



Salud Pública de México

ISSN: 0036-3634

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Instituto Nacional de Salud Pública
México

Bernstein, Jonine L.; López, Lizbeth; Wang, Lisa
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Salud Pública de México, vol. 41, núm. 2, 1999, pp. S114-S123
Instituto Nacional de Salud Pública
Cuernavaca, México

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The epidemiology of Her-2/*neu* and P53 in breast cancer

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Bernstein JL, López-Carrillo L, Wang L.
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Salud Publica Mex 1999;41 suppl 2:S114-S123.

Abstract

Breast cancer is an etiologically heterogeneous disease with marked geographical variations. Joint consideration of the relationship between specific molecular alterations and known or suspected epidemiologic risk factors for this disease should help distinguish subgroups of women that are at elevated risk of developing breast cancer. In this article, we present a comprehensive literature review of the etiologic and prognostic roles of Her-2/*neu* and P53 among women. In addition, we discuss the advantages and limitations of using biomarkers in epidemiological studies. We conclude that more research is needed to understand the complex relationships between genetic alterations and etiologic risk factors for breast cancer.

Key words: breast neoplasms; genes; risk factors; biological markers; racial stocks

Bernstein JL, López-Carrillo L, Wang L.
Epidemiología de los genes Her2/*neu*
y P53 en relación al cáncer mamario
Salud Publica Mex 1999;41 supl 2:S114-S123.

Resumen

El cáncer mamario es una enfermedad con gran variabilidad geográfica y cuya etiología es heterogénea. La evaluación conjunta de los factores de riesgo que se conocen por estudios epidemiológicos y de las alteraciones específicas a nivel molecular, podría ser útil para identificar subgrupos de mujeres con alto riesgo de padecer dicho tumor maligno. En este artículo presentamos una revisión de la literatura acerca del papel que el Her-2/*neu* y el P53 tienen en la etiología y el pronóstico del cáncer mamario en mujeres. Además, discutimos las ventajas y limitaciones de utilizar biomarcadores en los estudios epidemiológicos. Concluimos que se requieren nuevas investigaciones orientadas a dilucidar las complejas relaciones que existen entre las alteraciones genéticas y los factores de riesgo para el cáncer mamario.

Palabras clave: neoplasmas de la mama; genes; factores de riesgo; marcadores biológicos; razas

Worldwide breast cancer incidence and mortality rates vary widely by country. The highest mortality rates (25/100,000 women) are found in nations such as Great Britain, New Zealand, the Netherlands and Uruguay, while the lowest rates (10/100,000 women) are found in most East Asian and Latin American countries.¹ In the United States breast cancer is the most

commonly diagnosed cancer among women, accounting for 32% of all incident cancers in women while mortality from breast cancer is the second leading cause of cancer death, lung cancer being the first.²

Breast cancer is an etiologically heterogeneous disease and epidemiologic studies have pointed to particular subgroups of the population who are at increased

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Recibed on: June 3, 1998 • Accepted on: April 7, 1999

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risk of developing the disease. Molecular changes, such as overexpression of oncogenes (e.g., Her-2/*neu*) and tumor suppressor genes (e.g., P53), have been detected in breast tumors. However, they do not occur in 100% of the cases. The heterogeneity of molecular alterations may be indicative of distinct etiologic subgroups of breast cancer. Joint consideration of the relationship between specific molecular alterations and known or suspected epidemiologic risk factors associated with breast cancer and its treatment should help distinguish subgroups of women at high risk of breast cancer and resolve otherwise weak or inconsistent results.

Despite many epidemiologic studies identifying risk factors for breast cancer and numerous studies documenting the presence of molecular markers in breast cancer tissue, the relationship of molecular alterations with epidemiologic risk factors is practically unexplored. Since the study of molecular epidemiology is relatively new, most of the research has been conducted using hospital cases or small case series of patients, where risk factor information is either non-existent or extremely limited. Thus the type of associations that can be made have been quite restricted and the focus has been on prognostic utility rather than on etiology. Below we present a comprehensive review of the literature on risk factors for breast cancer among women and, to the extent possible, the etiologic and prognostic roles of Her-2/*neu* and P53.

Risk factors for breast cancer among Caucasian women

The many epidemiologic studies conducted on breast cancer have primarily focused on caucasian women. An increased risk of breast cancer among has been shown to be related to: older age; reproductive factors; higher socioeconomic status; urban residence; family history of breast cancer, fibrocystic breast disease,³⁻⁶ obesity;⁷⁻⁹ and ionizing radiation.¹⁰⁻¹² The odds in relation to several of these factors (such as obesity and family history of breast cancer) have been shown to vary with age at diagnosis or menopausal status.

Among these same women, oral contraceptive (OC) use in general has not been found to increase the risk of breast cancer¹³ while results regarding long-term use are less consistent. Other factors that have also been identified in some studies to affect breast cancer include: diet;^{14,15} alcohol;¹⁶⁻²⁰ smoking;²¹⁻²⁴ lactation;^{15, 25,26} parity;^{15,27} abortions;^{11,28} and physical activity.^{11,29,30}

In general, the longer the reproductive lifespan, the greater the risk of developing breast cancer. That

is, early age at menarche,³¹⁻³⁴ late age at menopause,^{33,35-37} and late age at first birth,³⁸⁻⁴⁰ are all known to increase a women's risk. These consistent associations found in epidemiologic studies, suggest an important role of cyclic hormones (time between menarche and menopause) in breast cancer etiology.^{9,41} Cumulative exposure to estrogens may provide a selective environment for the clonal outgrowth of cells which contain somatic mutations.⁹ Although consistent, the relative risks associated with reproductive factors and breast cancer risk are weak, generally ranging below 2.0.

Several epidemiologic studies have identified subgroups of women with a family history of breast cancer who are at an especially elevated risk of developing breast cancer themselves: women with a first-degree relative who was diagnosed with breast cancer at an early age; women with more than one affected relative; women with a family history of ovarian cancer; and women with a first degree relative who had bilateral breast cancer.⁴²⁻⁴⁷ Sattin *et al.* (1985) found that the relative risk for women with at least one affected first degree relative was 2.3, for women with at least one affected second degree relative the risk was 1.5, and for women with both an affected mother and sister the risk increased to 14.⁴⁸ In addition, a number of studies have examined the effect of age at onset on the relationship between a woman's risk of breast cancer and the presence of bilateral breast cancer in a first degree relative and found that relatives of younger breast cancer cases with bilateral disease are at an increased risk.^{43,49,50} Formal genetic analyses have provided strong evidence for one or more rare autosomal dominant inherited gene(s) associated with increased susceptibility to breast cancer.⁵⁰⁻⁵⁴ The elevated risk to carriers versus non carriers increases with decreasing age at onset, indicating that younger breast cancer cases are more likely to represent gene carriers than are older patients.

The actual extent to which the familial aggregation of most breast cancer is attributable to hereditary or environmental factors is not fully known. Some researchers suggest that the heritable component of breast cancer should only be considered in concert with environmental risk factors, such as diet, sun exposure, and smoking behaviors.⁵⁵ For example, perhaps mediated through genetics, there may be factors which predispose some women to an abnormal differentiation of cells in response to environmental risk factors.⁵⁶ It may be that genetic factors affect the probability of neoplastic transformation and/or expression of the

neoplastically transformed cells through control of hormonal or other stimuli and the cellular response to these stimuli.⁵⁷

Breast cancer risk factors among women of other ethnical backgrounds

Breast Cancer in Hispanic Women. Breast cancer incidence and mortality rates are consistently lower among Hispanic women than among white and black women.⁵⁸ In Central America for example, the annual incidence breast cancer rate in 1996, was 17 per 100,000 compared with 146.6 per 100,000 breast cancer cases in the U.S.A.⁵⁹ After cervical cancer, however, breast cancer is the second leading cause of female cancer mortality in most Latin American countries.⁵⁸

Information on breast cancer risk factors among Hispanic women is scarce. From two case-control studies performed in Mexico^{60,61} and one case-control study carried out in Colombia,⁶² it has been confirmed that nulliparity and late age at first pregnancy double the risk of breast cancer while the familial history of breast cancer increases this risk two to six times. In addition to finding similar results for nulliparity, age at first pregnancy and family history, another case-control study of Hispanic women in the U.S. found an increased risk for women previously diagnosed with benign breast disease.⁶³ One study, although based on small numbers, found that Hispanics had the lowest rate of familial breast cancer compared to whites and blacks.⁶⁴ To date no information has been published regarding the importance of a positive history of breast cancer in a relative (i.e. sister, mother etc.) among Hispanic women. A protective effect, i.e. a risk reduction of 55% to 75% has been reported for Mexican^{60,61} and Colombian women⁶² who breastfeed their first child for more than 12 months, as compared to those who had children but did not breastfeed them. Also, a significant correlation has been reported from an ecological study between a decreasing trend of fertility and an increasing trend of breast cancer mortality in Mexico.⁶⁵

It has been hypothesized that diet may play an important role in reducing breast cancer risk among Hispanics.⁶⁶ Such diet is generally rich in dietary fiber,⁶⁷ just as the Asiatic diet and both ethnic groups have low breast cancer rates. Experimental results showed that dietary fiber can reduce the levels of circulating estrogens^{66,67} but additional work is needed to confirm whether a reduction in breast cancer risk could truly be achieved.

Exposure to xenoestrogens and the risk of breast cancer was evaluated by a study in Mexico City. The

results indicated that the serum levels of Dichloro-diphenyl-trichloro-ethane (DDT), beta-hexachloro-cyclohexane and hexachloro-benzene were not associated with an increased risk for breast cancer.^{68,69} In contrast, exposure to polychlorinated biphenyls (PCBs) might be doubling the risk for that disease.⁶⁹ Currently, in Mexico, an estimated 8,000 tons of PCBs are still in the electrical power sector, mainly in operational equipment and as residues.⁶⁹

In the United States, breast cancer incidence and mortality rates for immigrant Hispanic women are also much lower than those reported for white or black women. However, those rates vary across geographic regions in the US with much higher incidence rates found among Hispanic women living in Illinois than those for to women who live in Texas.⁷⁰ Results from other studies in the US suggest that Hispanic women are also more likely to be diagnosed at a younger age ($p<.0001$) and have an increased likelihood of getting an advanced cancer when compared to Caucasians.⁷¹ However, in a more recent study where access to healthcare was not an issue because all participants had access to a single source of care, Hispanic women were still significantly younger at the time of diagnosis, but no longer at an increased risk for suffering advanced forms of breast cancer.⁷²

Breast Cancer in African-American Women. Among these female population, breast cancer is the most common cancer. The average annual age-adjusted incidence for breast cancer is lower among blacks (92.8 per 100,000) as compared with whites (112.2 per 100,000).⁷³ Age-specific incidence rates, however, vary by age and race. Among younger women blacks have a higher rate than whites, and among older women whites have higher rates than blacks, with the cross-over of rates occurring between the ages of 40 and 50 years.⁷⁴⁻⁷⁶ Reasons for this extreme effect modification by age and race on breast cancer risk are unknown.

Risk factors for breast cancer among African-American women are still poorly understood. Only four major epidemiologic studies focusing on blacks have been published to date: one population-based⁷⁷ and three hospital-based case control studies.^{29,78,79} All four, found that breast cancer among black women was positively associated with nulliparity or low parity. Other risk factors for breast cancer among whites were associated with higher risk among blacks in only one or two of the three studies (higher education, late age at first birth, larger body size among postmenopausal women, OC use, older age at menopause, history of benign breast disease, and family history of breast cancer). Meanwhile, other factors such as early age at

menarche were not associated with risk among blacks in any of the studies. In a more recent case-control study looking specifically at OC use and breast cancer risk among African American women, only moderate to long term OC use below the age 45 was found to increase the risk for breast cancer.⁸⁰ The only study which examined the effects of alcohol and smoking on breast cancer among black women found no association.⁷⁷ A fifth study, a segregation analysis using data from the Cancer and Steroid Hormone Study, found that a history of breast cancer among first-degree relatives is equally predictive of BC risk among black or white women.⁸¹

Molecular Alterations

It is clear that human cancers are partly caused by alterations of some genes (oncogenes, tumor suppressor genes) involved in growth regulation. In most cases, tumorigenesis probably requires alteration of several of these genes. Inheritance of a mutated gene may predispose an individual to cancer, but, in general, somatic alteration of other genes over the course of an individual's life is also required for development of cancer. Several oncogenes and tumor suppressor genes have been shown to be altered in breast cancer. Genetic alterations which have frequently been reported include overexpression of the Her-2/*neu* oncogenes and the tumor suppressor gene P53.

The Her-2/*neu* proto-oncogene encodes a growth factor receptor-like molecule that is inserted into the cell membrane⁸², and ligands that bind to Her-2/*neu* were identified recently.⁸³ Holmes et al. (1992) described the isolation, sequencing, and characterization of a family of Her-2/*neu* ligands and demonstrated their interaction with Her-2/*neu* protein.⁸⁴ They also showed biologic responses to treatment with the ligand in cell lines. A point mutation in the membrane spanning region in the Her-2/*neu* gene has been shown to cause oncogenic activation of the gene. Structurally normal Her-2/*neu* protein is overexpressed (2-40 fold) in a significant fraction (20-30%) of human breast cancers.^{85,86} Overexpression usually is due to gene amplification, but in some cases occurs despite the presence of a normal gene copy number. One possible explanation for Her-2/*neu* overexpression in the absence of amplification (increase in net gene copy number) would be transcriptional up-regulation or post-translational modification. In most studies, overexpression of Her-2/*neu* in breast cancer has been associated with aggressive biological behavior and poor survival.⁸⁶⁻⁸⁸ Several studies have shown the association between

overexpression of the Her-2/*neu* oncogene and early stages of breast carcinogenesis in distinct histologic types of breast cancer,^{86,89} perhaps suggesting a more important role in initiation than in progression.

The P53 gene encodes a nuclear protein that is found at low levels in virtually all cells.^{90,91} It is thought that the P53 gene product normally acts to restrain inappropriate cellular proliferation. Although the precise mechanism by which P53 acts as a growth inhibitor is unknown, it binds to specific regions of DNA where it may regulate expression of other genes.^{92,93} Loss of P53 due to deletion of this gene from the short arm of chromosome 17 has been associated with a malignant phenotype in vitro. In addition to its role as a tumor suppressor, it has been shown that P53 genes that have undergone mutations can act as dominant transforming genes to elicit malignant transformation, similar to proto-oncogenes.⁹⁴ This is thought to occur, in part, due to mutant P53 protein complexing with and inactivating the normal wild type P53 present in the cell.⁹⁵

The frequency of P53 overexpression detected by immunohistochemistry in breast tumors varies from approximately 15% to 60%,^{93,96,97} whereas frequency of mutations varies from 15% to 35% in breast cancers analyzed for P53 in only the conserved regions of the gene (exon 5-8, sometimes 4 or 9 too).⁹⁸ The broad range of P53 overexpression might be due to: a) the varying ways overexpression is defined,⁹⁹⁻¹⁰² b) differences in fixation of tumor tissue,¹⁰² and c) the diversity of antibodies and immunohistochemical procedures used.^{101,103,104} Why P53 overexpression is observed in breast cancers which apparently lack P53 mutations is a question that remains to be solved. It is possible that some of these cases have mutations in exons which were not analyzed or that overexpression is caused by stabilization of the P53-protein by other cell constituents.¹⁰⁵ On the contrary, there is also a proportion of cases (10 to 20%) with mutations which lack P53 immunostaining. Deletions, nonsense- and frame-shift mutations are the aberrations found in most of these cases.^{98, 99,103,106,107} However, the most frequently observed type of P53 gene alteration in breast tumors is a single-base missense substitution which is expected to alter a single amino acid in the P53 protein and stabilize it.^{96,97,108,109} The correlations found between overexpression of P53 protein and mutation are around 0.8 in the majority of studies.^{99,100,106,109-111}

Risk Factors and Molecular Alterations

Her-2/*neu* is one of the most commonly involved oncogenes in breast cancer etiology and P53 is one of the

most commonly involved tumor suppressor gene. Two studies compared risk factor patterns of breast tumors categorizing by Her-2/*neu* status.^{112,113} The results showed that Her-2/*neu* amplification was more frequently found among early oral contraceptive users,¹¹² and overexpression of the Her-2/*neu* protein (as a result of amplification) was associated with not having breast fed and also with a later age at first full-term pregnancy.¹¹³ The prognostic value of Her-2/*neu* is generally accepted, since the larger studies support an association between Her-2/*neu* and poor prognosis.¹¹⁴

Studies comparing P53 mutational patterns of breast tumors between different parts of the United States and Europe,¹⁰⁷ and between the United States, Europe, and Japan,¹¹⁵ suggest that the various patterns found may indicate variations and differences in exposures to specific risk factors. Biggs *et al* (1993) also suggested that exogenous factors may contribute to the P53 mutational patterns in breast tumors, by comparing mutational spectra of P53 in colorectal, lung, and breast cancer.¹¹⁶ Several studies have implicated P53 protein expression as an independent prognostic factor in carcinomas of the breast and other cancer sites as well.¹¹⁷ Studies have also shown that P53 mutations are associated with significantly reduced disease-free periods and/or overall survival.⁹⁷ Since P53 mutations correlate with other indicators of poor prognosis,⁹⁷ careful analyses are needed to assure that P53 status adds information to established prognostic markers.

Survival and Overexpression of Her-2/*neu* and P53

As stated above, previous studies suggest that an overexpression of Her-2/*neu* is associated with poor prognosis. In a study performed by Slamon *et al.*, Her-2/*neu* amplification was found to be independent of other prognostic factors predicting overall survival among breast cancer patients.⁸⁵ This finding was confirmed by Press *et al.* in a multivariate analysis where they showed Her-2/*neu* overexpression to be a marker of poor prognosis independent of histopathologic grade, tumor size, and involvement of regional lymph nodes.¹¹⁸ However, a similar study published by Thor *et al.* did not confirm this finding.¹¹⁹ Univariate analyses in the latter study suggested that there was an association between Her-2/*neu* overexpression and overall survival in certain patient subpopulations.¹¹⁹ More recently, Thor *et al.*, using immunohistochemical techniques demonstrated a significant association, independent of other prognostic factors, between P53

protein accumulation and overall survival in 199 breast cancer patients.¹²⁰

The frequency of alterations in both Her-2/*neu* and P53 positively correlates with clinical stage at diagnosis of breast cancer. One of the largest studies to date, found correlations between Her-2/*neu* and various prognostic factors for breast cancer, including: premenopausal status, estrogen receptor status, and young age at diagnosis.⁸⁹ Importantly, these relationships were modified by stage at diagnosis. Press and coworkers found Her-2/*neu* amplification/overexpression level to be correlated with risk of developing recurrent disease among women with node-negative breast cancer.¹¹⁸ They found the risk of developing recurrent disease in node negative women with any level of Her-2/*neu* overexpression to be 3 times greater than among women whose breast cancer lacked overexpression while the group of patients with high overexpression had a risk of recurrence 9.5 times greater than those whose breast cancers had normal expression ($p=0.0001$). This effect seemed to be significantly elevated across menopausal status.

Molecular Expression among Non-White Women

Differences in molecular expression among various racial groups can also contribute to our understanding of breast cancer etiology and risk, however, published research among non-white women is very limited.

Among Hispanic women, very few studies have been conducted looking at expression of molecular indices and breast cancer. The majority of studies have focused on estrogen and progesterone receptor status with prognosis.^{71,121} One study of 253 white, Hispanic and black women undergoing breast biopsies, looked at several prognostic factors (including Her-2/*neu* expression) in relation to ethnicity but found no significant difference in Her-2/*neu* expression levels. For each ethnic group, overexpression of Her-2/*neu* ranged from 10-15%.¹²² A larger study of 4885 white, 1016 black and 777 Hispanic women by Elledge *et al.* also found no significant difference in Her-2/*neu* or P53 expression between the three ethnic groups.¹²³

A 1995 study by Shiao *et al.* comparing 45 black with 47 white breast cancer patients found that black patients with P53 gene alterations had a significant 4-5 fold excess risk of death from breast cancer when compared to black subjects without P53 alterations.¹²⁴ In addition, they observed significantly poorer survival associated with P53 alterations for blacks

SUMMARY OF RISK FACTORS FINDINGS PRESENTED IN TEXT FOR BREAST CANCER ACROSS ETHNICITY

Risk factor	Whites	African American	Hispanics
Age	Increased risk with increasing	Greater breast cancer rates at younger age compared to white women	-More likely to be diagnosed at younger age. -Increased risk with increasing age results are consistent to those found in white women)
Family history	Increased risk for women with family history of breast or ovarian cancer	Increased risk for women with family history	Increased risk for women with family history (RR= 2-6)
1 st degree relative (mother, sister) with breast cancer	Great risk if 1 st degree relative is diagnosed at an early age and/or had bilateral breast cancer	Greater risk if 1 st degree relative had breast cancer, magnitude of risk similar to those found in white women	
# of affected relatives	Greater risk if more than one affected relative		
Reproductive factors	Increased risk with longer exposure to endogenous estrogens/progesterones		
Parity	Increased risk among nulliparous and low parous	Similar results as those found in white women	Similar results as those found in white women (RR= 2)
Age at first birth	Increased risk with later age at first full term pregnancy	Similar results as those found in white women	Similar results as those found in white women (RR= 2)
Age at menarche	Increased risk with earlier age at menarche	No association found to date	No association found to date
Age at menopause	Increased risk with older age at menopause	Similar results as those found in white women	No association found to date
Socioeconomic status/level of education	Increased risk with higher socioeconomic status and years of education	Increased risk with higher levels of education	No association found to date however the study used low, middle low, middle class categories which may not have enough variation
History of benign breast disease	Increased risk with history of benign breast disease (e.g., Fibrocystic breast cancer)	Increased risk with history of benign breast disease	

than for whites ($p=0.012$). In another study, the types and frequency of P53 gene mutations found in an American black cohort of 45 breast cancer patients differed from previously studied white American and European population samples.¹²⁵ Specifically there was an excess of A:T to G:C transitions in this population of black women from Michigan, who have the highest breast cancer mortality rates in the US, compared to US white women from the midwest. These studies suggest that specific mutational patterns might exist in each ethnic group and may reflect ethnic variations in breast cancer etiology.

Some Epidemiologic Considerations for the Use of Molecular Markers

Although analyses concerning etiologic issues in the incidence of first primary breast cancer have fewer immediate clinical implications than those concerning survival and second primaries, their ultimate implications for the prevention of breast cancer could be considerable. However, it must be acknowledged that the results of such investigations may not always permit the distinction between the role of the molecular alterations as: a) the mechanism through

which a particular risk factor (e.g., use of oral contraceptives) has its possible influence on the occurrence of breast cancer *versus* b) its roles as a co-factor that interacts with the risk factor in producing cancer.

A major challenge in using molecular markers for epidemiological research comes in choosing which molecular alterations will be most effective and practical. Understanding the role of a molecular marker, such as Her2/*neu* or P53, in the development of cancer and establishing its association to other breast cancer risk factors or to breast cancer itself helps to determine its most appropriate use in a study design. For example, for the purpose of prevention or altering the course of disease development, a tumor marker and its relationship with etiologic factors should be examined; for clinical applications, a marker and its relationship with tumor characteristics and treatment should be evaluated. Although difficult in practice, additional understanding of alternative pathways that may lead to the same cellular change or about the way in which multiple exposures may lead to the same biological event allows an investigator to make adjustments in study design or analysis to account for these alternative pathways.

Other important considerations involve assessing the sensitivity and feasibility of molecular markers for large scale screening or testing. The type of assay used will also lead to practical decisions about the types and quantity of biological samples that must be collected (e.g., blood, urine, hair, tumor tissue) and how samples should be handled. Finally the ethical and legal issues surrounding privacy and protection of the study subjects especially in the areas of genetic testing, gene therapy, eugenics, and insurance/employment are becoming significant considerations in epidemiologic studies using molecular markers.

Wrap-up

Epidemiologic studies have identified many risk factors for breast cancer, including older age, family history of breast cancer, reproductive factors, and history of fibrocystic breast disease or prior breast cancer. Although consistent, the etiologic associations observed between these factors and breast cancer incidence are generally weak, with increases in risk mostly below 2.0. However, specific subgroups of women have been described in whom the incidence of breast cancer in relation to classic risk factors is substantially elevated. Variations in overexpression of oncogenes and tumor suppressor genes have here forth been virtually unexplored in relation to breast cancer risk. Now is the time to take advantage of recent insights into the mo-

lecular biology of breast cancer to classify breast cancer cases into more homogeneous subsets and to explore the interaction of nongenetic and genetic factors in its etiology. To a limited extent, this approach has already proven successful in relating Her-2/*neu* overexpression with increasing age at first pregnancy, ever having breastfed, and OC use at an early age.

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