Association of mammographically defined percent breast density with epidemiologic risk factors for breast cancer (United States)

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Abstract

Objective: Mammographically defined percent breast density is an important risk factor for breast cancer, but the epidemiology of this trait is poorly understood. Although several studies have investigated the associations between reproductive factors and density, few data are available on the associations of breast density and waist-to-hip ratio (WHR), physical activity, education, alcohol and smoking.

Methods: We investigated the associations of known and suspected breast cancer risk factors with breast density in a large breast cancer family study. Information was collected on members of 426 families through telephone interviews, mailed questionnaires and mammography. Mammographic films on 1900 women were digitized and breast density was estimated in discrete five-unit increments by one radiologist. Analysis of covariance techniques were used and all analyses were performed stratified by menopausal status.

Results: Similar to other reports, nulliparity, late age at first birth, younger age and lower body mass index were associated with increased percent density in both premenopausal and postmenopausal women, and hormone replacement therapy among postmenopausal women. Higher levels of alcohol consumption and low WHR were associated with increased percent density among both premenopausal and postmenopausal women (differences of 3–11% between high and low categories). However, smoking and education were inversely associated with percent density among premenopausal (p = 0.004 and p = 0.003, respectively) but not postmenopausal women (p = 0.52 and p = 0.90). Physical activity was not associated with percent density in either stratum (p values >0.25). Combined, these factors explained approximately 37% of the variability in the percent density measure in premenopausal women and 19% in postmenopausal women.

Conclusions: Many of these factors may potentially affect breast cancer risk through their effect on percent breast density.

Introduction

Mammographic density is a quantitative estimate of the proportion of fibroglandular elements to total breast area. Epidemiologic data suggest that percent mammographic density is an important independent risk factor for breast cancer. Several critical studies conclude that the magnitude of risk associated with the highest category of mammographic density, compared to the lowest category, may be as large as, or larger than, that for nearly every other established risk factor [1–4]. The biologic mechanism through which percent density may influence breast cancer risk is not understood. However, several characteristics that are associated with mammographic percent density are also risk factors for breast cancer [4–7]. There appears to be a hormonal influence on percent density, as evidenced by the positive associations of mammographic density with premenopausal status, later age at first birth, and nulliparity [3, 4, 6–9]. Additionally, hormone replacement therapy is associated with an increased mammographic density among current users in most studies [9–14]. Other
potential risk factors for breast cancer, such as waist-to-hip ratio (WHR), alcohol consumption, physical activity, smoking history, and education have been evaluated in fewer studies and their association with percent density is less clear.

The breast cancer risk factor profile differs somewhat by menopausal status [15–19]. It is not known whether the associations of known risk factors with breast cancer parallel the associations with percent density within strata defined by menopausal status. Studying these associations by menopausal status could provide clues to the relevance of timing of exposures to changes in breast tissue.

The current study examined the associations of known and suspected breast cancer risk factors with percent density among a group of 1900 women in a large breast cancer family study. Information on determinants of percent density may provide valuable insight into breast cancer etiology.

**Material and methods**

**Population**

This study was approved by the University of Minnesota Institutional Review Board. Details of the study design and methods have been published elsewhere [20]. Briefly, a family study of breast cancer was initiated in 1944 at the University of Minnesota. The probands in the families were female cases ascertained at the Tumor Clinic of the University of Minnesota Hospital with microscopic diagnosis (n = 527) or clinical evidence (n = 17) of breast cancer. Information on probands and history of cancer in first-degree relatives was obtained by interviews, medical history questionnaires, and death certificates.

A follow-up study of this cohort of families was initiated in 1990 and formed the cohort for the current investigation. Eligible family members included sisters, daughters, nieces, and granddaughters of the breast cancer probands and women identified as the spouses of corresponding male first- and second-degree relatives of the probands. Results of the cohort extension and risk of breast cancer have been presented elsewhere [21].

**Questionnaire data**

Telephone interviews were completed with all available first- and second-degree female relatives and marry-ins over the age of 18 years. Data were also collected on deceased relatives through surrogates. However, since mammograms were not available for these women, the current report included only those members of the cohort who were living and age-eligible for screening mammography. Specific topics in the telephone interview included: history of cancer, weight history, marital status, education, occupational class, medical history of conditions associated with reproductive dysfunction, benign or malignant breast disease, mammography, menstrual and pregnancy history, oral contraceptive and hormone replacement therapy use, usual physical activity, lifetime smoking and alcohol habits. Menopausal status was based on whether or not the participant had a menstrual period within the past year, excluding periods brought on by hormones. Following the telephone interview, subjects were mailed an anthropometric questionnaire designed to elicit replicated measures of current height and weight. Circumferences of the waist (2 inches above the umbilicus) and hips (maximal protrusion) were determined according to a validated protocol [22].

**Mammography to detect breast cancer and quantify percent density**

To verify the breast cancer status of relatives and spouses, and to estimate percent density, females over the age of 40 years were asked to obtain a routine mammogram through their personal physician if one had not been taken in the previous year (2 years if under age 50 years). These women were mailed a letter for their physician that explained the study and described our need to review the mammogram after it was obtained.

**Estimation of percent breast density**

The fraction of the breast image occupied by fibroglan- dular elements was estimated visually by a radiologist experienced in mammography (Dr Kuni). The estimate was made from a video display of the left mediolateral oblique view; the right mediolateral oblique view was used if the left was unavailable. The mammographic films were scanned with standard equipment to generate digital data. Contrast and brightness of the displayed images were routinely manipulated to facilitate density estimation, which was made in 5% increments. The radiologist was blinded to all risk factor data. Studies of intrareader reliability of breast density were conducted. Duplicate readings over varying time periods were made on all images, resulting in an intraclass correlation of 0.82. Two additional studies were performed on a sample of individuals to evaluate the correlation of our subjective estimate with other estimates of breast tissue, including a magnetic resonance imaging (MRI)