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Original Article

Association between *TCF7L2* polymorphisms and breast cancer susceptibility: a meta-analysis

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Abstract: Aim: Our aim was to investigate the relationship between transcription factor 7-like 2 (*TCF7L2*) polymorphisms and breast cancer susceptibility. Methods: PubMed, Embase and CNKI databases were used to search the related studies investigating the correlation between *TCF7L2* polymorphisms and breast cancer susceptibility. Pooled ORs and 95% CIs, based on five genetic models, were applied to estimate the association between*TCF7L2* polymorphisms and breast cancer. A fixed-effect model or a random-effect model was applied according to the between-study heterogeneity. Results: We analyzed six single nucleotide polymorphisms (SNPs) in *TCF7L2* gene, namely rs12255372, rs7903146, rs7900150, rs3750805, rs1225404 and rs7003146. The increased risk of breast cancer was associated with *TCF7L2* polymorphisms (22 vs. 11: OR=1.16, 95% CI=1.02-1.32; 22+12 vs. 11: OR=1.06, 95% CI=1.02-1.10; 22 vs. 11+12: OR=1.15, 95% CI=1.04-1.27; 2 vs. 1: OR=1.07, 95% CI=1.02-1.13; 12 vs. 11: OR=1.05, 95% CI=1.01-1.09). Among the locus, rs7903146 polymorphism was significantly associated with the risk for breast cancer under five genetic models (TT vs. CC: OR=1.29, 95% CI=1.08-1.53; TT+CT vs. CC: OR=1.09, 95% CI=1.01-1.18; TT vs. CC+CT: OR=1.24, 95% CI=1.05-1.48; T vs. C: OR=1.11, 95% CI=1.04-1.19; CT vs. CC: OR=1.08, 95% CI=1.00-1.17). Additionally, rs7900150 also showed effects on the susceptibility of breast cancer (TT vs. AA: OR=1.22, 95% CI=1.07-1.39; TT+AT vs. AA: OR=1.06, 95% CI=1.00-1.14; TT vs. AA+AT: OR=1.21, 95% CI=1.07-1.37; T vs. A: OR=1.09, 95% CI=1.02-1.15; AT vs. AA: OR=1.04, 95% CI=1.01-1.33). Meanwhile, we found that rs3750805 polymorphism could increased the risk for breast cancer (TT+AT vs. AA: OR=1.12, 95% CI=1.01-1.24). Conclusion: Our meta-analysis demonstrates that *TCF7L2* polymorphisms may increase the risk for breast cancer.

Keywords: *TCF7L2*, polymorphisms, breast cancer

Introduction

Breast cancer is one of the most common malignant tumors seriously threatening the health of women and patients with breast cancer account for 23% among all the patients with tumors. Every year, about 1.15 million breast cancer patients are diagnosed, and the highest incidence of breast cancer is found in Europe and America [1-4]. In China, the incidence of breast cancer is increased rapidly and the patients tend to be younger [5-7]. Some studies have demonstrated that breast cancer is caused by genetic and environmental factors, the pathogenesis of it is still unclear [8-10].

Transcription factor 7-like 2 (*TCF7L2*), also named T-cell factor 4 (*TCF4*), locates on l0q25.2 [11-13], which is part of the Wnt signaling pathway. And the activity of Wnt signaling pathway was significantly associated with the onset and development of tumors. In recent years, association between *TCF7L2* polymorphisms and breast cancer susceptibility has attracted

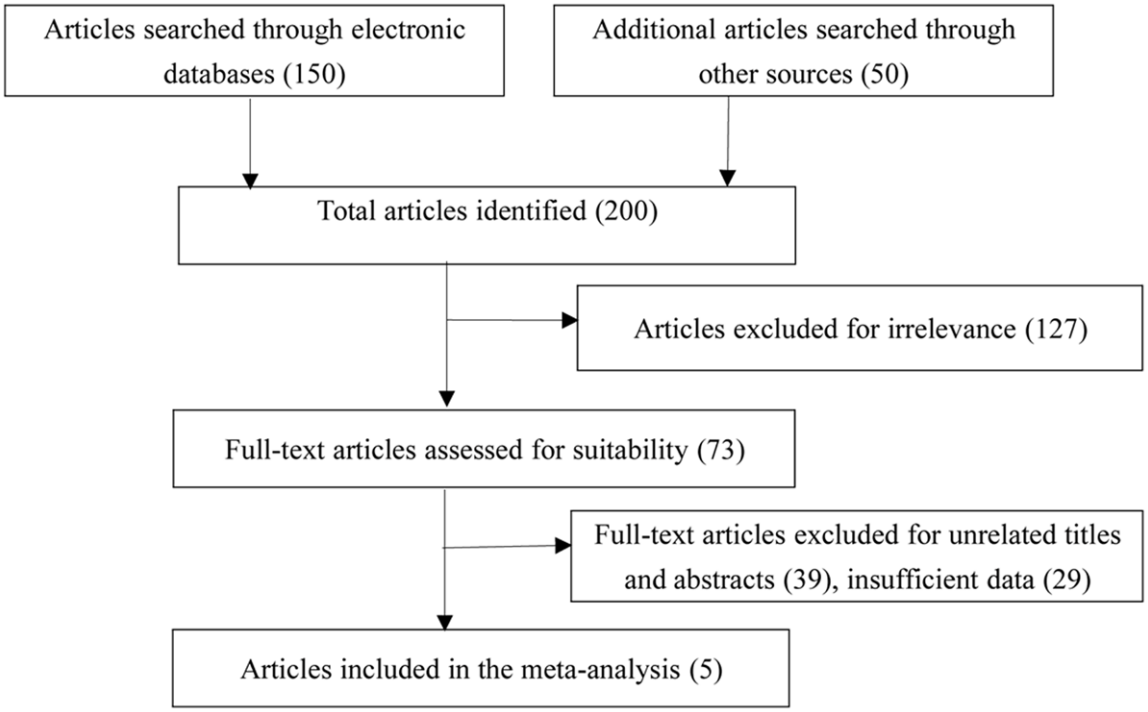

Figure 1. Flow diagram of included studies in the meta-analysis.

Table 1. Main characteristics of all studies included in the meta-analysis

First author	Year	Country	Ethnicity	Locus	Genotyping method	NOS Score	HWE
Burwinkel	2006	Germany	Caucasian	rs12255372	TaqMan	7	0.643
Naidu	2012	Malaysia	Asian	rs12255372	PCR-RFLP	7	1.000
Connor	2012	America	Caucasian	rs12255372	Multiplexed Bead Array	8	0.172
Alanazi	2013	Saudi Arabia	Asian	rs12255372	PCR	6	0.958
Naidu	2012	Malaysia	Asian	rs7903146	PCR-RFLP	7	0.518
Connor	2012	America	Caucasian	rs7903146	Multiplexed Bead Array	8	0.121
Connor	2012	America	Caucasian	rs7900150	Multiplexed Bead Array	8	0.005
Connor	2012	America	Caucasian	rs3750805	Multiplexed Bead Array	6	NA
Connor	2012	America	Caucasian	rs1225404	Multiplexed Bead Array	7	0.576
Wei	2013	China	Asian	rs7003146	Sequenom MassArray	8	0.993

TaqMan: TaqManSNP; PCR-RFLP: PCR-restriction fragment length polymorphism; PCR: polymerase chain reaction; 11: Wide-type homozygote; 12: Heterozygote; 22: Rare homozygote; HWE: Hardy-Weinberg equilibrium.

extensive attention. And the studies have showed that genetic mutations of *TCF7L2* may affect the risk for breast cancer [14, 15]. Due to the differences in ethnicity, region, country and experimental methods, the results about the relationship of *TCF7L2* polymorphisms and breast cancer are controversial. Our meta analysis, based on the published articles, was aimed to make sure the effects of *TCF7L2* polymorphisms in the pathogenesis of breast cancer.

Materials and methods

Search strategy and inclusion criteria

The related articles were searched in PubMed, Embase and CNKI databases with the key words of "*TCF7L2*", "breast cancer", "polymorphism" or "variants". Inclusion criteria were as followings: (1) case-control studies; (2) studies investigating the relationship of single nucleotide polymorphisms (SNPs) in *TCF7L2* gene and

Table 2. *TCF7L2* polymorphisms and breast cancer risk

TCF7L2		22 vs. 11	22+12 vs. 11	22 vs. 11+12	2 vs. 1	12 vs. 11
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Locus	rs12255372	1.17 (0.83, 1.64)	1.07 (1.00, 1.16)	1.14 (0.84, 1.54)	1.08 (0.95, 1.22)	1.07 (0.99, 1.15)
	rs7903146	1.29 (1.08, 1.53)	1.09 (1.01, 1.18)	1.24 (1.05, 1.48)	1.11 (1.04, 1.19)	1.08 (1.00, 1.17)
	rs7900150	1.22 (1.07, 1.39)	1.06 (1.00, 1.14)	1.21 (1.07, 1.37)	1.09 (1.02, 1.15)	1.04 (1.01, 1.13)
	rs3750805	NA	1.12 (1.01, 1.24)	NA	NA	NA
	rs1225404	1.05 (0.96, 1.15)	1.02 (0.96, 1.09)	1.07 (0.99, 1.17)	1.04 (0.99, 1.09)	1.03 (0.94, 1.12)
	rs7003146	0.57 (0.31, 1.07)	0.78 (0.56, 1.09)	0.67 (0.37, 1.21)	0.76 (0.58, 1.00)	0.78 (0.54, 1.12)
Total		1.16 (1.02, 1.32)	1.06 (1.02, 1.10)	1.15 (1.04, 1.27)	1.07 (1.02, 1.13)	1.05 (1.01, 1.09)

11: Wide-type homozygote; 12: Heterozygote; 22: Rare homozygote.

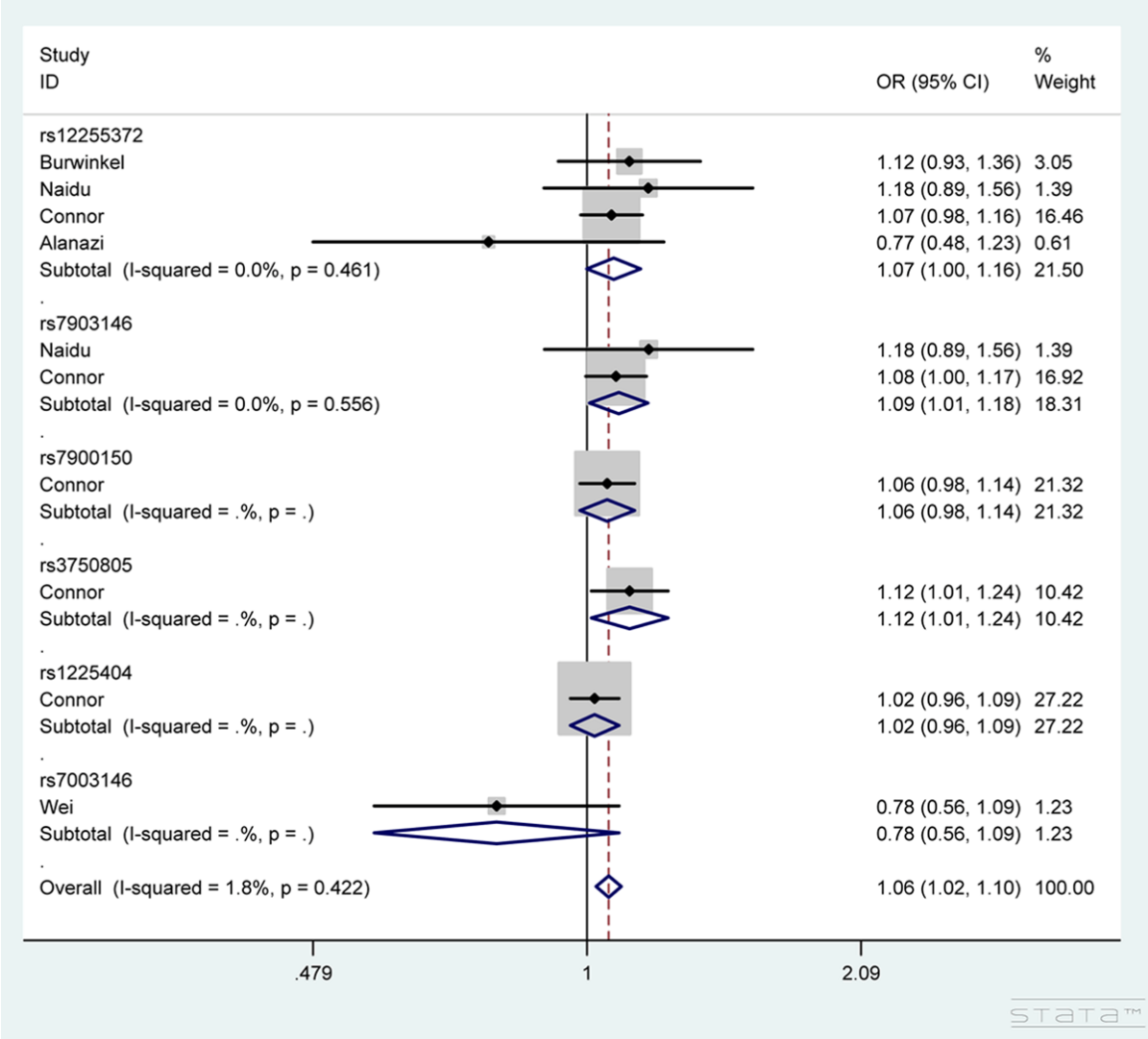

Figure 2. Forest plot of risk of breast cancer associated with *TCF7L2* polymorphisms.

breast cancer; (3) sufficient data for evaluating odds ratios (ORs) with 95% confidence intervals (95% CIs). For the publications with overlapping data, the largest publication was adopted.

Data extraction

Data were independently extracted by two investigators, and inconsistent results were

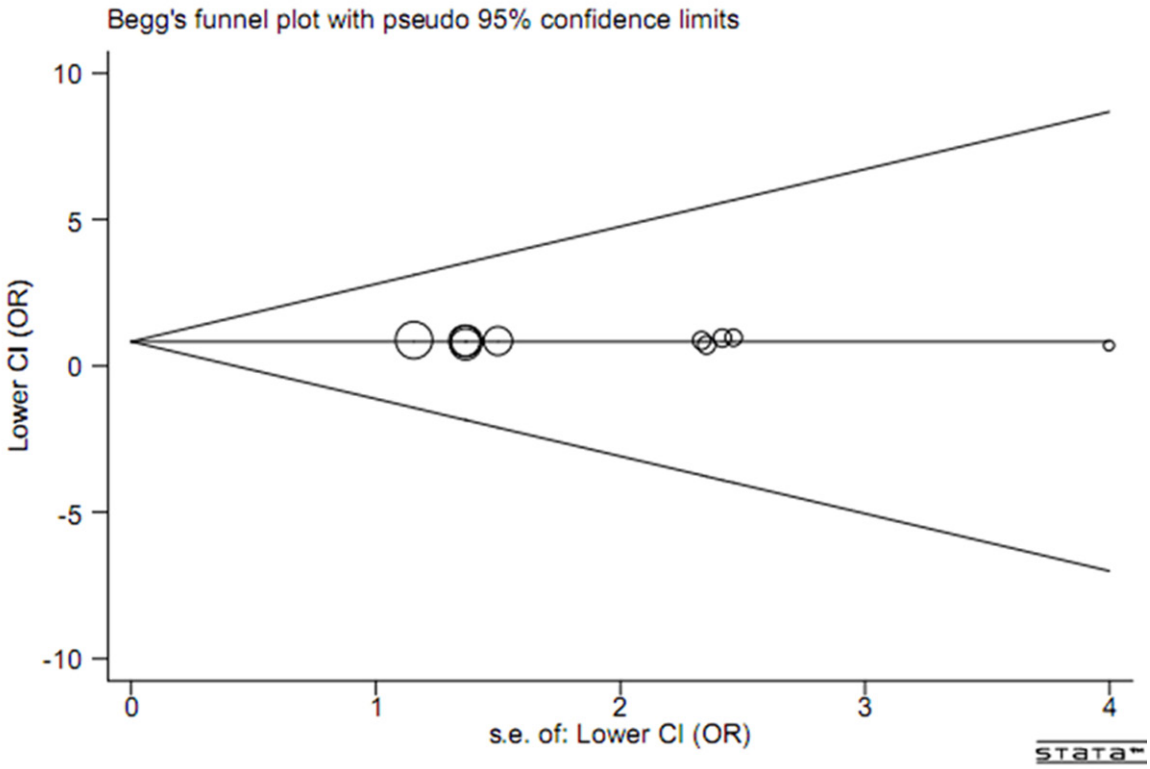

Figure 3. Begg's funnel plot of publication bias test.

solved through discussion. The extracted data included the first name of author, publication date, country, ethnicity, source of control, number of cases and controls, genotype frequencies and genotyping methods.

Statistical analysis

Hardy-Weinberg equilibrium (HWE) was checked by χ^2 test. The chi-square based Q-test was applied to testify between-study heterogeneity. Pooled ORs were calculated by the fixed-effects model when *P* (heterogeneity) > 0.05. Otherwise, the random-effects model was used. Pooled ORs with 95% CIs were used to assess the relationship between *TCF7L2* polymorphisms and breast cancer susceptibility. The calculation was performed based on the following five genetic models: 22 versus 11, 22+12 versus 11, 22 versus 11+12, 2 versus 1 and 12 versus 11. Z-test was used to testify whether the pooled ORs were significant, and *P*<0.05 was considered statistically significant. Sensitivity analysis was performed by precluding a single study to observe whether the pooled ORs changed. Egger's test and Begg's test were applied to evaluate the publication bias. The analysis was performed with STATA version 12.0 (Stata Corporation, College Station, TX, USA).

Results

Study characteristics

As shown in **Figure 1**, we searched 200 related studies through PubMed, Embase and CNKI databases in which 127 studies were precluded for obvious irrelevance, and 39 studies were excluded for unrelated titles and abstracts, and 29 studies were precluded for insufficient data, and finally 5 studies with 4800 cases and 5489 controls were included in our meta-analysis [15-19] (**Table 1**).

Association of TCF7L2 polymorphisms and the risk of breast cancer

Six SNPs in *TCF7L2* gene were analyzed and the results were showed in **Table 2**. The increased risk of breast cancer was found associated with *TCF7L2* polymorphisms (22 vs. 11: OR=1.16, 95% CI=1.02-1.32; 22+12 vs. 11:OR=1.06, 95% CI=1.02-1.10; 22 vs. 11+12:

OR=1.15, 95% CI=1.04-1.27; 2 vs. 1: OR=1.07, 95% CI=1.02-1.13; 12 vs. 11: OR=1.05, 95% CI=1.01-1.09). In the analysis, we found that rs7903146 was associated with breast cancer susceptibility (TT vs. CC: OR=1.29, 95% CI =1.08-1.53; TT+CT vs. CC: OR=1.09, 95% CI=1.01-1.18; TT vs. CC+CT: OR=1.24, 95% CI=1.05-1.48; T vs. C: OR=1.11, 95% CI=1.04-1.19; CT vs. CC: OR=1.08, 95% CI=1.00-1.17). In addition, rs7900150 could also increased the risk for breast cancer (TT vs. AA: OR=1.22, 95% CI=1.07-1.39; TT+AT vs. AA: OR=1.06, 95% CI=1.00-1.14; TT vs. AA+AT: OR=1.21, 95% CI=1.07-1.37; T vs. A: OR=1.09, 95% CI=1.02-1.15; AT vs. AA: OR=1.04, 95% CI=1.01-1.33). Meanwhile, rs3750805 was also a risk factor for breast cancer (TT+AT vs. AA: OR=1.12, 95% CI=1.01-1.24) (**Figure 2**).

Quality of the included studies

As shown in **Table 1**, the score of Newcastle-Ottawa quality assessment scale (NOS) was range from 6 to 8.

Sensitivity analysis

Sensitivity analysis was carried out repeatedly by precluding a single study at a time. The results demonstrated that the estimates before and after the deletion of each study were similar, suggesting our meta-analysis results were stable and credible.

Publication bias

As performed in **Figure 3**, the shape of funnel plot seemed symmetrical, and Egger's test and Begg's test provided no statistical evidence for publication bias (P=0.793, P=1.000). Thus, there existed no obvious publication bias influencing overall results in our meta-analysis.

Discussion

Breast cancer, a kind of malignant tumor, seriously threatens the health of women, the incidence and mortality of which are highest among all malignant tumors on female [20]. The incidence of breast cancer is increased rapidly in China in recent years. Therefore, it is urgent to improve the diagnosis and treatment of patients with breast cancer [21-23].

TCF7L2, an important component in Wnt signal pathway, involves in the regulation of cell proliferation and differentiation, which was one of susceptibility genes for T2D. For the relationship of *TCF7L2* polymorphisms and breast cancer, the results were controversial. Naidu et al. have reported that rs7903146 (T) variant could increase the risk of breast cancer [15]. The research conducted by Connor et al. showed that there were significant relationships between rs7903146, rs3750805, rs7900150 and rs1225404 polymorphisms and increased risk of breast cancer [18]. Burwinkel et al. reported that rs12255372 polymorphism could increase the risk for breast cancer [19]. However, Wei et al. found that rs7003146 was significantly associated with reduced risk of breast cancer in Chinese Han population [17]. And Alanazi MS1 et al. concluded that rs12255372 showed no effects on the onset of breast cancer [16].

With the improvement of medical techniques, meta-analysis has been broadly used in medical domain. It can increase sample sizes, comprehensively analyze multiple research results and further solve the inconsistency of results [24-30]. Our meta-analysis, with 4800 cases and 5489 controls, investigated the relationship of *TCF7L2* polymorphisms and the risk of breast cancer. And the results indicated that *TCF7L2* polymorphisms could increase the risk of breast cancer. Meanwhile, rs7903146, rs7900150 and rs3750805 polymorphisms were also associated with increased risk of breast cancer.

Some limitations in our study should be addressed. Firstly, different genotyping methods might result in some bias in the results. Secondly, lack of original data, such as menopausal state, age of menarche, smoking, drinking and family history could affect the comprehensiveness and preciseness of relationship between *TCF7L2* polymorphisms and breast cancer. Finally, limited research articles, to some extent, could affect the validity of the results. Further well-designed studies are needed to provide more comprehensive understanding on the result.

Disclosure of conflict of interest

None.

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References

[1] Parkin DM, Bray F, Ferlay J and Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005; 55: 74-108.

[2] Jensen OM, Esteve J, Moller H and Renard H. Cancer in the European Community and its member states. Eur J Cancer 1990; 26: 1167-1256.

[3] Siegel R, Naishadham D and Jemal A. Cancer statistics, 2012. CA Cancer J Clin 2012; 62: 10-29.

[4] Forouzanfar MH, Foreman KJ, Delossantos AM, Lozano R, Lopez AD, Murray CJ and Naghavi M. Breast and cervical cancer in 187 countries between 1980 and 2010: a systematic analysis. Lancet 2011; 378: 1461-1484.

[5] [No authors listed]. Cancer incidence in five continents. Volume VII. IARC Sci Publ 1997; i-xxxiv, 1-1240.

[6] Yang L, Parkin DM, Li L and Chen Y. Time trends in cancer mortality in China: 1987-1999. Int J Cancer 2003; 106: 771-783.

[7] Yu KD, Di GH, Wu J, Lu JS, Shen KW, Shen ZZ and Shao ZM. Development and trends of surgical modalities for breast cancer in China: a review of 16-year data. Ann Surg Oncol 2007; 14: 2502-2509.

[8] Hulka BS and Moorman PG. Breast cancer: hormones and other risk factors. Maturitas 2001; 38: 103-113; discussion 113-106.

[9] Jo YH, Kim HO, Lee J, Lee SS, Cho CH, Kang IS, Choe WJ, Baik HH and Yoon KS. MCPH1 protein expression and polymorphisms are associated with risk of breast cancer. Gene 2013; 517: 184-190.

[10] Wolff MS and Weston A. Breast cancer risk and environmental exposures. Environ Health Perspect 1997; 105 Suppl 4: 891-896.

[11] Nelson WJ and Nusse R. Convergence of Wnt, beta-catenin, and cadherin pathways. Science 2004; 303: 1483-1487.

[12] Turki A, Al-Zaben GS, Mtiraoui N, Marmmuoch H, Mahjoub T and Almawi WY. Transcription factor-7-like 2 gene variants are strongly associated with type 2 diabetes in Tunisian Arab subjects. Gene 2013; 513: 244-248.

[13] Peng S, Zhu Y, Lu B, Xu F, Li X and Lai M. TCF7L2 gene polymorphisms and type 2 diabetes risk: a comprehensive and updated meta-analysis involving 121,174 subjects. Mutagenesis 2013; 28: 25-37.

[14] Papa V, Reese CC, Brunetti A, Vigneri R, Siiteri PK and Goldfine ID. Progestins increase insulin receptor content and insulin stimulation of growth in human breast carcinoma cells. Cancer Res 1990; 50: 7858-7862.

[15] Naidu R, Yip CH and Taib NA. Genetic variations in transcription factor 7-like 2 (TCF7L2) gene: association of TCF7L2 rs12255372 (G/T) or rs7903146 (C/T) with breast cancer risk and clinico-pathological parameters. Med Oncol 2012; 29: 411-417.

[16] Alanazi MS, Parine NR, Shaik JP, Alabdulkarim HA, Ajaj SA and Khan Z. Association of single nucleotide polymorphisms in Wnt signaling pathway genes with breast cancer in Saudi patients. PLoS One 2013; 8: e59555.

[17] Wei W, Jiang M, Luo L, Li Z, Wang P and Dong WQ. Colorectal cancer susceptibility variants alter risk of breast cancer in a Chinese Han population. Genet Mol Res 2013; 12: 6268-6274.

[18] Connor AE, Baumgartner RN, Baumgartner KB, Kerber RA, Pinkston C, John EM, Torres-Mejia G, Hines L, Giuliano A, Wolff RK and Slattery ML. Associations between TCF7L2 polymorphisms and risk of breast cancer among Hispanic and non-Hispanic white women: the Breast Cancer Health Disparities Study. Breast Cancer Res Treat 2012; 136: 593-602.

[19] Burwinkel B, Shanmugam KS, Hemminki K, Meindl A, Schmutzler RK, Sutter C, Wappenschmidt B, Kiechle M, Bartram CR and Frank B. Transcription factor 7-like 2 (TCF7L2) variant is associated with familial breast cancer risk: a case-control study. BMC Cancer 2006; 6: 268.

[20] Jemal A, Bray F, Center MM, Ferlay J, Ward E and Forman D. Global cancer statistics. CA Cancer J Clin 2011; 61: 69-90.

[21] Smith RA, Saslow D, Sawyer KA, Burke W, Costanza ME, Evans WP, 3rd, Foster RS, Jr., Hendrick E, Eyre HJ and Sener S. American Cancer Society guidelines for breast cancer screening: update 2003. CA Cancer J Clin 2003; 53: 141-169.

[22] Etzioni R, Urban N, Ramsey S, McIntosh M, Schwartz S, Reid B, Radich J, Anderson G and Hartwell L. The case for early detection. Nat Rev Cancer 2003; 3: 243-252.

[23] Calzone KA. Genetic biomarkers of cancer risk. Semin Oncol Nurs 2012; 28: 122-128.

[24] Jiang T, Gao G, Fan G, Li M and Zhou C. FGFR1 amplification in lung squamous cell carcinoma: A systematic review with meta-analysis. Lung Cancer 2015; 87: 1-7.

[25] Zhu J, Du S, Zhang J, Wang Y, Wu Q and Ni J. Polymorphism of DNA methyltransferase 3B -149C/T and cancer risk: a meta-analysis. Med Oncol 2015; 32: 399.

[26] Li Q, Liu L, Liu Y, Zhou H, Yang Z, Yuan K and Min W. Five COX-2 gene polymorphisms and risk of breast cancer: an updated meta-analy-

sis based on 19 case-control studies. Med Oncol 2015; 32: 397.
[27] Petrelli F, Coinu A, Lonati V and Barni S. A systematic review and meta-analysis of adjuvant chemotherapy after neoadjuvant treatment and surgery for rectal cancer. Int J Colorectal Dis 2015; 30: 447-57.
[28] Zhang H, Xia J, Wang K and Zhang J. Serum autoantibodies in the early detection of esophageal cancer: a systematic review. Tumour Biol 2015; 36: 95-109.
[29] Chen C, Yang S, Chaugai S, Wang Y and Wang D. Meta-analysis of Hsa-mir-499 polymorphism (rs3746444) for cancer risk: evidence from 31 case-control studies. BMC Med Genet 2014; 15: 126.
[30] Stacey FG, James EL, Chapman K, Courneya KS and Lubans DR. A systematic review and meta-analysis of social cognitive theory-based physical activity and/or nutrition behavior change interventions for cancer survivors. J Cancer Surviv 2015; 9: 305-38.