The Effects of Sex Protein Receptors and Sex Steroid Hormone Gene Polymorphisms on Breast Cancer Risk

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Abstract: Breast cancer is a common disease and a major cause of death among women throughout the world. Various genes are believed to be involved in the initiation and progression of the disease. Some polymorphisms of these genes increase susceptibility to breast cancer in particular ethnicities. This study used electronic literature search to review the effects of different sex steroid hormone gene polymorphisms on breast cancer risk. Our findings indicated that some polymorphisms in estrogen receptor alpha (ER-α), ER-β, progesterone receptor (PGR), pregnane X receptor (PXR), and cytochrome P450 enzymes (CYPs) affected breast cancer susceptibility, especially in African American women.

Keywords: Breast cancer■Polymorphism■Sex steroid metabolic enzyme■Estrogen receptors

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INTRODUCTION

Due to its high frequency and death rates, breast cancer (BC) has turned into a major public health issue in both developing and developed countries.[1] Every year, more than one million new cases of BC are diagnosed and over 410,000 deaths occur due to the disease.[2] Although the mortality rates caused by BC have considerably decreased in many countries during the past two decades, the incidence rates continue to increase, especially in countries with historically low rates.[3]

Genome-wide association (GWA) studies provide evidence that genetic factors, such as mutations in BRCA1, BRCA2, PTEN, ATM, TP53, CHEK2, BARD1, CDH1, MLH1, MRE11, MSH2, MSH6, MUTYH, NBN, PMS1, PMS2, BRIP1, RAD50, RAD51C, STK11, and PPM1D, are important in the pathogenesis of BC.[4–6] Since the existence of single nucleotide polymorphisms (SNPs) in the mentioned genes increases the BC risk, related diagnostic markers are generally used for the reliable evaluation of BC prognosis. Although these may account for a small portion of BC cases (2–5%), germline mutations in highly penetrant BC susceptibility genes (e.g. BRCA1, BRCA2, TP53, CHEK2, ATM, PTEN, and PPM1D) confer a high risk of developing hereditary BC.[7,8] In fact, a link has been established between mutations in PPM1D gene and higher risk of BC, i.e. about 20% of women with PPM1D mutations develop BC.[8]

Various polymorphisms, such as SNPs, in genes involved in xenobiotic metabolism and biosynthesis and metabolism of estrogen may alter circulating estrogen levels, increase susceptibility to environmental carcinogens, and ultimately multiply the risk of BC. Inconsistent results have been reported about the effects of genetic variations in sex hormone-related genes on BC risk. Nevertheless, several GWA studies have confirmed significant relations between two SNPs near the estrogen receptor alpha (ER-α) gene, i.e. *rs2046210* and *rs12662670*, and BC risk.[9–11] Meanwhile, the estrogen receptor beta (ER-β) polymorphism plays a significant role in suppressing BC cell proliferation and acts as a negative modulator of ER-α activity.[4] While it is known that ER-β expression declines during breast tumorigenesis, the exact mechanisms involved in this process remain unclear.

This review article evaluated relevant systematic-analyses, research on candidate genes, and GWAS studies to clarify the role of hereditary genes involved in sex hormones function and metabolism in BC and to determine the effects of SNPs on BC risk. We believe that the identification of SNPs and gene mutations involved in BC development in various populations can facilitate the diagnosis and treatment of the disease.

METHODS

Literature search strategy

In order to identify relevant studies published in English language between January 1990 and March 2015, an electronic literature search was performed through MEDLINE electronic database (http://www.ncbi.nlm.nih.gov/sites/entrez). A number of key terms, including "breast cancer", "sex steroid genes", and "polymorphisms", and their different combinations were used during the database search. Each gene and its polymorphisms were also linked

Table 1. List of polymorphisms and related genes and their effects on breast cancer risk.

Gene	SNP name	Author	Case population	Control population	Age	Effect
ESR-α	rs11155813/rs11155818/rs11155833/rs11964865/ rs12055837/rs12154178/rs12212176/rs12523805/ rs13192678/rs13192976/rs1514348/rs17081703/ rs17081740/rs17082028/rs1709183/rs1801132/ rs1884049/rs1884053/rs2077647/rs2144025/ rs2207232/rs2207396/rs2459107/rs2474148/ rs2813543/rs2982684/rs2982699/rs2982712/ rs3003917/rs3003925/rs3020314/rs3020318/ rs3020364/rs3020368/rs3020371/rs3020375/ rs3020381/rs3020383/rs3020401/rs3020403/ rs3020404/rs3020407/rs3020410/rs3020434/ rs3778082/rs3778099/rs3798569/rs3798758/ rs3866461/rs4583998/rs4870056/rs532010/ rs6557170/rs6557171/rs6557177/rs6901451/ rs6903763/rs6905370/rs6911230/rs712221/ rs7739274/rs7754762/rs7755185/rs7759411/ rs7761133/rs7775047/rs827421/rs851982/ rs851984/rs926777/rs9322332/rs9322335/ rs9322336/rs9322337/rs9322338/rs9340817/ rs9340835/rs9340888/rs9340944/rs9340971/ rs9341008/rs9341052/rs9341062/rs9341070/ rs9371236/rs9383599/rs9383951/rs9397459/ rs9397462/rs9397472/rs985695/rs2881766/ rs3798577/rs2234693	Sarah J. Nyante et al (2015)	Caucasian and African-American women in North Carolina	Caucasian and African-American women in North Carolina	20–74	–
	rs6914211/rs9397463/rs985191					+
	rs9322331/rs3020377/rs3020390/rs3020317/ rs3020394/rs3020396/rs1884051/rs1884054/ rs3020405/rs726282/rs3020366/rs750686/ rs2228480/rs910416…	Byung Ho Son et al (2015)	Korean women	Korean women	Below 35 years in premenopausal and over 35 years in premenopausal	–
	rs2273206/rs926778…					+
	rs728524/rs9340799…	Min-Ying Sun et al (2015)	Han Chinese women	Han Chinese women	48.48 ± 10.18 and 44.59 ± 11.26 years	–
	rs2046210…	Lei Quan et al (2014)	European American/ African American	European American/African American	around 50	+
	rs3734805	Peng Xia et al (2014)	Han Chinese	Han Chinese	25–55≤	+
	rs9397456/rs2347867/rs985694/rs7757956…	Mark F Lipphardt et al (2013)	central European Caucasian	central European Caucasian	31–90	–
	rs3757318…	David Barzan et al (2013)	Chinese and German	Chinese and German	>50, 50>	+
	rs2046211…				20–75	p

continued…