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Towards an understanding of breast cancer etiology

Hans-Olov Adami †, Lisa B. Signorello† and Dimitrios Trichopoulos†*

We present an etiological model for breast cancer in humans, and we examine whether it accommodates the patterns of occurrence of this disease and the associated risk factors. The model has four components: (1) the likelihood of breast cancer occurrence depends on the number of cells at risk; (2) the number of target cells is partially determined early in life, perhaps even in utero*; (3) while a pregnancy stimulates the replication of already initiated cells, it conveys long-term protection through structural changes, terminal cellular differentiation, and perhaps other mechanisms; and (4) in adult life, mammotropic hormones, in conjunction with their receptors, affect the number of target cells, the likelihood of retention of spontaneous somatic mutations, and the rate of expansion of initiated clones. The model accommodates several hypotheses but also allows new insights.*

Key words: breast neoplasms / risk factors / etiology / causation

Introduction

WHETHER THE INCIDENCE of breast cancer is slightly decreasing, as is perhaps happening in the United States,[1] or definitely increasing, as is clearly happening in most countries worldwide,[2] primary prevention of breast cancer remains as elusive as our understanding of the etiology of the disease. Some investigators have argued that we can explain a substantial part of the variability of breast cancer incidence among populations.[3] No attempt, however, has been made to integrate established facts and plausible hypotheses into a coherent biologic model for breast cancer etiology in humans.

Recent findings from animal and epidemiological investigations led Adami *et al*[4] to postulate an etiological model for breast cancer in humans. Following their lead, we will attempt to expand on the theoretical arguments and on the biological evidence in support of this model, and we will try to assess how the model accommodates the established risk profile of breast cancer.

Breast cancer risk factors

The epidemiology of breast cancer has been reviewed by many authors,[5,6] and Kelsey[7–10] has followed the evolution of the relevant research over a period of 20 years. Breast cancer is almost 100 times more common among women than among men. The incidence of the disease increases sharply with age, with a characteristic inflection around the age of menopause. An earlier age at menarche and a later age at menopause are associated with increased risk whereas, for a given age at menopause, a surgical one resulting from bilateral oophorectomy conveys more protection than a naturally occurring one. A pregnancy conveys, in general terms, protection, but in a complex way.[11–13] The earlier the age at first full-term pregnancy, the more substantial the protection, so that after the age of approximately 35 a first pregnancy actually increases breast cancer risk. Subsequent full-term pregnancies have similar, but quantitatively much weaker effects. The net effect of a pregnancy results from a transient increase of breast cancer risk followed by a long-term reduction of this risk.[11] Prolonged lactation conveys some protection, but the effect is small and may be limited to premenopausal breast cancer.[14] Height is positively associated with breast cancer risk, whereas obesity is inversely related to this risk among premenopausal, but positively among post-menopausal women. Two

*From the *Department of Medical Epidemiology, Karolinska Institutet, Box 281, SE-171 77 Stockholm, Sweden and the †Department of Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115, USA*

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other risk factors are quantitatively important. Caucasian women in Europe and North America have a more than fivefold risk compared to women in Asia or Japan, and a high-density mammogram (75% or more of the total breast area with dense mammographic appearance) indicates an almost fourfold risk in comparison to a low-density mammogram (25% or less or total breast area with dense mammographic appearance).[15] It is not well-established to what extent mammographic patterns reflect forms of atypical hyperplasia, which is also an established risk factor for breast cancer.[16] Universally, breast cancer tends to be slightly more common among women of higher socioeconomic status and among urban rather than rural residents.

It has long been known that there is a familial aggregation of breast cancer,[5] and at least four genes that convey increased susceptibility to breast cancer have been identified, namely BRCA1, BRCA2, p53 and AT (ataxia telangiectasia). These genes are thought, however, to be responsible for less than 5% of breast cancer cases overall, although this proportion is higher among younger women and in certain population groups.[17–19]

Several environmental and lifestyle factors have been studied in relation to breast cancer, but the evidence appears adequate only for a few and, even for these, the respective associations are at most of moderate strength. Current or recent use of oral contraceptives and hormone replacement therapy slightly increase the risk for breast cancer,[20,21] whereas ionizing radiation is an established cause of the disease of limited quantitative importance.[5] There is also strong evidence for an association between consumption of alcoholic beverages and breast cancer risk that can not be explained in terms of confounding or bias.[22] In contrast, there is little, if any, evidence for a major influence of adult diet, physical activity, or exposure to organochlorines or electromagnetic fields.

An etiological model

Adami *et al*[4] have proposed an etiological model with four key components: (1) the likelihood of breast cancer occurrence depends on the number of cells at risk; (2) the number of target cells and their responsiveness to hormonal stimulation is partially determined early in life, perhaps even *in utero*; (3) while a pregnancy stimulates the replication of already initiated cells, it conveys long-term protection through structural changes, terminal cellular differentiation, and perhaps other mechanisms; and (4) in adult life, mammotropic hormones, in conjunction with their receptors, affect the number of target cells, the likelihood of retention of spontaneous somatic mutations, and the rate of expansion of initiated clones. We will consider, in turn, the evidence in support of each of these components.

The number of cells at risk

It is intuitively appealing that the magnitude of breast cancer risk should depend on the transition rates of susceptible cells or, equivalently, the number of these proliferating cells.[23] The empirical evidence in support of this thesis is indirect, but fairly strong.[24] Mammographic density is a powerful predictor of breast cancer risk, and this density is nothing more than the expression of mammary gland mass as a fraction of the total breast area.[15,25] Moreover, small-breasted women who were motivated to have augmentation mammoplasty, and whose mammary gland mass had to be small, were found to have substantially reduced breast cancer risk, as were women who had undergone surgical reduction of their breasts.[26,27] Mammary gland mass is likely to reflect total number of mammary cells at risk.

Perinatal influences on breast cancer risk

There is substantial interindividual structural variability in newborn mammary tissue, ranging from a rudimentary ductal system without lobules to well-developed branching ducts with terminal lobules.[28] Several authors have considered the possibility that intrauterine factors and perinatal events or conditions could affect breast cancer risk in the offspring.[29–41] Throughout the prenatal period, the mammary gland tissue exists in a partially undifferentiated state that creates a 'fertile soil' for cancer initiation and several chemicals have been found to cause prenatal carcinogenesis in several animal species. A recent study by Hilaviki-Clarke *et al*[35] reported that the female offspring of pregnant rats fed a high-fat diet had a higher incidence of mammary tumors when exposed to dimethylbenzanthracene than did the female offspring of pregnant rats fed a low-fat diet. Another observation compatible with intrauterine factors affecting breast cancer risk in the offspring is that familial risk of breast cancer among first degree relatives is higher when the sister rather than the mother is affected.[42,43]

Birthweight and, to a lesser extent, other birth size indicators are crucial variables for the documentation of intrauterine influences on disease risk. A large study in Sweden suggested a positive association between birthweight and breast cancer risk,[29] although in a subsequent paper the association was very weak and far from significant.[33] In yet another study in Sweden, high risk adult mammographic patterns were significantly associated with higher placental weight.[38] Lastly, in a case-control study nested within the large Nurses' cohort in the USA, a strong and statistically significant association was found between birthweight and breast cancer risk.[37] Mechanisms that have been advanced to explain the empirical evidence linking perinatal events or conditions to breast cancer in adult life have invoked modulation of physiologic processes by exogenous factors, including maternal nutrition, or poorly specified 'programming' during fetal life.[44]

Pregnancy effects on mammary cells

The parenchymal or ductal system of the human breast undergoes profound changes from neonatal life to old age. Russo and Russo[41,45–49] have pioneered research in this area, mostly in rats, but also in humans. During and after the peri-menarcheal years, the mammary ducts divide in a dichotomous manner, eventually creating terminal end buds, occasionally with rudimentary alveolar formations. These primitive ducts and associated alveolar buds have been termed lobules type 1 and 2. Differentiation of the glandular epithelial cells takes place gradually and culminates in the generation of lobules type 3 and 4, characterized by terminally differentiated glandular tissue. These changes happen mostly after the occurrence of the first full-term pregnancy and, to a lesser extent, after the occurrence of subsequent pregnancies and lactation. The rate of cellular proliferation is much higher in lobules type 1 and 2, and a high rate of cellular replication is intimately linked to the likelihood of genetic errors that could lead to loss of growth control.[50] Thus, a first full-term pregnancy reduces the cellular population at risk and makes many of the previously susceptible cells fully or partially refractory to cancer-initiating events.

Mammotropic hormones

Exposure to mammotropic hormones, mainly estrogens, but also progesterone, prolactin, and insulin-like growth factor 1, during adolescence and in adult life can affect breast cancer risk by: (i) increasing the cellular population at risk during the pre-initiation stage; (ii) influencing clonal expansion; and (iii) modulating growth enhancement of subclinical tumors. Estrogens are likely to be the dominant actors in this process, but their effect depends on the presence of a sufficient number of estrogen receptors in the target tissue. Several case-control investigations have indicated that estrogen levels are likely to be higher among women with breast cancer than among controls,[51,52] and recent studies confirmed this association prospectively.[53,54] Estrogen production rates and blood levels are generally higher among Caucasian than among Asian women,[55,56] but the differences are not sufficiently large to explain the fivefold contrast of breast cancer incidence between these two groups. In a small study, estrogen receptors were significantly more frequently positive in the normal breast of Caucasian than of Asian and African women.[57] Moreover, in the endometrium, the concentration of cytoplasmic estrogen receptors has been found to be at least four times higher in Finnish than in Japanese women.[58] Lastly, the proportion of women with estrogen receptor positive breast cancer is lower among Asian than among Caucasian patients.[59–61] It may be that higher prevalence of estrogen receptor positivity may be a characteristic of populations at increased risk for breast cancer. In fact, it has recently been reported that overexpression of estrogen receptors in normal breast epithelium may increase breast cancer risk in individual women.[62] Several recent studies also indicate that IGF-1 is positively associated with breast cancer risk among premenopausal women.[63–66]

Pregnancy estrogens have been found in a recent study to be higher among Chinese than among white American women,[67] raising the possibility that high prenatal exposure to estrogens permanently down-regulates estrogen receptor expression in the mammary and other estrogen-responsive tissues.[57,58] A similar phenomenon has been described with respect to post-natal cholesterol intake and serum cholesterol homeostasis in later life—a relatively high cholesterol intake during the immediate post-natal period has been associated with more effective catabolism of the compound in adult life and lower blood cholesterol levels.[68–72] The phenomenon has been described as a form of physiologic 'training' which occurs early in life in response to certain stimuli.

Breast cancer risk factors in light of the proposed etiological model

In this section, we will examine how the proposed etiological model accommodates the established risk factors of breast cancer. Our approach will be a biological, rather than statistical, one. We will not address histopathological factors (e.g. atypical dysplasia), because the importance of these variables can be easily conceptualized in the context of the well-established natural history of cancer from hyperplasia to metaplasia to dysplasia. Nor will we consider genes, whose mode of action remains at present poorly understood.

Gender

In adult life, mammotropic hormones are likely to interact with mammory gland mass, the latter reflecting numbers of cells at risk. Because estrogen production in later life is not substantially different between the two genders, the sharply higher breast cancer risk among women than among men could plausibly be explained, at least in part, in terms of the correspondingly higher mammary gland mass among the former.

Age

The increasing incidence of breast cancer with age reflects, as for many other cancers, the accumulation of somatic mutations over time. The characteristic inflection of breast cancer incidence around the time of menopause, however, is likely to reflect the cessation of ovarian function and thus decreasing exposure to gonadal hormones.

Age at menarche

An earlier age at menarche increases duration of exposure to ovarian hormones. Earlier age at menarche also appears to be associated with a more rapid establishment of regular ovulatory cycles (i.e. a smaller number of anovulatory cycles in the peri-menarcheal period) and perhaps with higher levels of estrogens throughout the reproductive life of the woman.[73]

Age at menopause

A later age at menopause necessarily prolongs exposure to ovarian hormones. A surgical menopause confers more protection than a natural menopause at the same age because bilateral oophorectomy eliminates the gonadal source of estrogens abruptly, whereas natural menopause is typically characterized by a gradual decline in estrogen levels.

Age at first full-term pregnancy

A pregnancy is accompanied by many-fold increases of estrogens and other mammotropic hormones that can boost already initiated clones but also makes a large fraction of previously susceptible cells refractory to carcinogenesis after undergoing terminal differentiation. When the first pregnancy occurs at an early age, fewer cells are likely to have already been initiated. In addition, the period of protection covers a larger fraction of the remaining life span. The transient increase in risk following a pregnancy explains a longstanding enigma, namely, why breast cancer risk is higher among parous than among nulliparous women of premenopausal age.[8]

Subsequent pregnancies and lactation

Subsequent full-term pregnancies, and perhaps even lactation, may impart terminal differentiation to cells that have not already been switched to that stage under the influence of the first full-term pregnancy.

Height

Adult height, mammary gland mass and number of cells at risk are likely to be positively interrelated, albeit weakly, since all reflect, to a certain extent, overall growth.

Obesity and premenopausal breast cancer

The prevalence of high-risk mammograms, that is, mammograms with a high fraction of total breast size occupied by mammary gland tissue, as opposed to fat, is four times higher among lean women than among obese women, as the large study by Byrne *et al*[15] has conclusively demonstrated. The inverse association between obesity and breast density underlies the inverse association between obesity and breast cancer risk among premenopausal women, because the associations of breast density with obesity and breast cancer risk (inverse and positive, respectively) are both strong. It has been argued that obese women are at lower risk for premenopausal breast cancer because they have a higher frequency of anovulation, but the relations of anovulation to obesity and breast cancer risk (positive and inverse, respectively) are, at best, weak.

Obesity and post-menopausal breast cancer

Among post-menopausal women, the adipose tissue is the principal source of estrogens that enhance the expansion of initiated clones and the growth of subclinical tumors. Obesity also increases bioavailability of estrogen through reduction of sex-hormone binding globulin. Women who were thin and gained considerable weight between early adulthood and the post-menopause would be at increased breast cancer risk post-menopausally on two accounts: the high risk mammographic pattern that characterizes thin premenopausal women and the increased estrogen bioavailability imparted by adiposity in later life.

Mammographic patterns

Mammographic patterns mostly describe the fraction of breast occupied by mammary gland mass, and this mass is a direct correlate of the number of cells at risk.

The low breast cancer risk of Asian women

Asian women are shorter than Caucasian women and the small size of their breasts implies small mammary gland mass. Small-breasted Asian women should be contrasted to small-breasted, but typically taller, Caucasian women. Among the latter, small breasts are associated with high breast density,[15,38] whereas among the former, small breasts are not associated with this pattern.[74] Lower levels of estrogens[55,56] and possibly estrogen receptors[57] among Asian women as compared to Caucasian women, may also contribute to the striking breast cancer risk differential.[55–61]

Socioeconomic status

The socioeconomic gradient of breast cancer risk is characteristically stronger in countries that are currently developing. Birthweight, a possible breast cancer risk factor,[37] is generally higher among women of higher socioeconomic status, except perhaps among women of countries that have been economically advanced for a long time.

Exogenous estrogens

Oral contraceptives and menopausal estrogens obviously possess estrogenic properties, which can explain the small excess in breast cancer risk associated with their use.

Ionizing radiation

Ionizing radiation is an established cause of somatic mutations.

Alcoholic beverages

Ethanol has been found to increase levels of circulating estrogens in both pre- and post-menopausal women.[75,76]

Physical activity

Physical activity in adolescence delays menarche[77] and, during adulthood, may reduce estrogen levels.[78] The link between exercise and hormone levels is not strong, but the evidence for an inverse association between physical activity and breast cancer is also weak.

Diet

Because Asian migrants to the United States eventually acquire the breast cancer incidence pattern of the host country, it can be inferred that some lifestyle factor(s) are responsible.[79–81] Diet has been a prime candidate because it has provided a plausible explanation for the change in incidence of other cancer types among these migrants, notably stomach and colorectal cancer. However, adult diet has been found to exercise, at most, a minimal effect on breast cancer risk. The fact that breast cancer incidence assimilation appears to require at least two, and perhaps several, generations points to early life as a critical period,[82] and the positive association between height and breast cancer risk in both ecological and analytical epidemiological studies suggests that excessive energy intake or reduced expenditure in early life could be important. There are indications that consumption of vegetables and fruits,[83] olive oil,[84] and soy-based foods[85] may have preventive potential, perhaps on account of antioxidant properties but, at this stage, it is more important to firmly document these associations than to speculate about the underlying biology.

Conclusion

In the etiological model we propose, breast cancer risk increases with the number of susceptible cells which, in turn, depend on early-life or even prenatal

influences that modulate the number of the relevant stem cells. Susceptible cells become refractory following a full-term first pregnancy, with subsequent pregnancies and lactation complementing this process. Mammotropic hormones, primarily estrogens in conjunction with their receptors, affect both the pre-initiation and the post-initiation stages in the natural history of breast cancer. The proposed etiological model accounts for most aspects of the epidemiology of breast cancer in humans. The formulation of this model has, however, largely relied on the results of epidemiologic studies. Thus, the compatibility of model-based predictions with existing empirical evidence does not provide powerful independent documentation of its validity. There are, however, several model-based predictions that can be empirically evaluated and a number of model links amenable to preventive interventions. These interventions, however, may require substantial life-style changes and have long latency periods.

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References

1. Smart CR, Byrne C, Smith RA, Garfinkel L, Letton AH, Dodd GD, Beahrs OH (1997) Twenty-year follow-up of the breast cancers diagnosed during the Breast Cancer Detection Demonstration Project. Ca: a Can J Clin 47:134–149
2. Ursin G, Bernstein L, Pike MC (1994) Breast cancer. Cancer Surv 19–20:241–264
3. Madigan MP, Ziegler RG, Benichou J, Byrne C, Hoover RN (1995) Proportion of breast cancer cases in the United States explained by well-established risk factors. J Natl Cancer Inst 87:1681–1685
4. Adami H-O, Persson I, Ekbom A, Wolk A, Ponten J, Trichopoulos D (1995) The aetiology and pathogenesis of human breast cancer. Mutat Res 333:29–35
5. Adami H-O, Adams G, Boyle P, Ewertz M, Lee N, Lund E, Miller A, Olsson H, Steel M, Trichopoulos D, Tulinius H (1990) Breast cancer etiology. Int J Cancer 5(Suppl.):22–39
6. Lipworth L (1995) Epidemiology of breast cancer. Eur J Cancer Prev 4:7–30
7. Kelsey JL (1979) A review of the epidemiology of breast cancer. Epidemiol Rev 1:74–109
8. Kelsey JL. (ed.) (1993) Breast cancer. Epidemiol Rev 15:1–263
9. Kelsey JL, Hildreth NG (1983) Breast and Gynecologic Cancer Epidemiology. Florida: CRC Press
10. Kelsey JL, Berkowitz GS (1988) Breast cancer epidemiology. Cancer Res 48:5615–5623
11. Lambe M, Hsieh C-c, Trichopoulos D, Ekbom A, Pavia M, Adami H-O (1994) Transient increase in the risk of breast cancer after giving birth. N Engl J Med 331:5–9
12. Hsieh C-c, Pavia M, Lambe M, Lan SJ, Colditz GA, Ekbom A, Adami H-O, Trichopoulos D, Willett WC. (1994) Dual effect of parity on breast cancer risk. Eur J Cancer 30A:969–973
13. Rosner B, Colditz GA, Willett WC (1994) Reproductive risk factors in a prospective study of breast cancer: the nurses' health study. Am J Epidemiol 139:819–835
14. Newcomb PA, Storer BE, Longnecker MP, Mittendorf R, Greenberg ER, Clapp RW, Burke KP, Willett WC, MacMahon B (1994) Lactation and a reduced risk of premenopausal breast cancer. N Engl J Med 330:81–87
15. Byrne C, Schairer C, Wolfe J, Parekh N, Salane M, Brinton LA, Hoover R, Haile R (1995) Mammographic features and breast cancer risk: effects with time, age, and menopause status. J Natl Cancer Inst 87:1622–1629
16. Marshall LM, Hunter DJ, Connolly JL, Schnitt SJ, Byrne C, London SJ, Colditz GA (1997) Risk of breast cancer associated with atypical hyperplasia of lobular and ductal types. Cancer Epidemiol Biomarkers Prev 6:297–301
17. Ford D, Easton DF, Peto J (1995) Estimates of the gene frequency of BRCA1 and its contribution to breast and ovarian cancer incidence. Am J Hum Genet 57:1457–1462
18. Easton D, Ford D, Peto J (1993) Inherited susceptibility to breast cancer. Cancer Surv 18:95–113
19. Egan KM, Newcomb PA, Longnecker MP, Trentham-Dietz A, Baron JA, Trichopoulos D, Stampfer M, Willett WC (1996) Jewish religion and risk of breast cancer. Lancet 347:1645–1646
20. Collaborative Group on Hormonal Factors in Breast Cancer (1996) Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53297 women with breast cancer and 100239 women without breast cancer from 54 epidemiological studies. Lancet 347:1713–1727
21. Collaborative Group on Hormonal Factors in Breast Cancer (1997) 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
22. Longnecker MP (1994) Alcoholic beverage consumption in relation to risk of breast cancer: meta-analysis and review. Cancer Causes Control 5:73–82
23. Moolgavkar SH, Day NE, Stevens RG (1980) Two-stage model for carcinogenesis: epidemiology of breast cancer in females. J Natl Cancer Inst 65:559–569
24. Trichopoulos D, Lipman RD (1992) Mammary gland mass and breast cancer risk. Epidemiology 3:523–526
25. Byrne C (1997) Studying mammographic density: implications for understanding breast cancer. J Natl Cancer Inst 89:531–533
26. Berkel H, Birdsell DC, Jenkins H (1992) Breast augmentation: a risk factor for breast cancer? N Engl J Med 326:1649–1653
27. Lund K, Ewertz M, Schou G (1987) Breast cancer incidence subsequent to surgical reduction of the female breast. Scand J Plast Reconstr Surg Hand Surg 21:209–212
28. Anbazhagan R, Bartek J, Monaghan P, Gusterson BA (1991) Growth and development of the human infant breast. Am J Anat 192:407–417
29. Ekbom A, Trichopoulos D, Adami H-O, Hsieh C-c, Lan S-J (1992) Evidence of prenatal influences on breast cancer risk. Lancet 340:1015–1018
30. Sanderson M, Williams MA, Malone KE, Stanford JL, Emanuel I, White E, Daling JR (1996) Perinatal factors and risk of breast cancer. Epidemiology 7:34–37
31. Weiss HA, Pitischman NA, Brinton LA, Brogan D, Coates RJ, Gammon MD, Malone KE, Schoenberg JB (1997) Prenatal and perinatal risk factors for breast cancer in young women. Epidemiology 8:181–187
32. Hilakivi-Clarke L (1997) Mechanisms by which high maternal fat intake during pregnancy increases breast cancer risk in female rodent offspring. Breast Cancer Res Treat 46:199–214
33. Ekbom A, Hsieh C-c, Lipworth L, Adami H-O, Trichopoulos

D (1997) Intrauterine environment and breast cancer risk in women: a population-based study. J Natl Cancer Inst 89:71–76
34. Swerdlow AJ, De Stavola BL, Swanwick MA, Maconochie NE (1997) Risks of breast and testicular cancers in young adult twins in England and Wales: evidence on prenatal and genetic aetiology. Lancet 350:1723–1728
35. Hilakivi-Clarke L, Clarke R, Onojafe I, Raygada M, Cho E, Lippman M (1997) A maternal diet high in n-6 polyunsaturated fats alters mammary gland development, puberty onset, and breast cancer risk among female rat offspring. Proc Natl Acad Sci USA 94:9372–9377
36. Rossing MA, Stanford JL, Weiss NS, Daling JR (1996) Indices of exposure to fetal and sperm antigens in relation to the occurrence of breast cancer. Epidemiology 7:309–311
37. Michels KB, Trichopoulos D, Robins JM, Rosner BA, Manson JE, Hunter DJ, Colditz GA, Hankinson SE, Speizer FE, Willett WC (1996) Birthweight as a risk factor for breast cancer. Lancet 348:1542–1546
38. Ekbom A, Thurfjell E, Hsieh C-c, Trichopoulos D, Adami H-O (1995) Perinatal characteristics and adult mammographic patterns. Int J Cancer 61:177–180
39. Hilakivi-Clarke L, Clarke R, Lippman ME (1994) Perinatal factors increase breast cancer risk. Breast Cancer Res Treat 31:273–284
40. Sandson TA, Wen PY, LeMay M (1992) Reversed cerebral asymmetry in women with breast cancer. Lancet 339:523–524
41. Russo IH, Russo J (1996) Mammary gland neoplasia in long-term rodent studies. Environ Health Perspect 104:938–967
42. Claus EB, Risch NJ, Thompson WD (1990) Age at onset as an indicator of familial risk of breast cancer. Am J Epidemiol 131:961–972
43. Eby N, Chang-Claude J, Bishop DT (1994) Familial risk and genetic susceptibility for breast cancer. Cancer Causes Control 5:458–470
44. Hall JG (1990) Genomic imprinting: review and relevance to human diseases. Am J Hum Genet 46:857–873
45. Russo J, Russo IH (1987) Development of the human mammary gland, in The Mammary Gland (Neville MC, Daniel CW, eds) pp. 67–93. Plenum Publishing Corporation
46. Russo J, Gusterson BA, Rogers AE, Russo IH, Wellings SR, van Zwieten MJ (1990) Biology of disease. Comparative study of human and rat mammary tumorigenesis. Lab Invest 62:244–278
47. Russo J, Rivera R, Russo IH (1992) Influence of age and parity on the development of the human breast. Breast Cancer Res Treat 23:211–218
48. Russo J, Calaf G, Sohi N, Tahin Q, Zhang PL, Alvarado ME, Estrada S, Russo IH (1993) Critical steps in breast carcinogenesis, in breast cancer: from biology to therapy. Ann NY Acad Sci 698:1–20
49. Russo J, Romero AI, Russo IH (1994) Architectural pattern of the normal and cancerous breast under the influence of parity. Cancer Epidemiol Biomark Prev 3:219–224
50. Preston-Martin S, Pike MC, Ross RK, Jones PA, Henderson BE (1990) Increased cell division as a cause of human cancer. Cancer Res 50:7415–7421
51. MacMahon B, Cole P, Brown J, Paffenbarger R, Trichopoulos D, Yen S (1982) Urine estrogens, frequency of ovulation and breast cancer risk: case-control study in premenopausal women. J Natl Cancer Inst 70:247–250
52. Bernstein L, Yuan J-M, Ross RK, Pike MC, Hanisch R, Lobo R, Stanczyk, Gao Y-T, Henderson BE (1990) Serum hormone levels in pre-menopausal Chinese women in Shanghai and white women in Los Angeles: results from two breast cancer case-control studies. Cancer Causes Control 1:51–58
53. Toniolo PG, Levitz M, Zeleniuch-Jacquotte A, Banergee S, Koenig KL, Shore RE, Strax P, Pasternack BS (1995) A prospective study of endogenous estrogens and breast cancer in postmenopausal women. J Natl Cancer Inst 87:190–197
54. Hankinson SE, Willett WC, Manson JE, Hunter DJ, Colditz GA, Stampfer MJ, Longcope C, Speizer FE (1995) Alcohol, height, and adiposity in relation to estrogen and prolactin levels in postmenopausal women. J Natl Cancer Inst 87:1297–1302
55. Shimizu H, Ross RK, Bernstein L, Pike MC, Henderson BE (1990) Serum oestrogen levels in postmenopausal women: comparison of American whites and Japanese in Japan. Br J Cancer 62:451–453
56. MacMahon B, Cole P, Brown JB, Aoki K, Lin TM, Morgan RW, Woo N (1971) Oestrogen profiles of Asian and North American women. Lancet 2:900–902
57. Ricketts D, Turnbull L, Ryall G, Bakhshi R, Rqwson NSB, Gazet J-C, Nolan C, Coombs RC (1991) Estrogen and progesterone receptors in the normal female breast. Cancer Res 51:1817–1822
58. Punnonen R, Lukola A, Kudo R (1984) Cytoplasmic estrogen receptor concentrations in the endometrium of Finnish and Japanese women. Eur J Obstet Gynecol Reprod Biol 17:321–325
59. Nomura Y, Kobayashi S, Takatani O, Sugano H, Matsumoto K, McGuire WL (1977) Estrogen receptor and endocrine responsiveness in Japanese versus American breast cancer patients. Cancer Res 37:106–110
60. Nomura Y, Tashiro H, Hamada Y, Shigematsu T (1984) Relationship between estrogen receptors and risk factors of breast cancer in Japanese pre-and postmenopausal patients. Breast Cancer Res Treat 4:37–43
61. Stemmermann GN (1991) The pathology of breast cancer in Japanese women compared to other ethnic groups: a review. Breast Cancer Res Treat 18(Suppl.):S67–S72
62. Kahn SA, Rogers MA, Khurana KK, Meguid MM, Numann PJ (1998) Estrogen receptor expression in benign breast epithelium and breast cancer risk. J Natl Cancer Inst 90:37–42
63. Peyrat JP, Bonneterre J, Hecquet B, Vennin P, Louchez MM, Fournier C, Lefebvre J, Demaille A (1993) Plasma insulin-like growth factor-1 (IGF-1) concentrations in human breast cancer. Eur J Cancer 29A:492–497
64. Bruning PF, Van Doorn J, Bonfrer JMG, Van Noord PAH, Korse CM, Linders TC, Hart AAM (1995) Insulin-like growth-factor-binding protein 3 is decreased in early-stage operable pre-menopausal breast cancer. Int J Cancer 62:266–270
65. Bohlke K, Cramer DW, Trichopoulos D, Mantzoros CS (1998) Insulin-like growth factor-I in relation to premenopausal ductal carcinoma *in situ* of the breast. Epidemiology 9:570–573
66. Hankinson SE, Willett WC, Colditz GA, Hunter DJ, Michaud DS, Deroo B, Rosner B, Speizer FE, Pollak M (1998) Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. Lancet 351:1393–1396
67. Lipworth L, Hsieh C-c, Wide L, Ekbom A, Yu S-z, Yu G-p, Xu B, Hellerstein S, Sacks B, Carlstrom K, Trichopoulos D, Adami H-O (in press) Maternal pregnancy hormone levels in an area with high incidence (Boston, USA) and low incidence (Shanghai, China) of breast cancer. Br J Cancer (in press)
68. Bergstrom E, Hernell O, Persson LA, Vessby B (1995) Serum lipid values in adolescents are related to family history, infant feeding, and physical growth. Atherosclerosis 117:1–13
69. Cruz ML, Wong WW, Mimouni F, Hachey DL, Setchell KD, Klein PD, Tsang RC (1994) Effects of infant nutrition on cholesterol synthesis rates. Pediatr Res 35:135–140
70. Kolacek S, Kapetanovic T, Zimolo A, Luzar V (1993) Early determinants of cardiovascular risk factors in adults. A. Plasma lipids. Acta Paediatr 82:699–704
71. Innis SM (1985) The role of diet during development on the regulation of adult cholesterol homeostasis. Can J Physiol Pharmacol 63:557–564
72. Marmot MG, Page CM, Atkins E, Douglas JW (1980) Effect of

breast-feeding on plasma cholesterol and weight in young adults. J Epidemiol Comm Health 34:164–167
73. MacMahon B, Trichopoulos D, Brown J, Andersen A, Cole P, DeWaard F, Kauraniemi T, Polychronopoulou A, Ravnihar B, Stormby N, Westlund K (1982) Age at menarche, urine estrogens and breast cancer risk. Int J Cancer 30:427–431
74. Gravelle IH, Bulbrook RD, Wang DY, Allen D, Hayward JL, Bulstrode JC, Takatani O (1991) A comparison of mammographic parenchymal patterns in premenopausal Japanese and British women. Breast Cancer Res Treat 18(Suppl. 1):S93–S95
75. Hankinson SE, Willett WC, Manson JE, Hunter DJ, Colditz GA, Stampfer MJ, Longcope C, Speizer FE (1995) Alcohol, height, and adiposity in relation to estrogen and prolactin levels in postmenopausal women. J Natl Cancer Inst 87:1297–1302
76. Reichman ME, Judd JT, Longcope C, SchatzkinA, Clevidence BA, Nair PP, Campbell WS, Taylor PR (1993) Effects of alcohol consumption on plasma and urinary hormone concentrations in premenopausal women. J Natl Cancer Inst 85:722–727
77. Petridou E, Syrigou E, Toupadaki N, Zavitsanos X, Willett W, Trichopoulos D (1996) Determinants of age at menarche as early life predictors of breast cancer risk. Int J Cancer 68:193–198
78. Kramer MM, Wells CL (1996) Does physical activity reduce risk of estrogen-dependent cancer in women? Med Sci Sports Exer 28:322–334
79. Buell P (1973) Changing incidence of breast cancer in Japanese-American women. J Natl Cancer Inst 51:1479–1483
80. Trichopoulos D, Yen S, Brown J, Cole P, MacMahon B (1984) The effect of westernization on urine estrogens, frequency of ovulation and breast risk. A study of ethnic Chinese in the Orient and the USA. Cancer 53:187–192
81. Ziegler RG, Hoover RN, Pike MC, Hildesheim A, Nomura AM, West DW, Wu-Williams AH, Kolonel LN, Horn-Ross PL, Rosenthal JF, Hyer MB (1993) Migration patterns and breast cancer risk in Asian-American women. J Natl Cancer Inst 85:1819–1827
82. Trichopoulos D (1990) Hypothesis: does breast cancer originate *in utero*? Lancet 335:939–940
83. World Cancer Research Fund/American Institute for Cancer Research (1997) Food, Nutrition and the Prevention of Cancer: A Global Perspective pp. 252–288. American Institute for Cancer Research, Washington, DC
84. Trichopoulou A (1995) Olive oil and breast cancer. Cancer Causes Control 6:475–476
85. Wu AH, Ziegler RG, Horn-Ross PL, Nomura AM, West DW, Kolonel LN, Rosenthal JF, Hoover RN, Pike MC (1996) Tofu and risk of breast cancer in Asian-Americans. Cancer Epidemiol Biomarkers Prev 5:901–906