

# Gonadal Hormones and Breast Cancer Risk: The Estrogen Window Hypothesis Revisited

John C. Arpels and Robert D. Nachtigall

*Department of Obstetrics and Gynecology, California Pacific Medical Center, and Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco, California, U.S.A.*

---

**Abstract:** The etiology for breast cancer remains elusive. The epidemiologic and in vitro evidence for the role played by exogenous ovarian hormones shows no consistent trend for or against causation. This review will look at three aspects of this problem. Many breast cancers are hormone independent, potentially driven by proto-oncogenes and genetic alterations. The breast has the ability to make its own endogenous estrogen, irrespective of exogenous hormone use. Progesterone plays an important role in normal breast homeostasis, one which may continue to be needed in the postmenopausal era. **Key Words:** Breast cancer—Gonadal hormones—Estrogen window hypothesis—Hormone replacement—Receptors, estrogen/progesterone.

---

The evidence that hormone replacement affords overall preventive health benefits and improved quality of life for menopausal women is increasing (1). Yet the fear of developing cancer is a frequently voiced concern of both those patients who accept and those who forgo hormone use.

The increased risk of developing uterine cancer has been addressed by the use of an appropriate progestin regime along with the estrogen (2). There is even emerging evidence that under some circumstances successful treatment of uterine cancer need not preclude the use and benefits of hormone replacement (3).

The question regarding the risk for breast cancer remains unclear, although it seems evident from both epidemiologic and in vitro data that gonadal hormones play some role, either directly or indirectly. A number of recent reviews on this subject (4,5) underscore the variability of the data and are further complicated by the fact that most of the ma-

ior studies used unopposed estrogen. A recent analysis of those studies, which used an estrogen plus progestin regime, has shown equally inconsistent results, some studies showing an increase in risk, some with no effect on risk, and others with a trend toward a decrease in risk (6).

The scientific data to date show no consistent role played by gonadal hormones in the etiology of breast cancer. In the absence of compelling scientific data as to a cause and effect relationship between gonadal hormones and breast cancer, physicians are left to determine the clinical relevance of the available data (7). The purpose of the article is to offer a hypothesis that suggests that the absence of progesterone in the latter half of life may be a significant factor in the etiology of breast cancer, while the role of exogenous estrogen may be insignificant.

Evidence for this hypothesis comes from the natural history and the biology of both normal and malignant breast tissue, the presence of a subpopulation of breast cancer whose ability to grow may be autonomous of the presence of hormones, and the ability of the postmenopausal breast to selectively concentrate estrogen independent of exogenous ste-

---

Received October 13, 1993; accepted January 18, 1994.  
Address correspondence and reprint requests to John C. Arpels, M.D., Assistant Clinical Professor, Department Obstetrics, Gynecology and Reproductive Sciences, UC San Francisco, 3838 California St., San Francisco, CA 94118-1522, U.S.A.

roid use. These observations point to the possible benefit for exogenous postmenopausal progestin in a milieu of unopposed endogenous breast estrogen.

### THE FAMILY OF BREAST CANCERS

Although it is generally assumed that breast cancer is a homogenous disease, it can be divided into different subgroups.

Premenopausal breast cancer behaves generally more aggressively, is more often estrogen- and progesterone-receptor-negative (8) with a higher percentage of cells in S-phase as compared with postmenopausal breast cancer (9).

The presence of estrogen and progesterone receptors are among those tumor characteristics that are generally associated with a less aggressive breast cancer. Although being estrogen receptor positive alone affords some benefit, the presence of functional progesterone receptors improves the prognosis (10–12). These cancers are less often aneuploid and generally of low S-phase percentage when compared with estrogen- and progesterone-negative tumors.

Carcinogenesis involves multiple steps and the presence of promoting agents such as oncogenes (13). Human breast cancer has been found to be positive for the HER-2 oncogene in 15–30% of invasive ductal carcinomas and in 13–40% of ductal carcinomas in situ (14–16). This proto-oncogene, which in some patients was amplified up to 20-fold, encodes for a major growth factor involved with cellular proliferation. Increase in tumor size and positive lymph nodes correlated positively with the amplifications of this oncogene, as did a less favorable prognostic outcome. Recently a mutation in the p53 suppressor gene on chromosome 17, which seems to be found in families with a high incidence of breast cancer, has been identified (17,18). The normal cellular kinetic response to ovarian hormones may be altered in the presence of these genes, just as cell proliferation may be independent of hormones in estrogen-receptor-negative tumors.

The very existence of these subgroups alone is likely to preclude a unified hormonal etiology for breast cancer. Differing biology of the various subtypes of breast cancer may explain the variation in findings from different studies on this subject. A reassessment of the major studies dealing with the role played by hormones in the etiology of breast cancer, taking into account the presence of absence

of receptors, proto-oncogenes, and p53 mutations, might provide new insight.

### THE NATURAL HISTORY

There has been an increase in breast cancer risk, but the rise is a minor one until the age group 65–85 (19). The increased incidence seen in the later menopausal years might be attributable to the use of hormone replacement therapy. However, it has been estimated that in 1987 only 10%, and most recently only 20–30%, of menopausal women are on such medication in this country, with 20% of those using progestins in their regime (20). It seems therefore unlikely that the ever-increasing rise in postmenopausal risk for breast cancer as a woman ages is due to exogenous hormones, most of these cancers occurring in non-hormone users.

It is well known that most endometrial cancer is estrogen dependent and that after menopause the major source of this is estrone from the peripheral conversion of androgens (21). If postmenopausal breast cancer were in part due to endogenous estrogen production, then the incidence curves for endometrial and breast cancer might be expected to have a similar shape. In fact, they do not. There is a rise in incidence of endometrial cancer at menopause that parallels that of breast, but endometrial cancer then plateaus around 10 years thereafter and subsequently declines steadily as a woman ages, while the curve for breast cancer continues to climb (22). The ability of the breast to selectively concentrate endogenous estrogen may explain this phenomenon.

The steeper slope of the incidence curve for breast cancer during the premenopausal years has been interpreted as reflecting a role for progesterone in the etiology of this disease (6). Progesterone production is generally well established by age 15 and parallels high fecundity rates until age 35, after which it steadily declines (23). Of those studies that show a possible increase in risk for breast cancer, most show that this effect begins after 15–20 years of estrogen use (5). Even assuming a latency period of 20 years, the greatest incidence for progesterone-abetted breast cancer should then be seen between ages 35 and 55. However, this is not the case. The incidence is a quite low 50 per 100,000 women annually at 35 years and rises to slightly over 200 per 100,000 at age 55. From there it climbs by an additional 100 cases per 100,000 for every decade until finally plateauing around the mid 70s at 450 per

100,000 women annually (24). Since endogenous production of progesterone is essentially zero after menopause (25), it is difficult to attribute this steady rise in incidence to progesterone.

### BREAST FLUID

The biology of breast fluid may provide an explanation for the shape of the cancer incidence curve. The breast has the capacity to concentrate estrogen selectively in ductal fluid so that the level of estrogen that bathes the breast epithelium is from 10- to 40-fold higher than that found in serum (26,27). Although serum levels drop at menopause, breast fluid estrogen stays at very high levels. When replacement estrogen is given both serum and duct fluid estrogen levels rise further. Even without exogenous estrogen use, the duct fluid estrogen level in both pre- and postmenopausal women is higher than that in serum at the midcycle ovulatory peak. The breast has a far greater ability to concentrate estrogen than does endometrium (28), which may account for the difference in shape of their cancer incidence curves. In fact, epithelium from breast cancer patients concentrates tissue levels of estrogen to a higher degree than does normal breast tissue (28).

Although it is possible that duct fluid estrogen is concentrated against a serum gradient, it is currently thought to originate within the breast itself (29). It has been shown that breast adipose tissue contains the aromatase enzyme necessary to convert androgens into estrone and estradiol and that breast tissue adjacent to a carcinoma has the highest such ability (30).

The ability to produce estrogens from androgens is opposed by the action of progesterone, which decreases aromatase activity in endometrium (31) and in breast cancer cells *in vitro* (32). Another function of progesterone is to increase the activity of estradiol dehydrogenase, an enzyme that deactivates estrogen into its weaker metabolites. Progesterone has been shown to have this same activity in breast ductal epithelium *in vitro* where, not only did the activity of the enzyme increase, but estrogen-mediated cell proliferation was inhibited by the progesterone (33).

The premenopausal breast can selectively concentrate progesterone in duct and cyst fluid in concentrations 10-100 times that found concomitantly in serum (34). Although a very small amount of progesterone is produced from the adrenal gland after

menopause (35), it has not yet been shown that the postmenopausal breast selectively concentrates progesterone. Thus, the postmenopausal breast epithelium may be exposed to very high levels of unopposed endogenous estrogen. The significantly lower annual breast cancer incidence in the premenopausal years may be due to the local presence of progesterone.

### THE ROLE OF ESTROGEN

Cell growth is modulated by both promoter as well as suppressor genes. By definition a malignant cell is no longer under this normal control but rather has the ability for autonomous unoppressed growth. It is well established that estrogen causes proliferation of both normal and oncogenically transformed breast epithelial cells in both organ and cell cultures (36). What has not been demonstrated, however, is that the addition of estrogen to cultures of normal breast cells leads to their transformation into malignant ones.

Although it is generally considered that estrogen is probably not a direct inducer of breast cancer, it may facilitate malignant transformation under certain conditions. The estrogen window hypothesis (37) proposes that the susceptibility to malignant transformation is greatest at puberty and in the perimenopausal period, when anovulation leads to unopposed estrogen production unopposed by the action of progesterone.

It is generally believed that a proliferating cell is most susceptible to mutation during the DNA synthesis period of S-phase. Once a fully differentiated cell has completed its cell growth cycle and is now at rest in G<sub>0</sub> phase, it is said to no longer be at risk for mutation (38).

It is estrogen's ability to promote proliferation that opens the window of increased risk. It is progesterone, in sufficient quantity to fully differentiate the breast epithelial cell, that closes the window (39). Pregnancy is considered to have the most efficient effect on decreasing this risk. Women with early menarche, who thereby may experience a greater number of years of estrogen until first pregnancy, and women whose first pregnancy is after age 34, are known to be at increased risk for breast cancer.

Further support for the estrogen window hypothesis comes from epidemiologic studies on the incidence of breast cancer in Japanese women exposed to atomic bomb radiation. The highest risk groups

were those aged 10–14, with the next highest being those aged  $\geq 50$  years. There was no increased risk for prepubertal girls below age 10 (40). Similar data were found in patients who underwent diagnostic fluoroscopy for tuberculosis in the 1940s, where the age group encompassing puberty was at greater risk for breast cancer (41), as was also seen in a group of young pubertal girls who underwent radiation treatment for Hodgkin's lymphoma (42).

The ability of the postmenopausal breast to maintain very high levels of endogenous estrogen well beyond ovarian senescence may extend the unopposed estrogen window through the entire postmenopausal era. This phenomenon could explain the early steep rise seen in the premenopausal years, the subsequent change in slope at menopause, Clemmenson's hook, and lastly the continued rise in the postmenopause era.

In contrast to its potential permissive role, estrogen may also play a protective one. It has been observed that breast cancers that occur in women who are on oral contraceptives or estrogen replacement at the time of detection are lower grade, smaller in size, less metastatic, and have a more favorable prognosis when compared with age-matched breast cancer patients not on exogenous hormones (43–45). When compared to estrogen alone, the use of estrogen plus progestin replacement conferred even greater protection with a relative risk for mortality of RR 0.50 compared to RR 0.87 for the former group (45).

This phenomenon has also been reported to exist for certain other forms of cancer when comparing young girls with young boys. The survival rates between boys and girls were equal until the girls became pubertal, at which point survival began to favor the girls, and this survival advantage continued to climb until by ages 15–19 there was a 55–65% decrease in death rate compared to the males (46).

This apparent survival advantage may be hormone mediated. Estrogen has been shown to help enhance the immune system via T-cell activation (47) and differentiation *in vitro* (48). The susceptibility of breast cancer to natural killer cells is also increased *in vitro* by estrogen (49). Some of these changes are secondary to estrogen's effect on enhancement of thymic factors (50) via stimulation of reticuloendothelial cells, which were found to contain both estrogen and progesterone receptors (48). From these studies emerges a caution that, since *in vitro* culture media rarely also contain viable hematopoietic or thymic cells, it may therefore be diffi-

cult to transpose results obtained from cell cultures into clinically relevant data.

It also must be remembered that one subset of breast cancer is estrogen receptor negative. Whatever role is played by estrogen in promoting susceptibility, it remains to be seen how this impacts on this receptor-negative subgroup. To date, none of the epidemiologic studies on this subject has separated out this particular fraction of cancer patients from those with positive estrogen receptors.

### THE ROLE OF PROGESTINS

Although progestins have a protective effect against endometrial cancer, whether this is true for breast cancer remains in question. Indeed, concern has been voiced that progestins may promote the growth of breast cancer (51), based on the observation that maximal mitotic activity in breast epithelium occurs during the mid to late luteal phase of the menstrual cycle (52). The clinical relevance of this observation has been challenged because proliferation does not necessarily imply that oncogenic transformation will ensue. Carcinogenic change involves a number of interrelated steps where mutations to promoter as well as to suppressor genes occur in conjunction with DNA damage. Once progesterone-abetted proliferation has occurred, the end result is that of an intermediate epithelial cell now transformed into a fully differentiated cell capable of secretory activity. This terminal differentiation is thought to be protective against mutation (38). Many tissues remain benign despite rapid cell proliferation such as skin, gastrointestinal epithelium, and bone marrow (13).

In general, *in vitro* studies show that progestins ultimately down-regulate estrogen-induced proliferation and return cells to a resting state (36). Studies showing a stimulatory effect from progestins have been criticized because the culture medium used significantly slowed the growth rate of the control cells when compared to normal culture conditions. Furthermore, growth was limited to those cells that had already embarked upon the early phase of their cell cycle. Further growth was arrested once these cells completed that cycle. Progestins may also play an indirect protective role by their ability to decrease both tumor angiogenesis factor and fibroblast growth factor *in vivo* using a mouse model. Both are factors implicated in tumor growth rate (53).

Almost all major epidemiologic studies prior to

1980 done on menopausal hormone replacement were without added progestins. A recent epidemiologic review of oral contraceptive and hormone replacement therapy use concluded that the addition of a progestin did not appear to be an increased risk factor for breast cancer (6). However, neither did it show a statistically significant protective effect from the progestin.

### BREAST PROGESTERONE RECEPTORS

Estrogen stimulates production of its own receptor and also that of progesterone. By binding with its receptor, progesterone ultimately decreases the number of estrogen receptors and counteracts estrogen's proliferation effect. Left unopposed by progesterone's down-regulation, estrogen continues to increase the number of its own receptors in a cyclic fashion called "replenishment." This type of receptor control and modulation between estrogen and progesterone has been shown to exist in normal breast epithelium *in vivo* (54). Breast epithelium contains receptors for both estrogen and progesterone. It has been shown that breast progesterone receptors increase in number steadily throughout the menstrual cycle and are maximal during the luteal phase (55). Estrogen receptors are highest during the follicular phase and apparently down-regulate as progesterone rises. This cyclicity can be lost in some premenopausal breast cancers, evidenced by finding equal *in vivo* distributions of estrogen receptors between early and late phases of the menstrual cycle (56).

It has been shown in premenopausal women that in normal breast tissue the mean percentage of cells containing progesterone receptors is greater than those positive only for estrogen receptors. This progesterone dominance is steadily lost as breast epithelium converts, first from normal into atypical hyperplasia, where the two receptors are equal, and eventually to cancer, where the estrogen receptor now is dominant (55). Inadequate, or loss of, progesterone production has been linked epidemiologically to an increased risk for breast cancer in patients with obesity, luteal phase defects, early menarche, and late menopause (57). The postmenopausal era may also represent progesterone inadequacy.

Even in oncogenically transformed breast cancer cells, those that are positive for the progesterone receptor have significantly lower rates of growth compared with cells positive only for the estrogen

receptor (58), and their nuclear uptake of estrogen is decreased *in vitro* by progesterone (59).

The clinical relevance of these data is still unclear, yet progesterone may play an important role in normal breast tissue homeostasis. After ovulation ceases, the subsequent 30–40 years represent endogenous estrogen dominance for breast tissue. Progesterone receptors continue to be made, evidenced by the 50% of breast cancer that is estrogen- and progesterone-receptor-positive. Yet unless supplied exogenously, there is no more ligand for the progesterone receptor to be activated by, and thus it may become functionless.

### CONCLUSION

Breast cancer risk rises with aging, yet the small percentage of replacement hormone in current use cannot account for the magnitude of this risk. The breast is capable of sequestering very high levels of endogenous estrogen irrespective of whether or not an exogenous source of hormone is supplied. The epidemiologic evidence does not support a role for progesterone as a risk factor, yet the absence of progesterone may allow unopposed estrogen to play a permissive role throughout the last decades of life, evidenced by the steady increase in breast cancer risk once ovulation ceases (24,37,57). Other breast cancers may be driven by genetic mechanisms independent of hormone use (15,18).

Why do estrogen and progesterone, which play such an integral role in the normal physiology of the premenopausal breast, no longer play the same role after menopause? If unopposed estrogen is a permissive factor in sensitizing the breast to oncogenic transformation, then until progestins are found to be a significant detriment to both breast and overall menopausal homeostasis, the risks of their omission must be weighed against the unsubstantiated risk of their use. The fear that estrogen's cardiovascular protective effect might be lost by the addition of a progestin has not been clinically demonstrated (60–62).

Until such time as the experimental and epidemiologic data supply the clinician with sound insight, the only help available with which to address our patients' inquiries and fear about breast cancer is to assess as best as possible the clinical relevance of what we do already know.

### REFERENCES

1. Stampfer MJ, Colditz GA, Willett WC, et al. Postmenopausal estrogen therapy and cardiovascular disease. Ten

- year follow-up from the nurses health study. *N Engl J Med* 1991;325:756-62.
2. Persson I, Adami HO, Bergkvist L, et al. Risk of endometrial cancer after treatment with estrogens alone or in conjunction with progestogens: results of a prospective study. *BMJ* 1989;289:147-51.
  3. Lee RB, Burke TW, Park RC. Estrogen replacement therapy following treatment for stage I endometrial carcinoma. *Gynecol Oncol* 1990;36:189-91.
  4. Brinton LA. Menopause and the risk of breast cancer. *Ann NY Acad Sci* 1990;592:357-62.
  5. Hulka BS. Hormone-replacement therapy and the risk of breast cancer. *CA-Cancer J Clin* 1990;40:289-96.
  6. Staffa JA, Newschaffer CJ, Jones JK, et al. Progestins and breast cancer: an epidemiologic review. *Fertil Steril* 1992;57:473-91.
  7. Peterson HB, Kleinbaum DG. Interpreting the literature in obstetrics and gynecology: I. Key concepts in epidemiology and biostatistics. *Obstet Gynecol* 1991;78:710-7.
  8. Axelrod DM, Menendez-Botet CJ, Kinne DW, et al. Levels of estrogen and progesterone receptor proteins in patients with breast cancer during various phases of the menses. *Cancer Invest* 1988;6:7-14.
  9. McGuire WL. Prognostic factors for recurrence and survival in human breast cancer. *Breast Cancer Res Treat* 1987;10:5-9.
  10. McGuire WL, Clark GM. Role of progesterone receptors in breast cancer. *CA-Cancer J Clin* 1986;36:302-9.
  11. Gelbfish GA, Davidson AL, Kopel S, et al. Relationship of estrogen and progesterone receptors to prognosis in breast cancer. *Ann Surg* 1988;207:75-9.
  12. Alexieva-Figusch J, van Putten WLJ, Blankenstein MA, et al. The prognostic value and relationships of patient characteristics, estrogen and progesterone receptors and site of relapse in primary breast cancer. *Cancer* 1988;61:758-68.
  13. Weinstein IB. Mitogenesis is only one factor in carcinogenesis. *Science* 1991;251:387-8.
  14. Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of HER-2/neu oncogene. *Science* 1987;235:177-82.
  15. Van de Vijver MJ, Peterse JL, Mooi WJ, et al. Neu-protein overexpression in breast cancer. *N Engl J Med* 1988;319:1239-45.
  16. McCann AH, Dervan PA, O'Regan M, et al. Prognostic significance of c-erbB-2 and estrogen receptor status in human breast cancer. *Cancer Res* 1991;51:3296-303.
  17. Malkin D, Li FP, Strong LC, et al. Germ line p53 mutations in familial syndrome of breast cancer, sarcomas and other neoplasms. *Science* 1990;250:1233-8.
  18. Poller DN, Hutchings CE, Galea M, et al. p53 protein expression in human breast carcinoma: relationship to expression of epidermal growth factor receptor, c-erbB-2 protein overexpression, and estrogen receptor. *Br J Cancer* 1992;66:583-8.
  19. Kelly P. *Understanding breast cancer risk*. Philadelphia: Temple Univ Press, 1991:35.
  20. Harris RB, Laws A, Reddy VM, et al. Are women using postmenopausal estrogens? A community survey. *Am J Public Health* 1990;80:1266-8.
  21. Judd HL, Shamonki IM, Frumar AM, et al. Origin of serum estradiol in postmenopausal women. *Obstet Gynecol* 1982;59:680-6.
  22. Gambrell RD. Cancer and the use of estrogen. *Int J Fertil* 1986;31:112-3.
  23. Spira A. The decline of fecundity with age. *Maturitas* 1988;(suppl 1):15-22.
  24. Division of Cancer Prevention and Control Surveillance Program. Cancer statistics review 1973-87: US Department of Health and Human Services, National Cancer Institute, Bethesda, MD, 1990:NIH90-2789.
  25. Speroff L, Glass RH, Kase NG. *Clinical gynecologic endocrinology and infertility*. Baltimore: Williams and Wilkins, 1989:629.
  26. Rose DP, Lahti H, Laakso K, et al. Serum and breast duct prolactin and estrogen levels in healthy Finnish and American women and patients with fibrocystic disease. *Cancer* 1986;57:1550-4.
  27. Ernster VL, Wrensch MR, Petrakis NL, et al. Benign and malignant breast disease: initial study results of serum and breast fluid analyses of endogenous estrogens. *J Natl Cancer Inst* 1987;79:949-60.
  28. Thijssen JHH, Van Landeghem AAJ, Poortman J. Uptake and concentration of steroid hormones in mammary tissue. *Ann NY Acad Sci* 1986;464:106-16.
  29. Schurz B, Schön HJ, Wenzl R, et al. Breast cyst fluid concentrations of beta-endorphin, steroids and gonadotrophins in premenopausal women with gross cystic disease. *Maturitas* 1991;13:123-8.
  30. O'Neill JS, Miller WR. Aromatase activity in breast adipose tissue from women with benign and malignant breast diseases. *Br J Cancer* 1987;56:601-4.
  31. Tseng L. Estrogen synthesis in human endometrial epithelial glands and stromal cells. *J Steroid Biochem* 1984;20:877-81.
  32. Perel E, Danilescu D, Kharlip L, et al. Steroid modulation of aromatase activity in human cultured breast carcinoma cells. *J Steroid Biochem* 1988;29:393-9.
  33. Gompel A, Malet C, Spritzer P, et al. Progesterin effect on cell proliferation and 17- $\beta$  hydroxysteroid dehydrogenase activity in normal human breast cells in culture. *J Clin Endocrinol Metab* 1986;63:1174-80.
  34. Rose DP, Tilton K, Lahti H, et al. Progesterone levels in breast duct fluid. *Eur J Cancer Clin Oncol* 1986;22:1111-3.
  35. Speroff L, Glass RH, Kase NG. *Clinical gynecologic endocrinology and infertility*. Williams and Wilkins, 1989:19.
  36. Clarke CL, Sutherland RL. Progesterin regulation of cellular proliferation. *Endocr Rev* 1990;11:266-301.
  37. Korenman SG. Estrogen window hypothesis of the etiology of breast cancer. *Lancet* 1980;1:700-1.
  38. McCarty KS, Jr, McCarty KS, Sr. Steroid modulation of the expression of growth factors and oncogenesis in breast tissue. In: Lippman M, Dickson R, eds. *Regulatory mechanisms in breast cancer*. Boston: Kluwer Academic Publishers, 1991:197.
  39. Russo IH, Russo J. Progestagens and mammary gland development: differentiation versus carcinogenesis. *Acta Endocrinol (Copenh)* 1991;125(suppl 1):7-12.
  40. Tokunaga M, Norman JE, Asano M, et al. Malignant breast tumors among atomic bomb survivors, Hiroshima and Nagasaki, 1950-74. *J Natl Cancer Inst* 1979;62:1347-59.
  41. Boice JD, Jr, Monson RR. Breast cancer in women after repeated fluoroscopic examinations of the chest. *J Natl Cancer Inst* 1977;59:823-32.
  42. Hancock SL, Tucker MA, Hoppe RT. Breast cancer after treatment of Hodgkin's disease. *J Natl Cancer Inst* 1993;85:25-31.
  43. Matthews PN, Millis RR, Haywood JL. Breast cancer in women who have taken contraceptive steroids. *BMJ* 1981;282:774-6.
  44. Vessey MP, McPherson K, Doll R. Breast cancer and oral contraceptives: findings in Oxford-Family Planning Association contraceptive study. *BMJ* 1981;282:2093-4.
  45. Bergkvist L, Adami HO, Persson I, et al. Prognosis after breast cancer diagnosis in women exposed to estrogen and estrogen-progestogen replacement therapy. *Am J Epidemiol* 1989;130:221-8.
  46. Adami HO, Bergstrom R, Holmberg L, et al. The effect of female sex hormones on cancer survival. A register-based

- study in patients younger than 20 years at diagnosis. *JAMA* 1990;263:2189-93.
47. Fox HS, Bond BL, Parslow TG: Estrogen regulates the IFN-gamma promoter. *J Immunol* 1991;146:4362-7
  48. Kawashima I, Sakabe K, Seiki K, et al. Hormone and immune response, with special reference to steroid hormone. 3. Sex steroid effect on T-cell differentiation. *Toku J Exp Clin Med* 1990;15:213-8.
  49. Screpanti I, Felli MP, Toniato E, et al. Enhancement of natural-killer-cell susceptibility of human breast-cancer cells by estradiol and v-Ha-ras oncogene. *Int J Cancer* 1991;47:445-9
  50. Erbach GT, Bahr JM: Enhancement of in vivo humored immunity by estrogen, permissive effect of a thymic factor. *Endocrinology* 1991;128:1352-8.
  51. Key TJA, Pike MC: The role of oestrogens and progestagens in the epidemiology and prevention of breast cancer. *Eur J Cancer Clin Oncol* 1988;24:29-43.
  52. Going JJ, Anderson TJ, Battersby S, et al. Proliferative and secretory activity in human breast during natural and artificial menstrual cycles. *Am J Pathol* 1988;130:193-204.
  53. Fujimoto J, Hosoda S, Fujita H, et al. Inhibition of tumor angiogenesis activity in C3H mouse mammary tumor by medroxyprogesterone acetate. *Nippon Sanka Fujinka Gakkaï Zasshi* 1989;41:77-82.
  54. Söderqvist G, von Schoultz B, Tani E, et al. Estrogen and progesterone receptor content in breast epithelial cells from healthy women during the menstrual cycle. *Am J Obstet Gynecol* 1993;168:874-9.
  55. Jacquemier JD, Hassoun J, Torrente M, et al. Distribution of estrogen and progesterone receptors in healthy tissue adjacent to breast lesions at various stages—immunohistochemical study of 107 cases. *Breast Cancer Res Treat* 1990;15:109-17
  56. Markopoulos C, Berger U, Wilson P, et al. Oestrogen receptor content of normal breast cells and breast carcinomas throughout the menstrual cycle. *BMJ* 1988;296:1349-51
  57. Cowan LD, Gordis L, Tonascia JA, et al. Breast cancer incidence in women with a history of progesterone deficiency. *Am J Epidemiol* 1981;114:209-17
  58. Ballare C, Bravo AI, Sorin I, et al. The expression of progesterone receptors coincides with an arrest of DNA synthesis in human breast cancer. *Cancer* 1991;67:1352-8.
  59. Pasqualini JR, Gelly C, Nguyen BL, et al. Importance of estrogen sulfates in breast cancer. *J Steroid Biochem* 1989;34:155-63.
  60. Barrett-Connor E, Wingard DL, Criqui MH: Postmenopausal estrogen use and heart disease risk factors in the 1980s. Rancho Bernardo, Calif, revisited. *JAMA* 1989;261:2095-100.
  61. Falkeborn M, Persson I, Ter'ent A, et al. Hormone replacement therapy and the risk of stroke. Follow-up of a population-based cohort in Sweden. *Arch Intern Med* 1993;24:1201-9.
  62. Nabulsi AA, Folsom AR, White A, et al. Association of hormone-replacement therapy with various cardiovascular risk factors in postmenopausal women. *N Engl J Med* 1993;328:1069-75.