Biochimica et Biophysica Acta 1856 (2015) 73–85

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbacan

Review

Established breast cancer risk factors and risk of intrinsic tumor subtypes

Mollie E. Barnard *, Caroline E. Boeke, Rulla M. Tamimi

Department of Epidemiology, Harvard T.H. Chan School of Public Health, 677 Huntington Avenue, Boston, MA 02115, USA
Channing Division of Network Medicine, Brigham and Women's Hospital, 181 Longwood Avenue, Boston, MA 02115, USA

ARTICLE INFO

Article history:
Received 20 January 2015
Received in revised form 7 June 2015
Accepted 8 June 2015
Available online 10 June 2015

Keywords:
Breast cancer
Subtype
Risk factor
Luminal
HER2
Triple negative

ABSTRACT

Breast cancer is a heterogeneous disease with multiple intrinsic tumor subtypes. These subtypes vary in tumor gene expression and phenotype, and are most commonly grouped into four major subtypes: luminal A, luminal B, HER2-overexpressing and triple negative (or basal-like). A growing number of studies have evaluated the relationship between established breast cancer risk factors and risk of one or more intrinsic tumor subtypes. We conducted a systematic review of 38 studies to synthesize their results and identify areas requiring more research. Taken together, published studies suggest that most established breast cancer risk factors reflect risk factors for the luminal A subtype of breast cancer, and some breast cancer risk factors may be differentially associated with other intrinsic tumor subtypes. Future breast cancer research will need to consider etiologic differences across subtypes and design studies focused on understanding the etiology and prevention of less common tumor subtypes.

Contents

1. Introduction

Breast cancer is the second most common cancer in women, with more than 1.5 million incident cases diagnosed globally each year [1]. Advances in breast cancer screening and treatment have decreased breast cancer mortality for luminal and HER2-overexpressing cancers;

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; CK, cytokeratin; OC, oral contraceptive; HT, postmenopausal hormone therapy

* Corresponding author at: Department of Epidemiology, Harvard T.H. Chan School of Public Health, 677 Huntington Avenue, Boston, MA 02115, USA.
E-mail address: mollie.barnard@mail.harvard.edu (M.E. Barnard).

http://dx.doi.org/10.1016/j.bbcan.2015.06.002
0304-419X/

however, triple negative cancers continue to have high mortality rates [2]. Understanding breast cancer heterogeneity and improving subtype-specific prevention, diagnosis and survival are current priorities in both clinical and epidemiologic research [2,3].

For more than fifty years, histopathology has recognized breast cancer as a heterogeneous disease with both inter- and intra-tumor variability [4]. More recently, advances in molecular analysis and genetic sequencing have further described the diversity of breast tumors using a combination of microarray analyses and next-generation DNA sequencing [5,6]. Current methods of breast cancer classification group tumors into genetically- and molecularly-defined intrinsic subtypes including, but not limited to: luminal A, luminal B, HER2-overexpressing, and triple negative cancers [3]. Surrogate definitions of these subtypes are typically based on the results of immunohistochemical (IHC) staining for estrogen, progesterone, and HER2 receptors as well as confirmation of HER2 status using fluorescent in situ hybridization. More recent tumor classification systems also consider markers of tumor proliferation and aggressiveness, such as histologic grade or Ki-67 status, to differentiate between luminal A and luminal B cancers [3].

It is well established that breast cancer subtypes have unique prognoses and differ in their responsiveness to chemoprevention and chemotherapy [2,3]. The distinct natural history of each subtype suggests that breast cancer subtypes may also have unique risk profiles. Elucidating which established breast cancer risk factors are pervasive across all subtypes and which are subtype-specific could be important to understanding tumor etiology and essential to developing prevention strategies. More specifically, if established breast cancer risk factors reflect only the risk factors and etiology of luminal A cancer, the most common subtype, alternate or additional strategies may be needed to reduce the risk of luminal B, HER2-overexpressing or triple negative cancer. A growing number of small- to mid-size studies have started to explore whether breast cancer subtypes have unique risk profiles; however, the comparisons presented in these studies are highly variable and difficult to synthesize. We conducted a systematic review to illustrate what is currently known about the associations between established breast cancer risk factors and risk of specific tumor subtypes.

2. Methods

On January 22, 2014 we conducted a PubMed literature search to identify original, peer-reviewed research related to breast cancer risk factors and risk of intrinsic tumor subtypes. We considered all types of established risk factors, including family history of breast cancer, reproductive factors, lifestyle factors, and exogenous exposures [7–10]. Our final search included the following terms: “breast cancer” AND (“luminal” OR “basal-like” OR “HER2” OR “triple-negative”) AND (“menarche” OR “menopause” OR “menopausal” OR “age at first birth” OR “parity” OR “nulliparous” OR “parous” OR “breastfeeding” OR “lactation” OR “hormone replacement therapy” OR “HRT” OR “postmenopausal hormone” OR “hormone therapy” OR “estrogen therapy” OR “oral contraceptive” OR “oral contraceptives” OR “family history” OR “benign breast disease” OR “BMI” OR “weight” OR “obese” OR “obesity” OR “alcohol” OR “mammographic density” OR “breast density”).

We eliminated by title all duplicate articles and any publications that clearly were not on the topic of breast cancer, were not original research, were conducted in animal models, focused on cancer clinical outcomes, or addressed topics in pharmacology, genetics, or epigenetics. Two independent reviewers (MB and CB) considered the content of the remaining articles and selected for inclusion every article that studied one or more established breast cancer risk factors as an exposure, identified at least one breast cancer subtype as an outcome, adjusted for confounding by age or menopausal status, and included at least 200 cases with known subtypes. Our initial search resulted in 708 articles. Four hundred and ninety-four articles were eliminated by title, and another 176 were eliminated after assessing the content of each paper. The remaining 38 original research articles are included in this review.

The studies included in this review are presented in Supplementary Table 1. They include nine cohort studies [11–19], twelve population-based case–control studies [20–31], four hospital-based case–control studies [32–35], twelve case-only studies [36–47], and one pooled analysis that included cohort studies, case–control studies and studies of mixed design [48]. The majority of studies were conducted using unique case populations, and all studies with similar or identical case populations are identified.

For each study, cases with known ER, PR, and HER2 status were regarded as cases with known subtypes irrespective of whether their designated subtypes were based solely on ER/PR/HER2 status or also based on expression of auxiliary tumor markers such as HER1 or CK5/6 (see table footnotes for study specific definitions of subtypes). Briefly, for the majority of studies, cases described as ER+ and/or PR+ and HER2− were labeled luminal A and cases described as ER and/or PR+ and HER2+ were labeled luminal B. For a small subset of studies, additional information on tumor proliferation was incorporated to differentiate between luminal A (low grade or Ki-67 absent or low) and luminal B (high grade or Ki-67 positive) subtypes [18,38,43]. Cases described as ER−, PR− and HER2+ were labeled HER2-overexpressing, and cases described as ER−, PR− and HER2− were labeled triple negative when information on HER1 and CK5/6 status was not available, basal-like when positive for HER1 or CK5/6, or unclassified when negative for both HER1 and CK5/6. Classifying tumors by ER/PR/HER2 status acknowledged that, while the exact biomarkers used to define each intrinsic subtype have varied over time, the subtype names and the tumors they encompass have been relatively consistent [3,6].

We methodically summarized the associations between established breast cancer risk factors and risk of each tumor subtype for every risk factor considered in five or more studies. These risk factors include age at menarche [14,18,20,21,25–30,33,35,39,41,42,46,48], parity [14,15,18,20,21,23,25–30,33,35–37,39,41,42,46–48], age at first birth [14,15,18,20,21,23–30,33,35,37,39,42,46,48], breastfeeding duration [14,18,20,21,23,25–27,29,30,33,35–37,39,41,42,46], age at menopause [14,18,21,24,28,33,39,41,42,46], BMI [13,19,20,22,26–30,34,35,37–41,43–45,48], family history of breast cancer [11,16,18,24,26–28,30,32,33,35,37,39,41,46], alcohol use [17,18,27,29,35,37], use of oral contraceptives [14,23,26,27,30,37,39,42], and use of menopausal hormone therapy [12,18,21,30,31,37,39,42,44]. Measures of association reflecting the most extreme exposure comparisons from each study were outlined in risk factor-specific tables. For example, when a study compared nulliparous women to parous women with 1, 2, 3, or 4+ children, we presented the association comparing women with 4 or more children to nulliparous women. Risk factors considered in ten or more studies with non-case reference groups were summarized in the main tables, while risk factors considered in more than five but fewer than nine studies with non-case reference groups were included in the supplementary tables.

Estimates from studies with the most informative comparisons (e.g. case–control and cohort studies that compared women with breast cancer to those without breast cancer) were used to create summary descriptions of the results. Associations were classified as “consistent” when the direction of association was consistent across studies and at least three studies reported a statistically significant association. We described associations as “probable” when the direction of association was consistent across most studies and at least two studies reported a statistically significant association. We indicated a “possible” association when most studies reported results that were either consistent in direction or null and one or two studies reported a statistically significant association. Associations were classified as “null or inconsistent” when fewer than two significant results were reported and any additional evidence was either sparse or inconsistent in direction.