European Journal of Cancer (2015) xxx, xxx–xxx

Available at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Novel and known genetic variants for male breast cancer risk at 8q24.21, 9p21.3, 11q13.3 and 14q24.1: Results from a multicenter study in Italy

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Received 15 April 2015; accepted 16 July 2015

KEYWORDS
Male breast cancer
BRCA1/2

Abstract Increasing evidence indicates that common genetic variants may contribute to the heritable risk of breast cancer (BC). In this study, we investigated whether single nucleotide polymorphisms (SNPs), within the 8q24.21 multi-cancer susceptibility region and within

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http://dx.doi.org/10.1016/j.ejca.2015.07.020

8q24.21
Low-penetrance BC alleles
SNPs
Clinical-pathologic characteristics

BC-associated loci widespread in the genome, may influence the risk of BC in men, and whether they may be associated with specific clinical-pathologic characteristics of male BC (MBC).

In the frame of the ongoing Italian Multicenter Study on MBC, we performed a case-control study on 386 MBC cases, including 50 *BRCA1/2* mutation carriers, and 1105 healthy male controls, including 197 unaffected *BRCA1/2* mutation carriers. All 1491 subjects were genotyped by Sequenom iPLEX technology for a total of 29 susceptibility SNPs.

By logistic regression models, we found a significant association with MBC risk for five SNPs: rs1562430 ($p = 0.002$) and rs445114 ($p = 0.026$) both within the 8q24.21 region; rs1011970/9p21.3 ($p = 0.011$), rs614367/11q13.3 ($p = 0.016$) and rs1314913/14q24.1 ($p < 0.0001$).

Differences in the distribution of rs614367/11q13.3 genotypes according to oestrogen receptor (ER) status ($p = 0.006$), and of rs1011970/9p21.3 genotypes according to human epidermal growth factor receptor 2 (HER2) status ($p = 0.002$) emerged. Association of rs1011970/9p21.3 risk genotype with HER2+ MBC was confirmed by a multivariate analysis. rs1314913/14q24.1 was associated with increased MBC risk in analyses restricted to male *BRCA1/2* mutation carriers ($p = 0.041$).

In conclusion, we provided the first evidence that the 8q24.21 region is associated with MBC risk. Furthermore, we showed that the SNPs rs1562430/8q24.21 and rs1314913/14q24.1 strongly influence BC risk in men and suggested that the SNP rs1314913/14q24.1 may act as a risk modifier locus in male *BRCA1/2* mutation carriers.

1. Introduction

Male breast cancer (MBC) is a rare disease representing less than 1% of all breast cancers (BCs) and less than 1% of all cancers in men [1]. About 20% of MBC patients show positive family history of BC and about 20% develop a second non-breast tumour, in particular prostate and colon cancer [2]. These observations point to a relevant genetic component in MBC predisposition.

Mutations in high-penetrance BC genes, *BRCA1* and, more frequently, *BRCA2*, and in moderate-penetrance genes, such as *CHEK2* and *PALB2*, have a relevant role in MBC susceptibility [3]. However, only about 10–15% of all MBCs are accounted for by mutations in these genes, thus, much of the genetic contribution to MBC risk still remains to be elucidated.

Growing evidence indicates that the genetic susceptibility to cancer can be attributed to the combined effects of low-penetrance susceptibility single nucleotide polymorphisms (SNPs) [4,5]. A large number of SNPs, identified through Genome Wide Association Studies (GWAS) or candidate gene approach, have been associated with many types of cancer, including BC [6,7].

Multiple GWAS have identified SNPs within 8q24.21 region that are linked to susceptibility for different types of cancer [8–15]. Five distinct 8q24.21 sub-regions have emerged, displaying patterns of association that appear to be specific for breast, colorectal and prostate cancer [16,17]. In particular, three regions were associated with prostate cancer only, one with prostate and colorectal cancer and one with prostate and breast cancer [18]. The 8q24.21 susceptibility region has been described as a gene-desert because of the lacking of annotated protein-coding genes [19]. However, the c-MYC oncogene, which is located 300 kb telomeric, seems the most likely candidate to be functionally linked to the susceptibility conferred by the 8q24.21 SNPs and there is evidence that its expression may be affected by SNPs within 8q24.21 region [17,20].

To date, a large number of studies have been performed to investigate low-penetrance genetic susceptibility in female BC (FBC), and susceptibility alleles have been reported in about 70 loci widespread in the genome [21]. By contrast, only a few studies addressed the role of low-penetrance alleles in MBC susceptibility [22–24].

Two SNPs, rs1314913 in *RAD51B* gene and rs3803662 near *TOX3* gene, were found to be associated with MBC risk by GWAS. In particular, rs1314913 was found specifically associated with increased BC risk in men, whereas rs3803662 was found associated with increased BC risk also in women [23]. Furthermore, by gene candidate approach *ESR1* locus was found to be associated with BC risk in men, and, in particular, with increased risk in oestrogen receptor (ER) negative MBC cases and in male *BRCA1/2* mutation carriers [22,24].

Based on the observation that MBC cases may frequently develop additional non-breast tumours, in this study we explored the possibility that the 8q24.21 multi-cancer susceptibility region may have a role in MBC risk. In addition, we aimed to evaluate whether other common low-penetrance susceptibility alleles, recently identified and associated with BC risk in women [15,25,26], may also influence BC risk in men. Finally, we explored possible associations between SNPs and clinical-pathologic characteristics of MBC, in order to provide further insight into the biological basis of BC

Please cite this article in press as: Silvestri V. et al., Novel and known genetic variants for male breast cancer risk at 8q24.21, 9p21.3, 11q13.3 and 14q24.1: Results from a multicenter study in Italy, Eur J Cancer (2015), http://dx.doi.org/10.1016/j.ejca.2015.07.020