BREAST CANCER RISK EVALUATION - A CORRELATION BETWEEN MAMMOGRAPHIC DENSITY AND THE GAIL MODEL

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ABSTRACT

The Gail model is a statistical tool, which assesses breast cancer probability, based on nonmodifiable risk factors. In contrast, the evaluation of mammographic breast density is an independent and dynamic risk factor influenced by interventions modifying breast cancer risk incidence.

The aim of the present study is to compare the possibilities for risk factor integration and analysis and to search for a correlation between mammographic density and the Gail model for breast cancer risk evaluation. The subject of this prospective study is a cohort of 107 women at ages from 37 to 71 years, who have had benign breast diseases, digital mammograms, and Gail model risk evaluation.

Mammographic density is evaluated in craniocaudal projection subjectively visually and objectively using the computer imaging software. (Image J software) The Gail risk evaluation is completed using the standardized NCI questionnaire (Breast Cancer Risk Assessment Tool).

In concordance with the Breast Imaging Reporting and Data System (BI-RAD) by ACR, mammographic density is evaluated using a four-grade scale. Low density D1 (less than 25%) was determined in 24 cases, D2 (25-50%) in 36 cases, D3 (51-75%) in 31 cases and high density D4 (greater than 75%) in 16 cases.

According to the Gail model, 80 (74.8%) of the examined patients did not have an increased risk (less than 1.67% for a five-year period), whereas the remaining 27 (25.2%) had a statistically significant increase in risk (greater than 1.67% for a term of five years). Women with increased risk more often present with denser breast (34% with D3, D4 versus 18.3% for D1, D2).

The Gail model does not fully explain the correlation between breast density and statistically calculated risk. The development of more detailed tools, which take into consideration breast density, as well as other risk factors, may be helpful for a more accurate evaluation of the individual risk for breast cancer.

KEYWORDS: breast cancer; risk evaluation; Gail model; mammographic density

Introduction

Mammographic density (MD) represents the ratio between the radiologically dense epithelial and connective tissue and the...
radiolucent adipose tissue. This indicator is variable and dependent on age and interventions, which modify breast cancer risk. Even though the exact mechanisms have not been sufficiently explained, it has been proven that increased breast density is an independent risk factor for breast cancer. Mammographically dense breasts have a 4 to 6 fold increase in risk in comparison with less dense breasts. (1,2,3)

The Gail model has been accepted in clinical practice as a tool for breast cancer risk evaluation. With the exception of age, the model is based on nonmodifiable factors such as: familial history, age at first period, age at the time of birth of first child, number of breast biopsies showing atypical hyperplasia. (4,5)

Regardless of the importance of these prognostic factors, there have been relatively few studies, evaluating the correlation between them. The aim of the present study is to compare the possibilities for risk factor integration and analysis and to search for a relationship between mammographic density and the Gail model for breast cancer risk evaluation.

Material and Methods

The subject of this prospective study is a cohort of 107 Bulgarian Caucasian women with benign breast diseases (BIRADS II-III) followed up from 2010 to 2014. The study was conducted in the Department of Thoracic Surgery of the Military Medical Academy, Sofia Bulgaria. The women were from 37 to 71 years old with a mean age of 51 years. The patients analyzed in this study came to be examined on their own, because they either had clinical symptoms or mammographic abnormalities. Bulgarian currently does not have a national breast cancer screening program.

In all cases, there was no medical history of breast cancer. Age, family history, age at first period, age at the time of birth of first child and number of breast biopsies showing atypical hyperplasia were noted.

The Breast Cancer Risk Assessment tool designed by the National Cancer Institute (http://www.cancer.gov/bcrisktool/) was used for the quantitative evaluation of the risk of developing invasive breast cancer according to the Gail model. Patients with results greater than 1,67% for a five-year period were considered to be with an increased risk. (6)

The statistical data analysis was completed using STATGRAPHICS Plus 2.1 and Excel. Digital mammograms of both breasts were performed in craniocaudal and lateromedial projection to premenopausal women within five to twelve days after the beginning of their menstrual cycle.

Mammographic density was estimated independently subjectively, visually, and objectively using a computer-assisted measurement of the craniocaudal projection. The program used was Image J software. Mammographic density was calculated as the ratio of the radiographically dense regions to the entire breast area. The program is accessible online and can be used on every PC with Java 1.4 or newer version. (7)

Mammogram findings were described in concordance with the recommendations from the Breast Imaging Reporting and Data System (BIRADS) of the American College of Radiology. Mammogram density was evaluated using a four-grade scale as follows: D1 (low density) – mostly fatty with less than 25% fibroglandular tissue; D2- scattered fibroglandular tissue from 25% to 50%; D3- heterogeneous density from 51% to 75%; D4 (extreme density) fibroglandular tissue greater than 75%. Values greater than 51% (D3 and D4) are considered to be dense.

Results

The age of examined patients ranged from 37 to 71 years with a mean of 51 years. Of all patients, 60 were postmenopausal (without menstruation for at least three years), whereas the remaining 47 were premenopausal.

Family history of breast cancer was evident in 10 (9,3%) of the examined patients. According to the age of first menstruation, 19 (17,8%) women were under 13 years old, 68 (63,6%) were between 13 and 14 years of age and 20 (18,7%) were older than 14 years old.

According to the time of birth of first child, 90 (84,1%) were under the age of 40, 9 (8,4%) were older than 30 years of age, and 8 (7,5%) had not given birth.

Most of the patients, 95 (88,8%) had not had preceding breast biopsies due to benign breast diseases. Only 12 had previously

| Risk Factors - 107 Cases | Gail Model - 27 at high-risk | High Mammographic Density - 47 |
|-------------------------|-----------------------------|-------------------------------|
| Age                     |                             |                               |
| Postmenopausal - 60     | 13 (21,7%)                  | 22 (36,7%)                    |
| Premenopausal - 47      | 14 (29,8%)                  | 25 (53,2%)                    |
| Family History          |                             |                               |
| Yes - 10                | 9 (90,0%)                   | 6 (66,7%)                     |
| No - 97                 | 18 (16,8%)                  | 41 (42,3%)                    |
| <13 - 19                | 5 (26,3%)                   | 9 (47,4%)                     |
| Menarche Age            |                             |                               |
| 13-17 - 68              | 17 (25,0%)                  | 28 (41,2%)                    |
| >17 - 20                | 5 (25,0%)                   | 10 (50%)                      |
| <30 - 90                | 37 (66,1%)                  | 37 (41,1%)                    |
| First Live Birth        |                             |                               |
| >30 - 9                 | 4 (44,4%)                   | 4 (44,4%)                     |
| Nulliparous - 8         | 6 (75,0%)                   | 6 (75,0%)                     |
| Breast Biopsy           |                             |                               |
| Yes - 12                | 5 (41,7%)                   | 5 (41,7%)                     |
| No - 95                 | 22 (23,2%)                  | 42 (44,2%)                    |
had diagnostic breast biopsies, and atypical hyperplasia was diagnostically verified in 1 case (0.9%). Table 1

The mean five-year risk for breast cancer is 1.51% (ranging from 0.7% to 5.5%). Of all patients, 27 (25.2%) have an increased risk (greater than 1.67%), whereas the remaining 80 (74.8%) have low risk (less than 1.67% for a five-year period).

Mammographic density revealed that 24 (22.4%) of patients were with low-density breasts (D1), 36 (33.6%) were with scattered fibroglandular regions (D2), 31 (30%) were with heterogeneously dense breasts (D3) and 16 (14%) were with extremely dense breasts (D4). (Fig.1.)

The mean subjective estimate of breast density of examined patients was 38% (from 0% to 90%), whereas the average computer-assisted estimate was 44.5% (from 5 to 92%). The distribution of examined patients is presented in Table 2.

Discussion

Breast density has a stronger association with breast cancer risk than most other risk factors. Relative risk estimates of similar

| MD   | Number (%) | High risk >1.67% | Low risk <1.67% |
|------|------------|------------------|----------------|
| D1   | 24 (22.4%) | 4                | 20             |
| D2   | 36 (33.6%) | 7                | 29             |
| D3   | 31 (30.0%) | 10               | 21             |
| D4   | 16 (14.0%) | 6                | 10             |
| Total| 107 (100%) | 27 (25.2%)       | 80 (74.8%)     |

or greater magnitude have been observed only in age, atypical hyperplasia, and mutations in BRCA genes (2,8).

The mammographic density we discovered was under 50% (D1 and D2) in 60 cases and over 50% (D3 and D4) in 47 cases, which broadly corresponds to the results from other studies. (2,3,9,10)

Both visual and computer-assisted mammographic density determination do not differ in the number of cases placed in the D1-D4 subgroups. We attribute the lack of difference in the large range of 25% for each subgroup. Regardless, the computer-assisted evaluation gives a significantly more precise estimate, which would be a useful advantage for screening programs, clinical studies in the field of oncology and particularly in the follow-up of patients’ disease dynamics.

By studying the correlation between the Gail model and mammographic density, we noticed that patients at higher risk have denser breast. Women at high risk and denser breasts were 34% or 16 out of 47 women with denser breast, whereas 18.3% of women were at high risk and lower breast density or 11 out of 60 women with lower breast density. (p = 0.1026) This statement is particularly clear for the subgroup of 13 patients with fatty breast composition (D1, MD <10%). In this subgroup, only 1 (7.7%) of 13 patients was determined to be at high risk for the Gail model. In contrast patients with very dense breasts (D4, MD>75%), 37.5% or 6 out of 16 were determined to be at high risk for the Gail model. (p = 0.0927). Our results lack statistical significance due to the relatively small number of analyzed cases.

According to some studies, there is a significant correlation between MD and premalignant lesions of the breast. (usual ductal hyperplasia, atypical ductal hyperplasia, lobular carcinoma in situ) (11,12,13) Other authors presume the connection between mammographic breast density and stromal proteins, which could be epithelial mitogens. In this regard, the relatively small number of breast biopsies (11,2%) in our study does not allow us to make conclusions.

Conclusion

Future large prospective studies are going to provide an answer to breast tumor biology and cancerogenesis as well as additional information regarding the role of mammographic density as a prognostic factor for the development of premalignant lesions and breast cancer.

Current models of breast cancer risk evaluation are limited in their predictive power because none of them consider a complete set of proven prognostic breast cancer factors. The development of better tools, which include MD, may turn out to be useful for
better individual breast cancer risk evaluation.

**Authors’ Statements**

**Competing Interests**
The authors declare no conflict of interest.

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