



This Week in the Journal

September 19, 2002

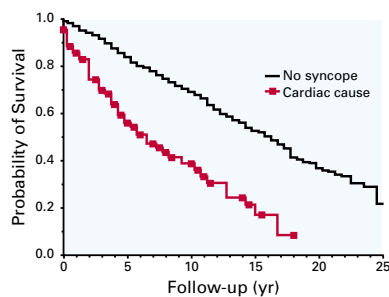
“The regulation of the resulting inflammatory responses through adaptive immunity is likely to be of key importance for the development of atopic illnesses.”

Environmental Exposure to Endotoxin and Its Relation to Asthma

Children with asthma have both a genetic predisposition to the condition and environmental exposure that modifies the genetic factors. It is known that children of elementary-school age who live on a farm are less likely to have asthma than their counterparts from nonfarming households. In this study of children from parts of Austria, Germany, and Switzerland where there were both farming and nonfarming households, the investigators related the level of exposure to endotoxin, determined by sampling dust from the mattresses where the children slept, to the prevalence of asthma and related conditions. The greater the endotoxin exposure, the less likely it was that children had asthma.

These findings indicate that exposure to endotoxin, which activates the innate immune response, appears to have a key modulatory role in the expression of asthma. This study focuses research on the identification of this protective factor in the environment; the lack of this factor may be responsible for the current epidemic of asthma.

see page 869 (editorial, page 930)



Syncope

Among 7814 participants in the Framingham Heart Study who were followed for an average of 17 years, 822 had at least one episode of syncope, and the incidence of a first report of syncope was 6.2 per 1000 person-years. Vasovagal and cardiac causes were most common; the cause was not identified in over a third of cases. Mortality was increased among all participants with syncope, among those with syncope of unknown cause, and particularly among those with cardiac syncope, as compared with participants who did not have syncope. Vasovagal syncope had a benign prognosis.

In a community-based population, syncope that is not due to a vasovagal event or to another defined benign cause is a marker of an increased risk of death.

see page 878 (editorial, page 931)

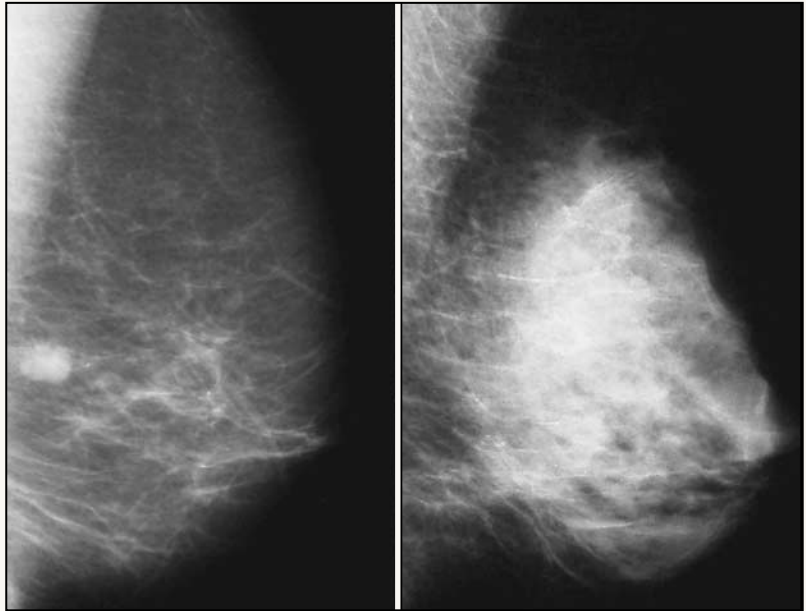
PERSPECTIVE

Breast Density and the Risk of Breast Cancer

There is great variation among women in the density of breast parenchyma as seen on mammograms. Mammographic density also varies inversely with age. Thus, younger women tend to have denser breasts than older women, but many older women also have dense breasts.

The mammographic density of breast parenchyma depends on the amount of connective tissue and glandular tissue in the breast. Breasts dominated by adipose tissue, which appear less dense, are easy to assess with mammography. Thus, the most important clinical implication of denser breasts is that they are more difficult to evaluate with mammography. Small breast cancers presenting as masses without spiculations or calcifications can be missed in dense breasts. A poorly differentiated breast cancer that is 1 cm in diameter is easily diagnosed in a breast containing substantial fat tissue but would be difficult to detect in a dense breast if it were superimposed on the dense tissue (see Figure). Ultrasonography should therefore be used along with mammography as an adjunctive diagnostic method in women with dense breasts.

The matter is complicated by the fact that women with dense breasts are also at increased risk for breast cancer. Four different mammographic patterns have been identified by John Wolfe: two are dominated by adipose tissue and two by dense tissue. These patterns or the percentage of dense tissue in the breast have been used to show that increased breast density is a risk factor for breast cancer. It is important to note that in population-



A Typical Fatty Breast with a Poorly Differentiated Breast Cancer 1 cm in Diameter (Left) and a Typical Dense Breast (Right).

based screening, most breast cancers were found by Laszlo Tabar in breasts dominated by adipose tissue.

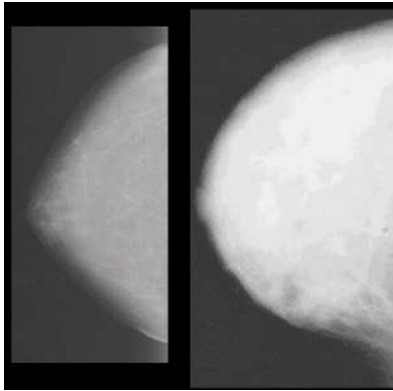
Why are dense breasts a risk factor for breast cancer? The simple explanation might be that there is more glandular tissue in a dense breast and therefore more cells with the potential to transform into cancer cells. But it is not clear exactly which mechanisms or genes lead to dense breasts.

Risk factors for breast cancer such as early menarche, low parity, and late menopause are clearly related to hormones. Hormone-replacement therapy places a woman in double jeopardy in terms of breast cancer. First, such therapy increases breast density in many women and can lead to impaired sensitivity of mammographic screening. Second, long-term hormone-replacement therapy increases the risk of breast cancer. Heredity is also a risk factor, but known mutations (*BRCA1* and *BRCA2*) cannot explain all familial aggregation of breast cancer. In a report on a large study involving 571 pairs of monozygotic twins and 380 pairs of dizygotic twins in this

issue of the *Journal*, Boyd et al. (see pages 886–894) show that mammographic density has a strong heritable component. Since dense breasts are common, heritability of this risk factor might contribute to the familial aggregation of breast cancer.

What are the clinical implications for a woman with dense breasts? She should undergo regular mammographic screening examinations following the same recommendations that apply to all women in her age group. When there is a palpable lump in a dense breast and the mammographic examination is inconclusive, ultrasonography should be used (although this is the responsibility of the radiologist). I would not inform a woman that the mammographic density of her breast increases her risk of breast cancer, since the absolute increase in risk is small. The provision of such information might lead only to unnecessary anxiety.

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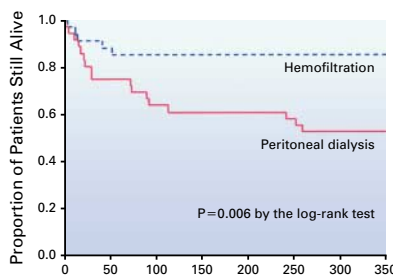


Heritability of Mammographic Density, a Risk Factor for Breast Cancer

Mammographic images can be dark due to the presence of fat or light due to radiologically dense connective and epithelial tissue. The overall percentage of dense areas in the image is the measure of mammographic density. Previous work has shown that a dense mammographic pattern is associated with an increased risk of breast cancer. This study involving 571 pairs of monozygotic twins and 380 pairs of dizygotic twins found a high degree of heritability of mammographic density.

Genetic factors most likely play an important part in susceptibility to breast cancer, but apart from mutations in BRCA1 and BRCA2, little is known about possible susceptibility alleles. This large study in twins points to important clues lying within the composition of the breast itself.

see page 886 (Perspective, page 866)

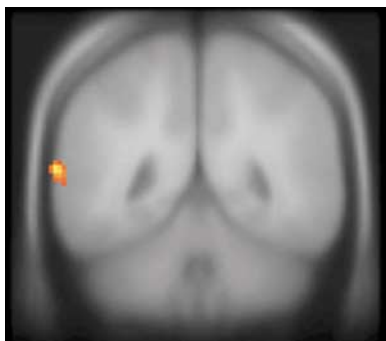


Hemofiltration and Peritoneal Dialysis in Infection-Associated Acute Renal Failure in Vietnam

In developing nations, infection-associated acute renal failure is associated with high morbidity and mortality. This open, randomized trial from Vietnam compared peritoneal dialysis, widely used in patients with this condition (with falciparum malaria or sepsis), with hemofiltration. Resolution of acidosis and a decrease in the serum creatinine concentration occurred more than twice as rapidly in the group assigned to hemofiltration, and renal-replacement therapy was required for a shorter period. Survival was improved in the group assigned to hemofiltration.

Hemofiltration is superior to peritoneal dialysis for infection-associated acute renal failure.

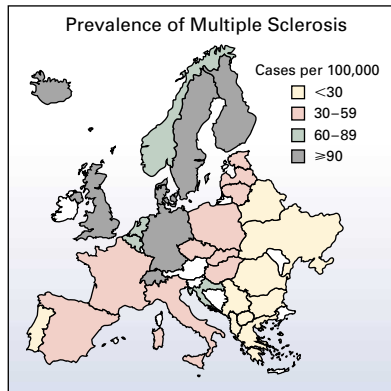
see page 895 (editorial, page 933)



Current Concepts: Tinnitus

Tinnitus is a common but poorly understood disorder that has a strong association with aging. This review explains how to differentiate subjective from objective tinnitus. Although tinnitus is often associated with hearing loss, in many cases the origin may be central. Multiple treatment options may help in the management of this chronic condition.

see page 904

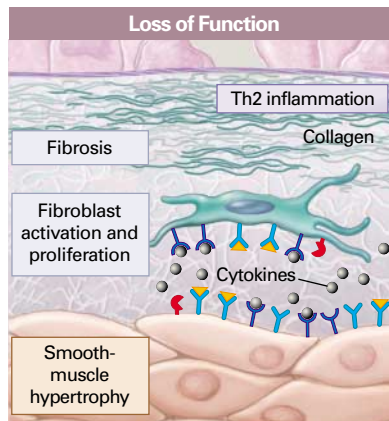


Mechanisms of Disease: Effect of Infectious Diseases on Susceptibility to Autoimmune and Allergic Diseases

The hygiene hypothesis postulates that an environment with a high incidence of infectious diseases protects against allergic and autoimmune diseases, whereas hygienic surroundings increase the incidence of these disorders. This review examines the evidence in support of the hygiene hypothesis and offers a number of mechanisms that could explain the relation between sanitary conditions and susceptibility to allergic and autoimmune diseases.

Growing experimental and epidemiologic support for the hygiene hypothesis has important clinical implications, especially with regard to policies on vaccination and the use of antibiotics during childhood.

see page 911



Clinical Implications of Basic Research: ADAM-33 Surfaces as an Asthma Gene

A recent study identified *ADAM-33* as an asthma gene. ADAMs are a subfamily of metalloproteinases, originally identified as proteins on the cell surface, that have two functional domains, a disintegrin and a metalloprotease domain (hence, the acronym ADAM). The authors speculate on the ways in which an excess or deficiency of *ADAM-33* could result in the expression of the asthma phenotype.

see page 936

“Large employers argue that providing consumers with compelling data on the quality of care and increasing their share of the costs will slow the increase in health care expenditures and improve the quality of care.”

Sounding Board: Large Employers Seeking New Strategies in Health Care

Large employers are major purchasers of health insurance and have a strong interest in maintaining the health of their employees and containing the costs of care. These efforts focus on giving employees financial incentives and data about quality to encourage them to choose lower-cost and higher-quality care. Several large employers formed a group that compiles and disseminates information about the quality of hospitals, with the goal of steering employees toward higher-quality care.

see page 939