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Benign Breast Disease and the Risk of Breast Cancer

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ABSTRACT

The purpose of this study was to investigate the degree of risk associated with the common nonproliferative benign entities and the extent to which family history influences the risk of breast cancer in women with proliferative or atypical lesions. Data for a study cohort of 9087 women with benign breast disease from the Mayo Clinic Surgical Index and Pathology Index from January 1, 1967, through December 31, 1991, was accessed for this study. Questionnaires were used to obtain information about family history and other possible risk factors for breast cancer. Stored hematoxylin-eosin–stained sections from each participant were evaluated, and relative risks (RRs) were estimated on the basis of standardized incidence ratios. The Cox proportional hazards regression analysis was used to examine the associations between the risk of breast cancer and histologic findings, the age at diagnosis of benign breast disease, and the strength of the family history of cancer, as well as pairwise combinations of these variables. In the cohort group, the estimated RR of breast cancer was 1.56 (95% confidence interval [CI], 1.45–1.68), of atypical hyperplasia was 4.24 (95% CI, 3.26–5.41), of proliferative disease without atypia was 1.88 (95% CI, 1.66–2.12), and of nonproliferative lesions was 1.27 (95% CI, 1.15–1.41). The RR for women with no known family history of breast cancer was only 1.18 (95% CI, 1.01–1.37), as compared with that for women with a weak family history of 1.43 (95% CI, 1.15–1.75) and that for those with a strong family history of 1.93 (95% CI, 1.58–2.32). The study concluded that the major risk factors for breast cancer after the diagnosis of benign breast disease are histologic features, the age at biopsy, and the degree of family history.

EDITORIAL COMMENT

(This study, published over 10 years ago and cited in over 300 subsequent publications, had important limitations that were not addressed at the time. First, family history was unknown in 47% of the cohort, and no information was provided on differences in other risk factors between respondents with known versus unknown family history status. Second, family history was not obtained at cohort entry; it was added in a questionnaire during the follow-up contact, by which time a cancer or precursor may have been discovered, introducing recall bias. Third, those with a strong family history may have been diagnosed with breast cancer sooner because they received more diagnostic imaging (surveillance bias). The study did not report the intensity of screening for the cohort as a whole or for family history subgroups during the 15 years of follow-up.

Although the RR was higher in women with a strong family history (1.93) than in women with a weak or negative family history (1.43, 1.18, respectively), the risk increases were small in magnitude. The RR of breast cancer in the entire cohort of women with benign breast disease was 1.56, also small in magnitude. Bias and uncontrolled confounding are ubiquitous in observational studies, making RRs between 0.5 and 2 more likely to be spurious than valid; only high-quality randomized trials are capable of detecting true effects this small (Grimes. *Hum Reprod.* 2015;30(8):1749–1752).

It makes intuitive sense to patients that family history is associated with breast cancer. The high

prevalence of breast cancer guarantees there will be many first-degree relatives sharing the disease who do not have an identifiable genetic predisposition. Family history is a valid risk factor in small population subgroups with hereditary breast cancer mutations such as BRCA1 and 2, where affected patients (1/300 to 1/800 women) have a lifetime risk of breast cancer between 65% and 74%. The small associations seen in observational studies such as the abstracted one do not support the risk-reducing interventions we recommend for women with BRCA mutations, such as increased surveillance, chemoprevention, and surgery.

Factors other than family history merit the attention of patients and women's healthcare providers. Women with atypical hyperplasia of the breast (ductal or lobular) have a nearly 300% risk increase for subsequent breast cancer (RR, 3.93; 95% CI, 3.24–4.76), a large and biologically plausible increase leading to a variety of risk-reducing strategies including tamoxifen, raloxifene, and aromatase inhibitors depending on menopausal status (ACOG Practice Bulletin 164, June 2016).

The story told by the abstracted study is not unique. As recounted by David Grimes in *Human Reproduction* (2015;30(8):1749–1752), many other statistically significant and clinically important "false alarms" have been ultimately invalidated in the fullness of time.—LAL)

Infertile Women Below the Age of 40 Have Similar Anti-Müllerian Hormone Levels and Antral Follicle Count Compared With Women of the Same Age With No History of Infertility

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ABSTRACT

The study investigates the extent to which poor response to ovarian stimulation in assisted reproductive technologies is associated with a lower ovarian reserve, estimated by serum concentrations of anti-müllerian hormone (AMH) and antral follicle count (AFC), in infertile patients when compared with women of same age with no history of infertility. A prospective cohort study of 382 infertile patients referred for fertility treatment at The Fertility Clinic, Rigshospitalet, at Copenhagen University Hospital between September 2011 and October 2013 were compared with a control group of 350 nonusers of hormonal contraception with no history of infertility between August 2008 and February 2010. Patients and controls selected were in the age group of 20 to 39 years. Those with polycystic ovary syndrome were excluded. A transvaginal ultrasonography was performed on CD 2–5 to estimate mean ovarian volume, and serum concentrations of Follicle Stimulating Hormone and Luteinizing Hormone were analyzed by electrochemiluminescence immunoassays. There were no significant differences in AMH levels (11%, 95% confidence interval [CI]: 21; 24%) or AFC (1%, 95% CI: 27; 8%) observed between the 2 cohorts after age adjustment. In addition to age, after adjustment for smoking status, body mass index, chronic disease, gestational age at birth, and previous conception to these findings persisted for both AMH (7%, 95% CI: 26; 21%) and AFC (0%, 95% CI: 29; 9%). The study concluded that infertile women younger than the age of 40 years have the same age-related depletion of the ovarian reserve as women of the same age with no history of infertility and that women with a low ovarian reserve were not overrepresented among newly referred infertile patients.