase in the risk of the development of breast cancer in postmenopausal women. High testosterone levels imply a heavy hormonal abnormality involving circulating estrogens as well. A protective effect was found for increasing levels of SHBG, the protein that influence the free, biologically active, fraction of sex steroids[3,17,52].

Alcohol. Alcohol consumption increases breast cancer risk with a dose-related effect starting from two drinks a day[38]. Two recent reports[11,23] have suggested an interesting relationship between alcohol consumption, estrogen administration and breast cancer risk. Increased risk of breast cancer was observed only in women who consumed alcohol[11] or in women who consumed at least 5 g of alcohol per day[22] compared with those who consumed less alcohol or none at all. Alcohol consumption enormously increases the blood concentration of estradiol in women taking exogenous estrogens[23]. Commenting on such results, Zumoff[54] suggested that estradiol levels may increase above the

threshold of a breast cancer-promoting effect of the hormone regardless of genetic predisposition in women taking estrogens and consuming alcohol.

Benign breast disease. The effect of HRT is particularly evident in women with a previous diagnosis of benign breast disease[5]. Proliferative lesions without atypia are associated with a RR of 1.7-1.9 in women without a family history of breast cancer, and the risk increases to a RR of 2.4-2.7 in women with positive familiarity. Atypical hyperplastic lesions are related to still higher risks of about 4 and about 11 in women with a negative or a positive family history for breast cancer, respectively. The interaction between benign breast disease and HRT in increasing breast cancer development is in agreement with the evidence that HRT stimulates the occurrence of benign breast disease[2,49], which in turn enhances breast cancer risk[18].

Familiarity. A consistent predictor of a woman's risk for breast cancer is a family history of the disease. It has been estimated that 5% of all breast cancers are hereditary[9], with most familial breast cancers linked to BRCA-1 and BRCA-2 germline mutations. BRCA1 and BRCA2 mutations substantially increase the risk of breast cancer, and the risk can be further enhanced by a hormonal stimulation. Estrogen stimulation is believed to increase the promotion of breast cancer, and the anti-estrogen tamoxifen has been used as a chemopreventive agent in women at increased risk for a family history of the disease and in women with known germline BRCA mutation.[8] Several studies have explored the association between the use of exogenous estrogens, oral contraceptives and HRT, and the incidence of breast cancer in women with a family history of breast cancer. Although the results of the studies are contradictory, Weber and Garber[50] suggested in their review to minimize exposure to exogenous estrogens in women at familial breast cancer risk.

Discussion

Epidemiologic and biologic evidence indicates that endogenous sex steroids affect the risk of breast cancer[29,36,45]. Estrogen stimulates the growth of both normal and transformed mammary cells[32], and the combined effect of estrogen and progesterone[15] largely enhances cell proliferation over stimulation by estrogen alone. The growth-promoting effect of steroid hormones occurs by binding to specific intracellular receptors, primarily discovered in breast tumors and subsequently found also in normal ductal and lobular epithelial cells[15]. In addition, sex steroids activate the expression of growth factors and other molecules involved in intracellular signal transduction. Thus, the growth factor system mediates and modulates the effect of steroid hormones on mammary cell proliferation through autocrine and paracrine mechanisms. Studies in animals suggest that exogenous estrogens can induce mammary tumors[13,33], and there is evidence that women submitted to high-dose long-term HRT have an increased risk of breast cancer[30,31,42]. The unanswered question is whether HRT increases the risk only in subjects bearing other factors of risk for breast cancer, like those described herein, or whether HRT alone can increase breast cancer development also in the absence of other risk factors.

Reasoning that the hormonal overstimulation of breast tissue is the unifying element common to the factors of risk of breast cancer and that overstimulation is the consequence of increased hormone concentrations or of increased sensibility to the hormonal stimulus, we consider benign breast disease, mammographic breast density and mammographic breast dysplasia as markers of increased exposure to estrogens in postmenopausal women. Excess hormone stimulation can also be assumed as a consequence of android obesity, alcohol consumption and high values of circulating sex steroids. A family history of breast cancer is the most widespread and reliable indicator of genetic predisposition to the disease. In such women, gene mutation is the main pathogenetic event, which can occur independently of hormonal stimulation. However, increased hormonal stimulation, even if only of a slight degree, can favor progression of initially transformed cells. Finally, it should also be emphasized that the association of two or more factors of risk largely increases the risk, as in the case of atypical hyperplasia of breast epithelium, whose RR is about 4 but reaches an RR of 11 in women with a family history of breast cancer. We conclude that existing evidence suggests that exogenous hormones are able to promote the late stages of carcinogenesis and to increase malignant cell proliferation mainly in breast tissues already submitted to abnormal endogenous hormonal stimulation. We feel it necessary and urgent that suitable studies are conducted to confirm and extend data on the relationship between factors of risk of breast cancer and HRT.

References

1. American College of Physicians. Guidelines for Counseling Postmenopausal Women about Preventive Hormone Therapy. Ann. Intern. Med., 117: 1038-1041, 1992.
2. Berkowitz G.S., Kelsey J.L., Holford T.R., Li Volsi V.A., Merino M.J., Beck G.J., Ort S., O'Connor T.Z., White C.: Estrogen replacement therapy and fibrocystic breast disease in postmenopausal women. Am. J. Epidemiol., 121: 238-245, 1985.
3. Berrino F., Muti P., Micheli A., Bolelli G., Krogh V., Sciajno R., Pisani P., Panico S., Secreto G.: Serum sex hormone levels after menopause and subsequent breast cancer. J. Natl. Cancer Inst., 88: 291-296, 1996.
4. Boyd N.F., Byng J.W., Jong R.A., Fishell E.K., Little L.E., Miller A.B., Lockwood G.A., Tritchler D.L., Yaffe M.J.: Quantitative classification of mammographic densities and breast cancer risk: results from the Canadian National Breast Screening Trial. J. Natl. Cancer Inst., 87: 670-675, 1995.
5. Brinton L.A., Hoover R., Fraumeni J.F. Jr.: Menopausal oe-

strogens and breast cancer risk: an expanded case-control study. Br. J. Cancer, 54: 825-832, 1986.
6. Byrne C., Schairer C., Wolfe J., Parekh N., Salane M., Brinton C.A., Hoover R., Haile R.: Mammographic features and breast cancer risk: effects with time, age, and menopause status. J. Natl. Cancer Inst., 87: 1622-1629, 1995.
7. Cauley J.A., Lucas F.L., Kuller L.H., Vogt M.T., Browner W.S., Cummings S.R.: Bone mineral density and risk of breast cancer in older women: the study of osteoporotic fractures. JAMA, 276: 1404-1408, 1996.
8. Chang J.C.: A review of breast cancer chemoprevention. Biomed. Pharmacother., 52: 133-136, 1998.
9. Claus E.B., Risch N.J., Thompson W.D.: Genetic analyses of breast cancer in the Cancer and Steroid Hormone Study. Am. J. Human Genetics, 48: 232-242, 1991.
10. Colditz G.A., Stampfer M.J., Willett W.C., Hennekens C.H., Rosner B., Speizer F.E.: Prospective study of estrogen replacement therapy and risk of breast cancer in postmenopausal women. JAMA, 264: 2648-2653, 1990.
11. Colditz G.A.: Relationship between estrogen levels, use of hormone replacement therapy, and breast cancer. J. Natl. Cancer Inst., 90: 814-823, 1998.
12. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52705 women with breast cancer and 108411 women without breast cancer. Lancet, 350: 1047-1059, 1997.
13. Cutts J.H., Noble R.L.: Estrone-induced mammary tumors in the rat. Cancer Res., 24: 1116-1123, 1964.
14. Cuzick J., Berridge D., Whitehead J.: Mammographic dysplasia as entry criterion for breast cancer prevention trials. Lancet, 337: 1225, 1991.
15. Dahmoush L., Pike M.C., Press M.F.: Hormones and breast-cell proliferation. In: Treatment of the postmenopausal woman: basic and clinical aspects, Lobor A. (Ed.), p. 325, Raven Press, New York, 1994.
16. deWaard F., Poortman J., Collette B.J.: Relationship of weight to the promotion of breast cancer after menopause. Nutr. Cancer, 2: 237-240, 1981.
17. Dorgan J.F., Longcope C., Stephenson H.E., Falk R.T., Miller R., Franz C., Khale L., Campbell W.S., Tangrea J.A., Schatzkin A.: Relation of prediagnostic serum estrogen and androgen levels to breast cancer risk. Cancer Epidemiol. Biomarker Prevent., 5: 533-539, 1996.
18. Ernster V.L.: The epidemiology of benign breast disease. Epidemiol Rev., 3: 184-202, 1981.
19. Ettinger B., Friedman G.D., Bush T., Quesenberry C.P.: Reduced mortality associated with long-term postmenopausal estrogen therapy. Obstet. Gynecol., 87: 6-12, 1996.
20. Folsom A.R., Kay S.A., Prineas R.J., Potter J.D., Gapstur S.M., Wallace R.B.: Increased incidence of carcinoma of the breast associated with abdominal adiposity in postmenopausal women. Am. J. Epidemiol., 131: 794-803, 1990.
21. Folsom A.R., Mink P.J., Sellers T.A., Hong C.P., Zheng W., Potter J.D.: Hormonal replacement therapy and morbidity and mortality in a prospective study of postmenopausal women. Am. J. Public Health, 85: 1128-1132, 1995.
22. Gapstur S.M., Potter J.D., Sellers T.A., Folsom A.R.: Increased risk of breast cancer with alcohol consumption in postmenopausal women. Am. J. Epidemiol., 136: 1221-1231, 1992.
23. Ginsburg E.L., Mello N.K., Mendelson J.H., Barbieri R.L., Teoh S.K., Rothman M., Gao X., Sholar J.W.: Effects of alcohol ingestion on estrogens in postmenopausal women. JAMA, 276: 1747-1751, 1996.
24. Glasziou P.P., Irwig L.M.: An evidence based approach to individualising treatment. BMJ, 311: 1356-1359, 1995.
25. Grady D., Rubin S.M., Petitti D.B., Fox C.S., Black D., Ettinger B., Ernster V.L., Cummings S.R.: Hormone therapy to prevent disease and prolong life in postmenopausal women. Ann. Intern. Med., 117: 1016-1037, 1992.
26. Hankinson S.E., Willet W.C., Manson J.A.E., Colditz G.A., Hunter D.J., Spiegelman D., Barbieri R.L., Speizer F.E.: Plasma sex steroid hormone levels and risk of breast cancer in postmenopausal women. J. Natl. Cancer Inst., 90: 1292-1299, 1998.
27. Hankinson S.E., Willett W.C., Manson J.E., Hunter D.J., Colditz G.A., Stampfer M.J., Longcope C., Speizer F.E.: Alcohol, height, and adiposity in relation to estrogen and prolactin levels in postmenopausal women. J. Natl. Cancer Inst., 87: 1297-1302, 1995.
28. Henderson B.E., Paganini-Hill A., Ross R.K.: Decreased mortality in users of estrogen replacement therapy. Arch. Intern. Med., 151: 75-78, 1991.
29. Henderson B.E., Ross R.K., Pike M.C., Casagrade J.T.: Endogenous hormones as a major factor in human cancer. Cancer Res., 42: 3232-3239, 1982.
30. Hiatt R.A., Bawol R., Friedman G.D., Hoover R.: Exogenous estrogen and breast cancer after bilateral oophorectomy. Cancer, 54: 139-144, 1984.
31. Hoover R., Gray L.A. Sr., Cole P., MacMahon B.: Menopausal estrogens and breast cancer. NEJM, 295: 401-405, 1976.
32. Howell A.: Clinical evidence for the involvement of oestrogen in the development and progression of breast cancer. Proc. Royal Society Edinburgh, 95B: 49, 1989.
33. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Human. Sex Hormones. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans, 21: 561, 1979.
34. Kato I., Beinart C., Bleich A., Su S., Kim M., Toniolo P.G.: A nested case-control study of mammographic patterns, breast volume and breast cancer (New York City, NY, USA). Cancer Causes Control, 6: 431-438, 1995.
35. Kaufman Z., Garstin W.H., Hayes R., Michell M.J., Baum M.: The mammographic parenchymal patterns of women on hormonal replacement therapy. Clin. Radiol., 43: 389-392, 1991.
36. Kelsey J.L.: Breast cancer epidemiology. Cancer Res., 48: 5615-5623, 1988.
37. Kirschner M.A., Samolijk E., Drejka M., Szmal E., Schneider G., Ertel N.: Androgen-estrogen metabolism in women with upper body vs lower body obesity. J. Clin. Endocrinol. Metab., 70: 473-479, 1990.
38. Longnecker M.P., Berlin J.A., Orza M.J., Chalmers T.C.: A meta-analysis of alcohol consumption in relation to risk of breast cancer. JAMA, 260: 652-656, 1988.
39. Moller D.E., Flier J.S.: Insulin resistance. Mechanism, syndromes and implications. NEJM, 325: 938-948, 1991.
40. Oza A.M., Boyd N.F.: Mammographic parenchymal patterns: a marker of breast cancer risk. Epidemiol. Rev., 15: 196-208, 1993.
41. Reid S.E., Murthy M.S., Kaufman M., Scanlon E.F.: Endocrine and paracrine hormones in the promotion, progression and recurrence of breast cancer. Br. J. Surg., 83: 1037-1046, 1996.
42. Ross R.K., Paganini-Hill A., Gerkins V.R., Mack T.M., Pfeffer R., Arthur M., Henderson B.E.: A case-control study of menopausal estrogen therapy and breast cancer. JAMA, 243: 1635-1639, 1980.
43. Secreto G., Zumoff B.: Abnormal production of androgens in women with breast cancer. Anticancer Res., 14: 2113-2117, 1994.
44. Sellers T.A., Kushi L.H., Potter J.D., Kaye S.A., Helson C.L., McGovern P.G., Folsom A.R.: Effect of family history, body fat distribution and reproductive factors on the risk of postmenopausal breast cancer. NEJM, 326: 652-656, 1992.
45. Thomas D.B.: Do hormones cause breast cancer? Cancer, 53: 595-604, 1984.
46. Thomas H.V., Key T.J., Allen D.S., Moore J.W., Dowsett M., Fentiman I.S., Wang D.Y.: A prospective study of endogenous serum hormone concentrations and breast cancer risk in postmenopausal women on the island of Guernsey. Br. J. Cancer, 76: 401-405, 1997.

47. Thomas H.V., Reeves G.K., Key T.J.: Endogenous estrogen and postmenopausal breast cancer: a quantitative review. Cancer Causes Control, 8: 922-928, 1997.
48. Toniolo P.G., Levitz M., Zeleniuch-Jacquotte A., Banerjee S., Koenig K.L., Shore R.E., Strax P., Pasternack B.S.: A prospective study of endogenous estrogens and breast cancer in postmenopausal women. J. Natl. Cancer Inst., 87: 190-197, 1995.
49. Trapido E.J., Brinton L.A., Schairer C., Hoover R.: Estrogen replacement therapy and benign breast disease. J. Natl. Cancer Inst., 73: 1101-1105, 1984.
50. Weber B.L., Garber J.E.: Familial breast cancer. In: Disease of the breast, J.R. Harris, M.E. Lippman, M. Morrow, S. Hellman (Eds.), pp. 168-185, Lippincott-Raven, Philadelphia, 1996.
51. Wolfe J.N.: Risk for breast cancer development determined by mammographic parenchymal pattern. Cancer, 37: 2486-2492, 1976.
52. Zeleniuch-Jacquotte A., Bruning P., Bonfrer J.M.G., Koenig K.L., Shore R.E., Kim M.Y., Pasternack B.S., Toniolo P.: Relation of serum levels of testosterone and dehydroepiandrosterone sulfate to risk of breast cancer in postmenopausal women. Am. J. Epidemiol., 145: 1030-1038, 1997.
53. Zhang Y., Kiel D.P., Kreger B.E., Cupples L.A., Ellison R.C., Dorgan J.E., Schatzkin A., Levy D., Felson D.T.: Bone mass and the risk of breast cancer among postmenopausal women. NEJM, 336: 611-617, 1997.
54. Zumoff B.: The critical role of alcohol consumption in determining the risk of breast cancer with postmenopausal estrogen administration (Editorial). J. Clin. Endocrinol. Metab., 82: 1656-1658, 1997.