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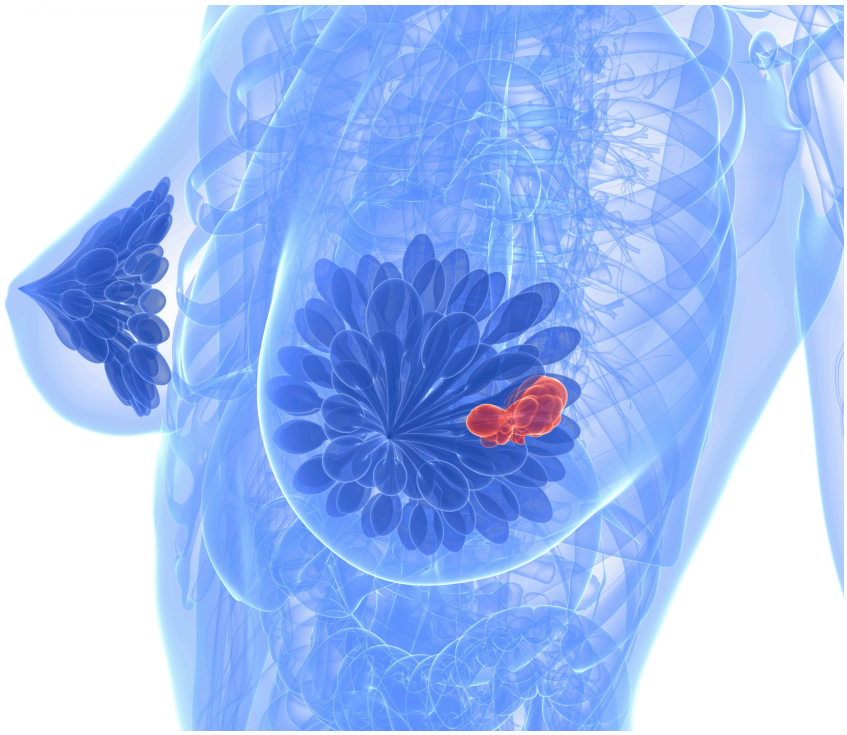

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Letter to Editor

Erythropoietin dose and survival of hemodialysis patients

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Keywords

Erythropoietin, Survival, Hemodialysis

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Chronic kidney disease (CKD) is known as a major health problem worldwide (Levey et al., 2007). The CKD is defined as a stage of disease in which the patient's kidney function is less than a half of normal capacity (2). If the kidney function is 10% to 15% less than the normal capacity, the patient has reached the End Stage Renal Disease (ESRD). At this stage, the kidney transplant or dialysis with hemodialysis or peritoneal dialysis is necessary for patient's survival (Levey et al., 2002).

The incidence of ESRD is rapidly increasing globally, so that the incidence of disease has had the ten-time increased in America during the past few years (Health and Services, 2011). On average, the number of patients, who receive hemodialysis treatment, has had the annual increase of approximately 7% (Lysaght, 2002). The prevalence of this disease varies in different parts of world. The highest incidence belongs to Taiwan with 2447 patients per one million people, but the lowest incidence belongs to the Philippines with 110 patients per one million people (Mongoh et al., 2008).

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There is a significant statistical relationship between the anemia with low survival in patients with chronic renal failure undergoing the hemodialysis (Pfeffer et al., 2009; Singh et al., 2006). In recent years, the Erythropoiesis-stimulating agent (ESA) has been widely used as a treatment for anemia in patients with chronic kidney disease (CKD) and patients with ESRD. However, the treatment of anemia results in the increased survival rates in these patients. According to the conducted clinical trial studies, the modified hemoglobin (Hb) rate to normal range through Erythropoiesis-stimulating agent (ESAs) will not lead to the improved outcomes in these patients (Besarab et al., 1998; Drüeke et al., 2006; Pfeffer et al., 2009; Singh et al., 2006), so that the ratio of myocardial infarction, congestive heart failure, stroke, hospitalization and mortality in a group with target hemoglobin level of 13g/dL is higher than the target hemoglobin level of 11g/dL in a randomized clinical trials (Pfeffer et al., 2009). Therefore, the higher dose of Erythropoietin in patients with higher target hemoglobin level leads to an increased risk of death and non-improved life quality compared to the group with lower target levels.

According to a research by Elani Streja *et al* for investigating the relationship between the received dose of Erythropoietin and mortality in dialysis patients, there is a positive dose-response relationship between weekly dose of Erythropoietin drug and the risk of death. According to this study, the higher dose of Erythropoietin drug is along with increased mortality, so that compared to base group (group with weakly does of less than 6000 units), the ratio of mortality in patients with weekly doses of 6000 to less than 12,000 units is equal to (1.02 95% CI 0.94-1.1), and (1.08 95% CI 1-1.18) in group with a weekly dose of 12,000 to less than 18,000 units, and (1.17 95% CI 1.06-1.28) in group with a weekly dose of 18,000 to less than 24,000 units, and (1.27 95% CI 1.15-1.41) in group with a weekly dose of 24,000 to less than 30,000 units, and finally (1.52 95% CI 1.37 to 1.69) in group with a weekly dose of 30,000 units and higher (Streja et al., 2016). Therefore, the scientific guidelines are approved and it is suggested modifying the partial hemoglobin levels in dialysis patients by erythropoietin drug, but it is not recommended obtaining the same hemoglobin level as the healthy people's standard levels in these patients by Erythropoietin drug (Drüeke et al., 2006).

Abbreviations

CKD:Chronic kidney disease

CI:Confidence Interval

ESAs: Erythropoiesis-stimulating agent

ESRD: End Stage Renal Disease

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Report

Inequality in Human Development Index and suicide death in Iran: A National Register-Based Study

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Abstract

Pay attention to the effects of inequality in health outcomes has steadily risen during recent years. It is necessary step to achieve the goal of health for all (HFA) in the coming decades. At the moment, our knowledge about the inequality and suicide is limited. Human Development Index (HDI) is summary measures that we can demonstrate current inequalities regarded to health outcomes. We have reanalyzed the national data by Statistical Centre of Iran for HDI and Iranian Forensic Medicine Organization for suicide to explicate of inequality in suicide death in Iran. Our results showed an inverse correlation between HDI and suicide death, so that deaths from suicide was more occurred in provinces with lower HDI. Therefore, results in current study showed a positive inequality in suicide in relation with HDI in Iran. According to this, we suggested that regional studies will be conducted to detect subgroups with a high suicide risk as well as components of HDI that cause inequality.

Keywords

Human Development Index (HDI), Inequality, Socioeconomic, Suicide

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Introduction

Suicide is considered as an important public health problem in both developing and developed countries, which lead to more than 800,000 deaths annually (Noorbala AA, 1998). The effects of inequality in health have been acknowledged in developed countries (Veisani et al., 2017). Researchers now aimed to reducing the inequalities in the coming decades through enhance knowledge about inequality sources. The connection between socioeconomic status (SES) and suicide has been controversial. Some have found that a deprived situations increasing the risk of suicide (Burrows and Laflamme, 2010; Yoder and Hoyt, 2005), while other concluded oppose it (Chan et al., 2009), this diversity may be due to variety in methods being used to measure SES. Human Development Index (HDI) is summary measures that can be demonstrated current inequalities and poverty in different contraries. In current study we aimed to obtain the relationship between inequality in HDI and suicide death in Iran using national data.

Materials-Methods

This is an ecological study on the relation of HDI and suicide death in Iran. Data obtained from Results of the Iranian Urban and Rural Household Income and Expenditure Survey in 2013 for HDI (Noorbala and Akhondzadeh, 2015), and the annual reports of Iranian Forensic Medicine Organization in 2012 for suicide rate (Kiadaliri et al., 2014). In this study, we defined inequality in the suicide death according to the HDI by using concentration index (CI) among provinces. The value of CI is between -1 to +1 and the negative value of this index is indicating that the related variable to health is more concentrated on the poor population and the positive value indicates that the related variable to health concentrated among the rich population (Mohammadi et al., 2003). We used the Stata software version 12 (Stata Corp, College Station, TX, USA) to perform all the analytical operations as well as Epi Info™ software for drawing maps. Significant level considered less than 5%.

Results

As shown in **Figure 1**, suicide rate in Iran ranged from 2.21 to 19.53 per 100,000 populations (average rate: 5.1). Among all provinces highest rate observed in Ilam with 19.53 and lowest in Hormozgan with 2.21 per 100,000 population. In addition, slightly more than half (56.6%) provinces had a suicide rate of 3–6 per 100,000 populations. Also figure 1 shown the HDI level for all provinces, accordingly Sistan & Baluchestan and Tehran had a lowest and highest rank

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(0.643 and 0.843), respectively. The CI is presented in **Figure 2**, which shows that suicide was more occurred in provinces with lower HDI. The overall CI was -0.234 (95% CI = -0.343 to -0.124). Therefore our results confirmed a positive inequality in suicide death result from HDI in Iran. A predictor graph was shown in **Figure 3**. It is evident that the higher HDI was associated with lower suicide death in Iran (r= -0.089, p< 0.001).

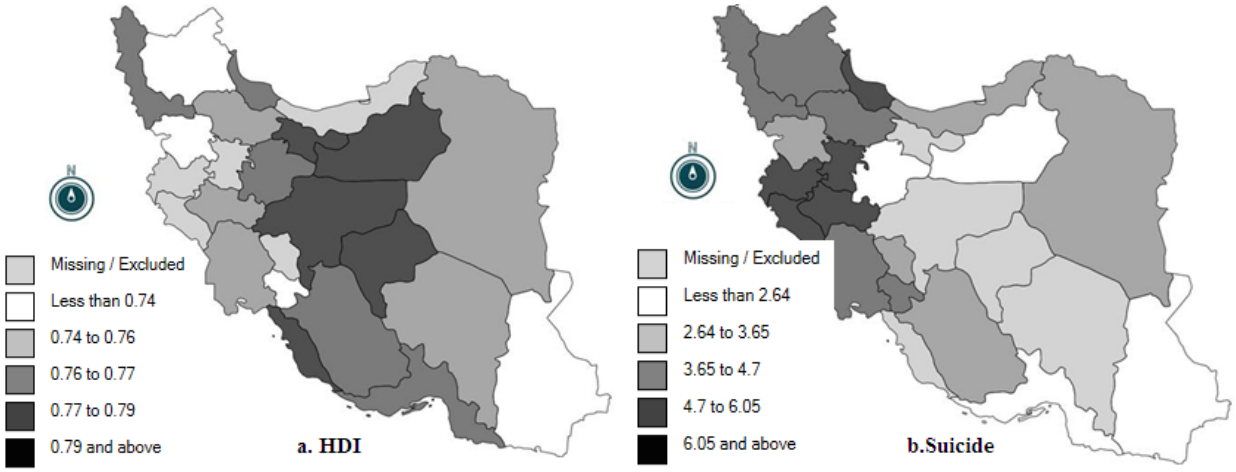

Figure 1. HDI level (A) and suicide rate (B) by province in 2013.

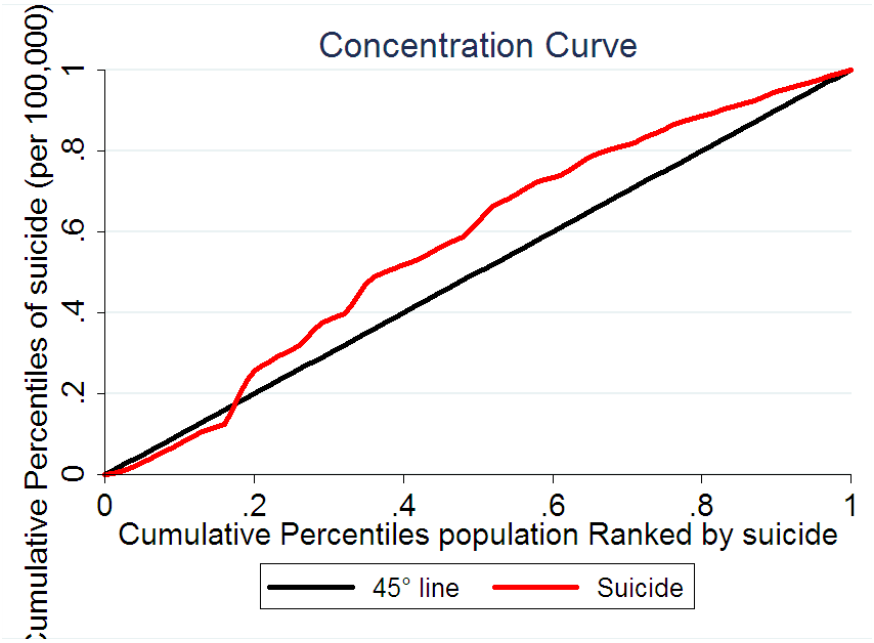

Figure 2. Concentration curve for relation between suicide rate and HDI level.

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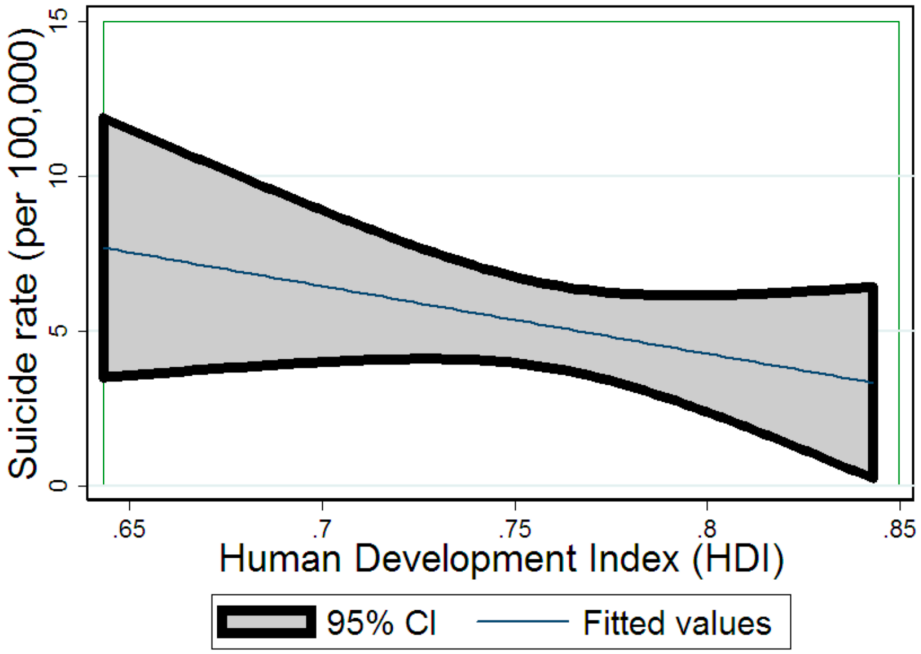

Figure 3. Predictor graph for suicide rate according HDI range.

Discussion

Our results were showed an inverse correlation between the HDI and suicide death in Iran. It comes to mind that people in the provinces with lower HDI rank generally have lower key dimensions of human development such as have a decent standard of living, a long and healthy life and being knowledgeable. The interesting point in our study is that provinces with high rank of suicide death such as Ilam (Veisani et al., 2016), Kermanshah, Lorestan and Hamadan (rank first to fourth) have a lowest HDI according to figure 1. One potential explanation for this finding can be the low SES of these provinces (Veisani and Delpisheh, 2015). This finding is in line with previous systematic review that found, 73% of previous studies had an inverse association between education level and suicide death and as well in relation to income and suicide in 50% of them. They also indicated that 94% of studies that preformed in Asia reign had a significant negative relationship between social rank and suicide death (Pearce et al., 2007).

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Conclusion

In summary, the present study indicated that a positive inequality in suicide death rate relation to HDI in Iran. According to this important finding more studies are needed to explore the origin of inequality in local area to design and apply of intervention programs in provinces especially with high prevalence rate of suicide.

Abbreviations

Human Development Index (HDI)

Socioeconomic status (SES)

Concentration index (CI)

Author contribution

All authors contributed in manuscript preparation. Veisani,Y and Khazaei,S obtained data and analyzed it. Delpisheh,A and Baghri,M interpreted of data analysis. Mohamadian,F designed of figures. All authors drafted the first version and approve the final draft.

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Review

Check for updates

Placenta previa after prior abortion: a meta-analysis

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Abstract

There is controversy regarding the role of prior abortion on placenta previa in subsequent pregnancies. We conducted an updated, comprehensive meta-analysis of placenta previa after prior abortion. The search was conducted from PubMed, Web of Science and Scopus databases from the database inception to January 31, 2017. The heterogeneity across studies was evaluated by Q-test and I^2 statistical test. Publication bias was assessed by Begg's test and Egger's test. Results of odds ratio (OR) estimates with their corresponding 95% confidence intervals (CI) were pooled using random-effects modeling. The literature search included 872 articles up until January 2017 with 2,134,529 participants. Based on OR estimates obtained from case-control and cohort studies, we found a significant association between prior spontaneous abortions and placenta previa (1.77; 95% CI: 1.60, 1.94) and between prior induced abortions and placenta previa (1.36; 95% CI: 1.02, 1.69). The meta-analysis study herein showed that prior abortion is a risk factor for placenta previa.

Keywords

Induced abortion, meta-analysis, placenta previa, spontaneous abortion

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Introduction

Placenta previa is defined as the implantation of the placenta in the lower segment of the uterus. It occurs in 3 out of every 1000 pregnancies (Findeklee and Costa, 2015). The risk factors for placenta previa are smoking, previous cesarean sections, advanced maternal age, multiparity and conception by in

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vitro fertilization (IVF) (Shobeiri et al., 2017). Abortions have been proposed to be associated with fetal pathology, congenital abnormality, low birth weight and preterm labor in subsequent pregnancies (Kashanian et al., 2006).

There is controversy regarding the role of prior abortion on placenta previa in subsequent pregnancies. Some studies have reported an increased risk of placenta previa following abortions (Chelmow et al., 1996; Eniola et al., 2002; Handler et al., 1994; Newton et al., 1984; ROSE and CHAPMAN, 1986; Thom et al., 1992), while others saw no correlation (Bakshi et al., 2015; Kashanian et al., 2006; Latif et al., 2015; Usta et al., 2005).

Two previous meta-analyses have shown a positive association between previous abortion(s) and placenta previa in subsequent pregnancies (Ananth et al., 1997a; Faiz and Ananth, 2003). However, such studies have encountered limitations, such as the limited number of primary databases. Thus, in this study, we performed meta-analysis, based on a larger number of subjects and databases to screen, to address the association of previous abortions and placenta previa. Thus, we conducted an updated and comprehensive meta-analysis of the placenta previa after previous abortion(s).

Materials-Methods

The present meta-analysis study was conducted based on the PRISMA guidelines.

Criteria for including studies

Observational studies (cross-sectional, retrospective and prospective studies) were included in participants declared development of placenta previa following a spontaneous or induced abortion. The following were factors which were excluded in the analysis based on the following criteria: placenta previa following abortion (spontaneous or induced), case report studies, review articles, editorials, and letters or miscellaneous in which full data was not accessible following request from the primary or corresponding authors. The factor of interest was abortion (spontaneous and induced) and the outcome of interest was placenta previa.

Search methods

Two independent authors searched PubMed, Medline and Scopus databases from their time of inception to January 31, 2017. The search terms were conducted based on the following: (placenta previa) and (miscarriage OR induced abortion OR spontaneous abortion OR elective abortion).

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After initial evaluation, the studies were independently and carefully evaluated by two authors, and data extraction was performed according to the selection criteria. We extracted the following variables: first author, year of publication, survey years, study country, total sample size, and odds ratio (OR) and their associated 95% confidence intervals (CI). Where discrepancies existed, discussions took place between the two authors until a consensus could be reached.

We assessed the methodological quality of each study independently by two authors via the Newcastle Ottawa Statement Manual (NOS) scale (Wells et al., 2012). The scale was from 0 to a maximum of nine stars, and included the following evaluation criteria: selection, comparability, exposure and outcome. Articles scored with seven stars or more were considered high-quality; articles scored with lower stars were considered low-quality (Poorolajal and Jenabi, 2016).

Heterogeneity and publication bias

Statistical heterogeneity was determined by the Q statistic test, which was quantified by the I-square values for assessing inconsistency across the studies (Higgins et al., 2003). Funnel plot and the Begg's and Egger's tests (Begg and Mazumdar, 1994) were used to evaluate the probability of publication bias. Data were analyzed and the outcomes were reported using the random effect model (DerSimonian and Laird, 1986). The Stata software, version 13 (StataCorp, College Station, TX) was used for statistical analysis; a statistical significance was set at $p< 0.05$.

Results

Description of studies

Our search yielded 872 publications of which 20 studies included met inclusion criteria until Jan 2017 **(Fig. 1)**. We found 3 cohort studies (Bakshi et al., 2015; Kashanian et al., 2006; Rosenberg et al., 2011) and 17 case-control studies (Chelmow et al., 1996; Eniola et al., 2002; Handler et al., 1994; Hung et al., 2007; Johnson et al., 2003; Kramer et al., 1991; Latif et al., 2015; Macones et al., 1997; Newton et al., 1984; ROSE and CHAPMAN, 1986; Sheiner et al., 2001; Shobeiri et al., 2017; Sumigama et al., 2014; Taylor et al., 1994; Thom et al., 1992; Usta et al., 2005; Williams et al., 1991) with 2,134,529 participants. All studies were published in English **(Table 1)**.

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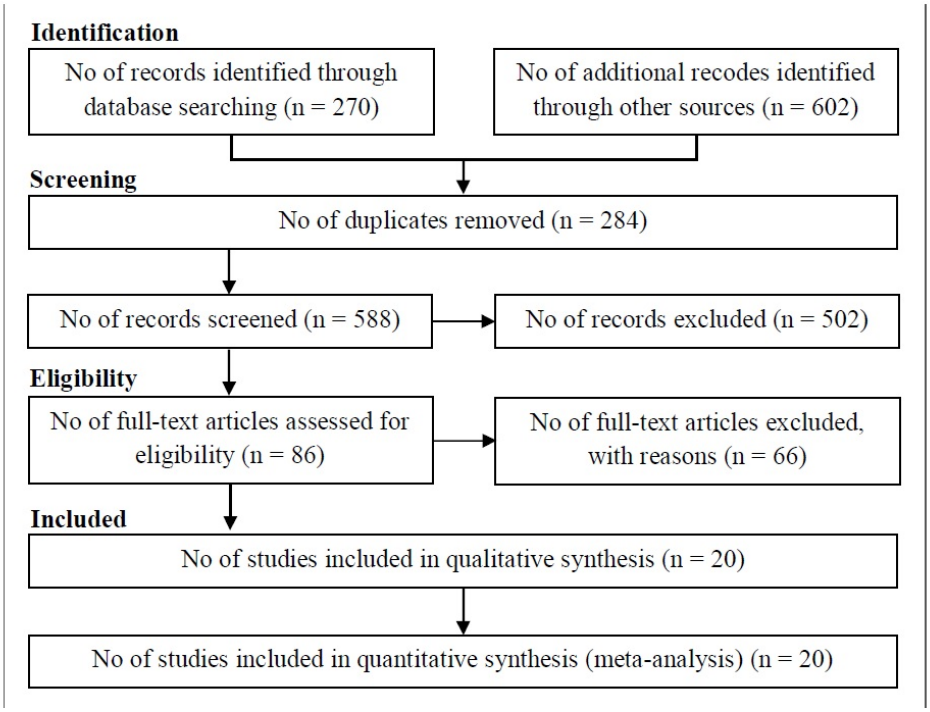

Figure 1. Flow of information through the different phases of the systematic review

Effects of exposure

In the present meta-analysis, the association between prior abortion and risk of placenta previa was based on observational studies (Fig. 2). Based on OR estimates obtained from case-control and cohort studies, there was a significant association between prior spontaneous abortion and the risk of placenta previa (1.77; 95% CI: 1.60, 1.94) and between prior induced abortion and the risk of placenta previa (1.36; 95% CI: 1.02, 1.69). The results indicated that the measure of the effect was homogenous.

Publication bias

The graphical funnel plots appeared to be symmetrical (Fig. 3). The Begg's (z = 0.90, P = 0.366) and Egger's test (t = 0.81, P = 0.428) indicated there was no evidence for publication bias.

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Table 1. Summary of the study results

1st author, Year	Country	Design	Sample	Estimate	Adjustment	Type of abortion	Quality
Rose 1986	USA	Case-control	160	OR	Crude	Spontaneous	Low
Macones 1997	USA	Case-control	240	OR	Adjusted	Induced	High
Chelmow 1996	USA	Case-control	128	OR	Crude	Spontaneous/induced	Low
Newton 1984	USA	Case-control	276	OR	Crude	Spontaneous/induced	Low
Thom 1992	USA	Case-control	5883	OR	Crude	Spontaneous	Low
Williams 1991	USA	Case-control	12420	OR	Adjusted	Spontaneous/induced	High
Hung 2006	Taiwan	Case-control	37702	OR	Crude	Induced	High
Handler 1994	USA	Case-control	3036	OR	Crude	Spontaneous/induced	Low
Johnson 2003	USA	Case-control	814	OR	Adjusted	Induced	High
Kramer 1991	USA	Case-control	3020	OR	Crude	Spontaneous	Low
Usta 2005	Lebanon	Case-control	347	OR	Crude	Spontaneous	Low
Rosenberg 2011	Israel	Ret-cohort	3216	OR	Crude	Spontaneous	Low
Bakshi 2015	India	Pros-cohort	800	OR	Crude	Spontaneous	Low
Shobeiri 2017	Iran	Case-control	260	OR	Adjusted	Spontaneous	High
Sumigama 2014	Japan	Case-control	98	OR	Crude	Induced	Low
Sheiner 2001	Israel	Case-control	28524	OR	Adjusted	Spontaneous	High
Taylor 1995	USA	Case-control	3727	OR	Crude	Induced	High
Latif 2015	Pakistan	Case-control	90	OR	Crude	Spontaneous	Low
Kashanian 2006	Iran	Pros-cohort	300	OR	Crude	Spontaneous	Low
Eniola 2002	Nigeria	Case-control	272	OR	Crude	Spontaneous/induced	Low

Quality of the studies

In this meta-analysis, seven studies were of high quality and thirteen studies were of low quality, based on the NOS scale (Table 1).

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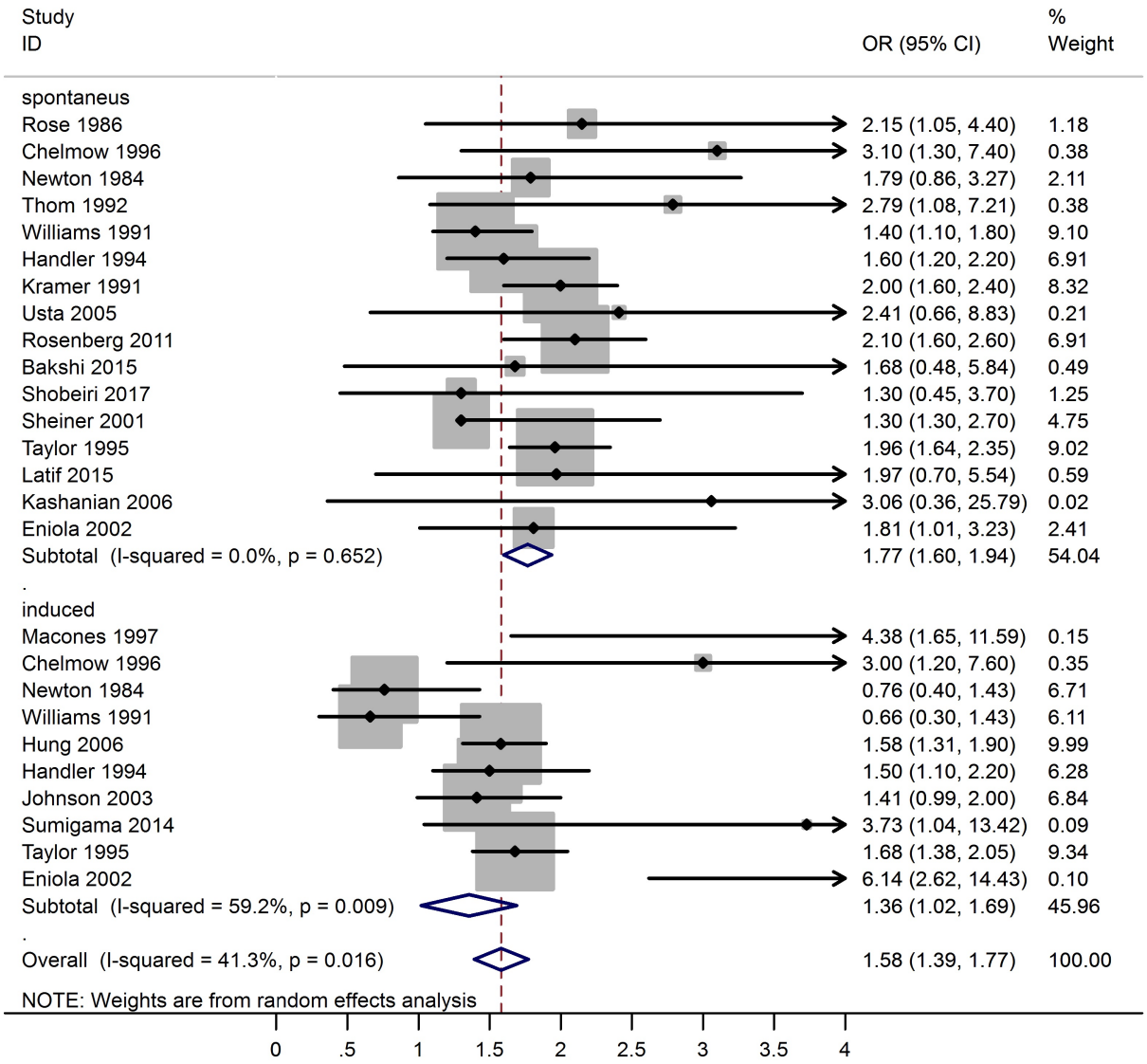

Figure 2. Forest plot of the association between prior abortion and placenta previa.

Discussion

The meta-analysis described herein and based on observational studies show that there is an association between prior abortion and placenta previa. Our results suggest that prior abortion is a risk factor for placenta previa. It has been

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previously reported that placenta previa is correlated with maternal and fetal complication, such as antenatal and post-partum hemorrhage, preterm delivery, intrauterine growth restriction, malpresentation and poor neonatal outcomes (Rombauts et al., 2014).

In a meta-analysis report published by Ananth et al. in 1997 (Ananth et al., 1997b), the authors showed that based on OR estimates from all the studies they evaluated, there was a significant increase in the risk of placenta previa after prior spontaneous abortions (1.7; 95% CI: 1.5, 2.0) and after prior induced abortions (1.5; 95% CI: 1.3, 1.7). However, this meta-analysis was limited to eight studies and they searched only the Medline database.

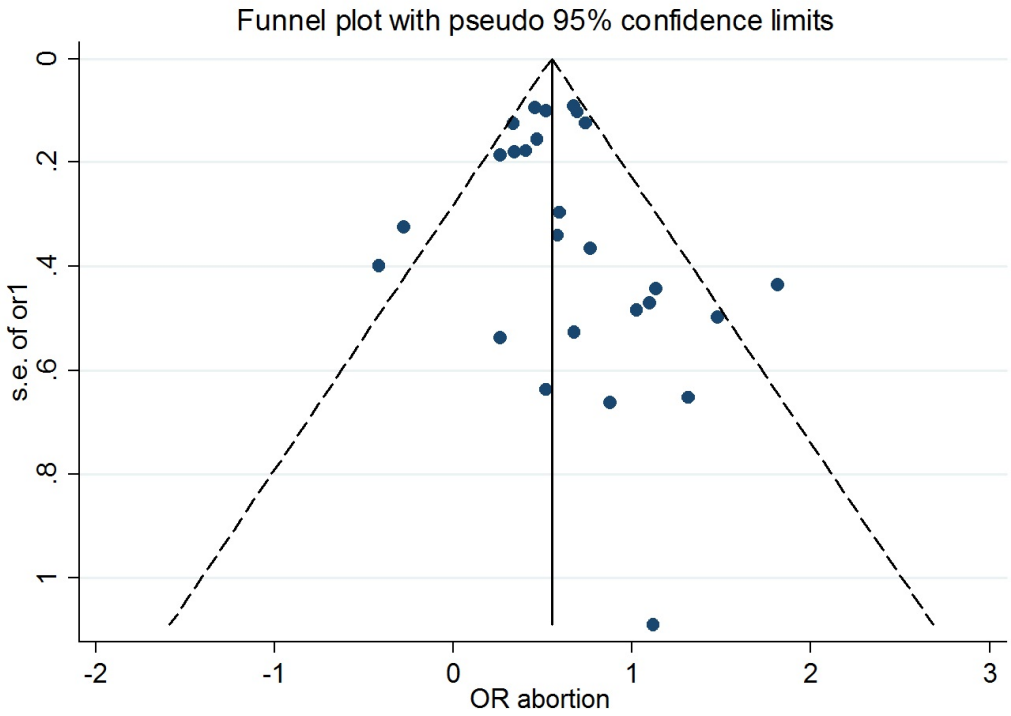

Figure 3. Funnel plot of the association between prior abortion and placenta previa.

In another meta-analysis, conducted in 2003 by Faiz et al. and which evaluated all articles up to year 2000, the authors showed that prior abortion increased the risk of placenta previa. Based on their results, there was significant association in the increased risk of placenta previa after prior spontaneous abortions (2.0; 95% CI: 1.7, 2.3) and after prior induced abortions (1.5; 95% CI: 1.3, 1.9) (Faiz and Ananth, 2003). For their analysis, the authors searched only the Medline database and the meta-analysis included 9 observational studies.

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The mechanisms involved in the association of prior abortions and placenta previa is unknown. The damage and scarring to myometrium and endometrium of the uterus during spontaneous and induced abortions may influence the low implantation of placenta in the uterus in subsequent pregnancies (Faiz and Ananth, 2003).

The meta-analysis described herein had two limitations. While some studies report only the unadjusted form of OR, we tried to use the adjusted form to control for risk factors which may have impacted the studies included in this meta-analysis. However, doing so might introduce information bias in our results. Also, in the present study, we attempted to identify all published studies. However, in spite of our efforts, we could not find two studies that might have reported data on placenta previa. Despite these limitations, the present meta-analysis study was drawn from a large sample size; the 20 studies should efficiently estimate the association between prior abortion and risk of placenta previa. Our results indicate, based on odds ratio reports in epidemiological studies, that prior abortion (spontaneous and induced) can increase the risk of placenta previa.

Conclusion

We showed based on our present meta-analysis of observational studies that prior spontaneous and induced abortions can increase the risk of placenta previa. Therefore, prior abortion is a risk factor for placenta previa.

Author contribution

EJ and MK designed the study and processed the data. MK and EJ performed the statistical analysis. EJ and MK interpreted the results and wrote the first draft. Two authors read and approved the final manuscript.

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Original Research

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Association between SNP rs9485372 in TAB2 gene and breast cancer risk in Vietnamese women

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Abstract

Background: Breast cancer is a complex and common cancer in women. In the purpose of prevention and treatment of the disease, many studies have been conducted recently all over the world. The genetic factor is known as an important factor has been studied to provide information for early diagnosis. Within several genetic factors involved in the development of breast cancer, *TAB2* gene in 6q25.1 is a breast cancer susceptibility locus. The SNP r9485372 in *TAB2* gene is associated with breast cancer in East Asian population including Chinese and Korean but not in Indian and Japanese. In this study, we conducted a case-control study to evaluate the association of this SNP with breast cancer risk in the Vietnamese population. **Methods**: 109 controls and 111 cases were genotyped by HRM method and logistic regression analysed. **Results**: We found that the frequency of SNP alleles is roughly similar to East Asian population: the major allele is G occupied 59.63%, the minor allele is A with 40.37% in the Vietnamese population. The allelic distribution of SNP rs9485372 was not significantly different between case and control group ($OR_{A\ vs.\ G}$ (95% CI) = 0.93 (0.64 - 1.37), P-value = 0.73). **Conclusion**: Our finding thus suggested that this SNP is not significantly associated with breast cancer in Vietnamese women. However, the power of this study is quite low at only 4.46% that was partly caused by a small sample size. Hence, a further study needs to be conducted with a larger sample size in the future to confirm the association of this SNP with breast cancer in Vietnamese women.

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Keywords

Breast cancer, rs9485372, Vietnamese population

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Introduction

Breast cancer (BC), one of the most common cancers in women, is the leading cause of cancer death of women in the world. There were 1,383,500 new cases of BC and these caused approximately 458,400 deaths worldwide in 2002 (Levin, 2008). Till 2012, incidence and mortality of BC have increased up to 1671,000 new cases and 522,000 deaths, respectively (Ferlay et al., 2015). In Vietnam, breast cancer incidence has risen steadily, with an estimated 11,067 new cases in the country (GLOBOCAN, 2012). Breast cancer was ranked first mortality of common cancer in Vietnamese women (with 4600 deaths in 2012) (GLOBOCAN, 2012). However, the mortality to incidence ratio of breast cancer in Vietnam is much higher than the world (0.42 and 0.32, respectively). One of the reasons for this difference is the late diagnosis. In Vietnam, almost patients were detected breast cancer in the late stages that decreases the efficiency of treatment and increases mortality (DucNB, 2010). A statistics analysis revealed that five-year relative survival rate decreased when the breast cancer was diagnosed in advanced stages (DeSantis, Siegel, & Jemal, 2013). According to DeSantis et al., five-year relative survival rate decreases sharply from 99% for localized stage to 24% for distant-stage. Early cancer detection plays an important role in extending survival time of patients. Early detection can greatly increase the chances for successful treatment (WHO, 2016). Breast cancer can be considered a sporadic disease because it is mainly caused by interplaying between the genetic factor and environmental factors such as alcohol consumption, smoking, and diet (Martin & Weber, 2000). The majority of breast cancer is sporadic, only 5%-10% of breast cancer cases are hereditary (Balmain, Gray, & Ponder, 2003; Rizzolo, Silvestri, Falchetti, & Ottini, 2011). Known genes (BRCA1 and BRCA2) which play roles in the the development of breast cancer count for approximately 20% of the familial risk, and less than 5% of total breast cancer (Balmain et al., 2003). Most of the genetic variants related to tumorigenesis of sporadic breast cancer are unknown (Balmain et al., 2003). It is suggested that remaining risk of breast cancer may result from the contribution of multiple common variants in the genome, namely polygenic model (Pharoah et al., 2002). Although a common variant has only a modest effect on tumorigenesis of disease, a combination of these variants can have a greater effect on the disease (Onay et al., 2006; Pharoah et al., 2002). Therefore, the discovery of common variants relating to breast cancer is important to fully understand the mechanism of this disease and predict the risk of breast cancer development.

Nowadays, there are many Single Nucleotide Polymorphisms (SNPs), common variants, have been identified to associate with cancers including breast cancer by GWAS studies (Cai et al., 2014; Easton et al., 2007; Long et al., 2010; Long et al., 2012; Shu et al., 2012; Zheng et al., 2009). In recent GWAS studies, scientists have identified approximately 100 genetic loci associated with breast cancer (Wen et al., 2016). The 6q25.1 chromosomal region was considered a breast cancer susceptibility locus. There are many GWAS studies suggested that

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various SNPs located on this region have significantly associated with breast cancer risk, such as rs2253407 (Gaudet et al., 2013), rs9383935, rs2228480, rs3798758 (Wang et al., 2014), rs2046210 (Zheng et al., 2009), rs3757318 (Turnbull et al., 2010). SNP rs9485372 (G>A) is also located on 6q25.1 region and has been proven to strongly associated with breast cancer in East Asian women by many studies (Long et al., 2012; Wen et al., 2016; Zheng et al., 2013). Rs9485372 is an intronic SNP and located on the TGF-beta activated kinase 1/ MAP3K7 binding protein 2 (TAB2) gene, which belongs to the 6q25.1 chromosomal region. TAB2 protein is encoded by *TAB2* gene and take part in TGF-beta pathway, which is critical in the development of breast cancer (Benson, 2004). TAB2 links signal from the transforming growth factor-β (TGF-β) receptor and TRAF proteins to the TGF-β-activated kinase 1 (TAK1) and activates TAK1 (Takaesu et al.). Activated TAK1 indirectly activates NF-κB.by phosphorylation inhibition kappa B kinase complex (IKK) (Takaesu et al.). Once activated, NF-κB will target genes promoting tumor cell proliferation, survival, migration (Van Waes, 2007). Although the biological mechanism of the association between SNP rs9485372 and breast cancer remains to be determined, it is possible that this association may be mediated through *TAB2* gene (Long et al., 2012). A 4-stage study conducted in East Asian women has showed that the $OR_{A\ vs.\ G}$ (95% CI) was 0.88 (0.81–0.95), 0.86 (0.81–0.92), 0.94 (0.88–1.00) and 0.90 (0.85–0.94) with p-value was 1.4x10-3, 6.3x10-6, 0.05, 4.2x10-5, respectively, for stage I to IV (Long et al., 2012). The pooled analysis which was then performed with all samples from 4 stages produced $OR_{A\ vs.\ G}$ (95% CI) of 0.90 (0.87– 0.92) and P-value of 3.8x10-12 (Long et al., 2012). These results have revealed a strong association of SNP rs9485372 with breast cancer risk. The positive association of this SNP was confirmed by studies of Zheng et al. and Wen et al. (Wen et al., 2016; Zheng et al., 2013). The results of these studies revealed that G allele of this SNP increased the risk of BC while A allele had an ability to reduce BC risk in East Asian women. Nevertheless, the association between this SNP and breast cancer was not significant in Indian population and African-American population (Long et al., 2013; Nagrani et al., 2017). Although many studies have demonstrated the association of SNP rs9485372 with breast cancer in Asian women, there was no study investigating this association in the Vietnamese population. Hence, the aim of our study is to estimate the association of SNP rs9485372 with breast cancer risk in Vietnamese women.

Materials-Methods

Study population

111 breast cancer women and 109 healthy women without breast cancer were recruited from Oncology Hospital, Ho Chi Minh city, Vietnam. Breast cancer was diagnosed by clinical and radiological examinations (mammography and/or ultrasonography), and was then confirmed by the histopathological assessment of biopsies. The participants had received and signed the consent form which

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was approved by the Ethical Committee of Oncology Hospital – HCMC Vietnam under the decision number 177/HĐĐĐ-CĐT, 18th November 2014. The collected whole blood samples were stored in EDTA containing tubes at -20°C till DNA extraction.

DNA extraction

Genomic DNA was extracted by salting-out method following protocol of Hue et al (Hue, Chan, Phong, Linh, & Giang, 2012) with some adjustments for whole blood samples, then stored at -20°C until performing PCR reaction.

Genotyping methods

HRM (high resolution melting) method was used to identify the genotypes of DNA samples in this study. The DNA sequence around the SNP rs9485372 was first obtained from NCBI SNP database and used as input data to design PCR primers which amplify a fragment including interested SNP by Primer3Plus (http://primer3plus.com/cgi-bin/dev/primer3plus.cgi). Next, designed primers were checked specificity at NCBI Primer-BLAST tool (https://www.ncbi.nlm.nih.gov/tools/primer-blast/). The PCR product was then predicted by using UCSC In-silico PCR tool (https://genome.ucsc.edu/cgi-bin/hgPcr). The melting curves of the product were predicted by uMelt HETS (https://www.dna.utah.edu/hets/). The best primer pair (rs9485372-F-5'-TCAATGTGGTACTGTGCCTAGTTTT-3' and rs9485372-R-5'-TCTCTCCACAGGGAATAGTGATATGT-3'), which amplified a 100bp-fragment including interested SNP and have 3 different curves corresponding to 3 genotypes (GG, GA, AA) were accepted for HRM analysis.

The PCR reaction was performed in LighCycler 96 System (Roche Diagnostics Penzberg Germany) and used Roche HRM master mix (Roche Diagnostics, Germany). Thermal cycle of PCR in HRM analysis consisted of an initial pre-incubation at 95°C for 5 minutes, followed by 40 cycles of denaturation at 95°C for 30 s, annealing for 30s at 58°C (Ta) and elongation at 72°C for 30 s. Heteroduplexes were then generated by heating the reaction to 95°C for 1.5 minutes and cooling to 40°C (Ramp rate of 2.2°C/s) for 60s. Finally, the heteroduplexes was heat to 65°C for 30s (ramp rate of 1.5°C/s) and to 95°C for 1s in order to record the fluorescent signal. The best conditions for HRM analysis was optimized with the controls and used for genotyping samples. HRM components for a 10µL reaction consisted of: 1X PCR buffer, 200µM each dNTP, 2.0mM $MgCl_2$, 0.3µM forward primer, 0.3µM reverse primer, 15ng DNA and molecular water.

Association analysis

Association analysis was conducted by R version 3.3.2. Firstly, Hardy–Weinberg equilibrium (HWE) had been analyzed. HWE P-value > 0.05 was considered the HWE in sample sets. The logistic regression analysis was then performed to

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estimate the association between SNP rs9485372 and breast cancer risk. All statistical tests which had a P-value < 0.05 were considered statistically significant. Finally, the statistical power of the case-control study was analyzed.

Results

Genotyping

To determine the genotype of samples, three controls corresponding three genotypes (GG, GA, AA) were first identified by the initial genotyping reaction of some random samples. **Figure 1A, B, C** show 3 HRM curves of 3 controls that were analyzed through 3 channels: melting peak, melting curve, and different plot. These controls were also confirmed by sequencing **(Fig. 1D,E,F)**. After identifying controls, these controls were used for genotyping optimization to get 3 best discriminate HRM curves. The optimal condition for genotyping reaction which was mentioned in the method was applied to identify the genotype of samples. Total 220 samples including 111 of case set and 109 of control set were successfully genotyped (**Fig. 2**).

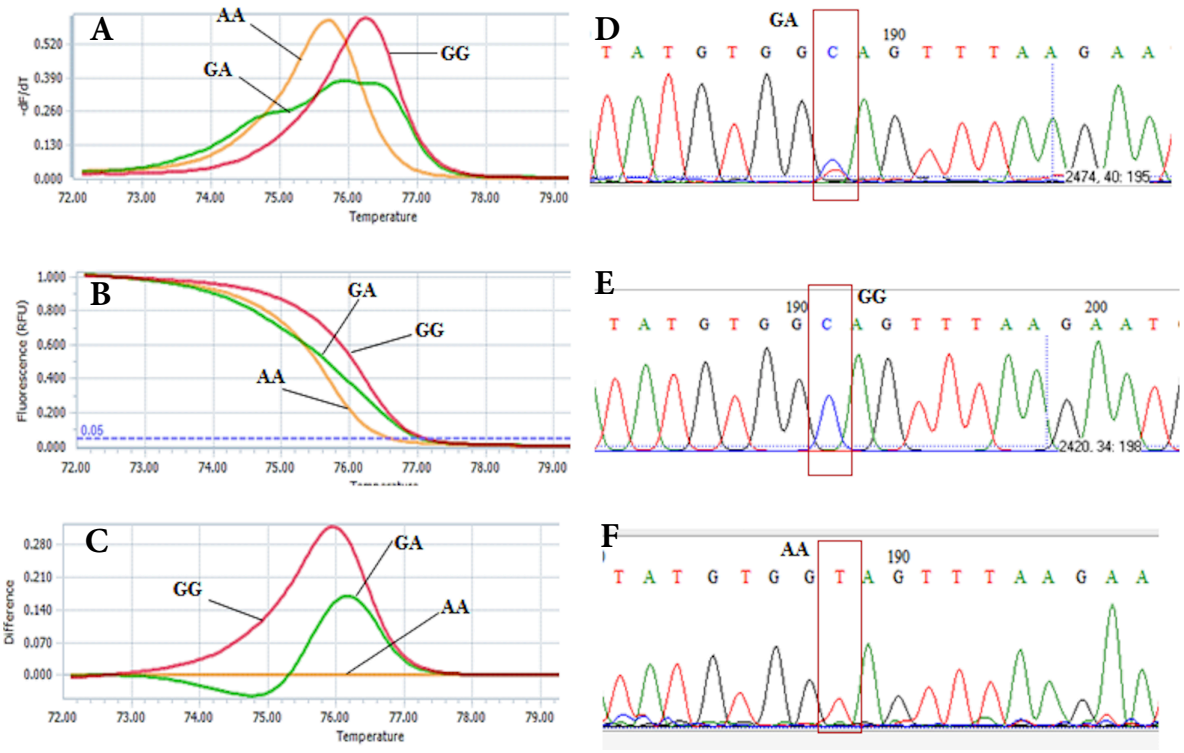

Figure 1. Identify 3 controls by HRM analysis and sequencing. GA, GG, AA genotype controls were identified by 3 analysis channels, melting peak (**A**), melting curve (**B**), different plot (**C**) and confirmed by sequencing (**D, E, F**).

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Alleles' frequency and Hardy-Weinberg equilibrium (HWE)

Allele and genotype frequencies were calculated based on the number of each allele and genotype that were identified by HRM analysis (Table 1). The frequency of minor allele (A allele) counted for 38.84% in case set and 40.37% in control set. It is likely that the A allele in control set appears more frequently than in case set.

HWE p-value was 1 in each group, indicating that both control and case groups were in Hardy Weinberg equilibrium (Table 1). Thus, the selected sample sets can represent the population. The association analysis of this SNP can be a reliable reflection of the relationship of this SNP and breast cancer in Vietnamese.

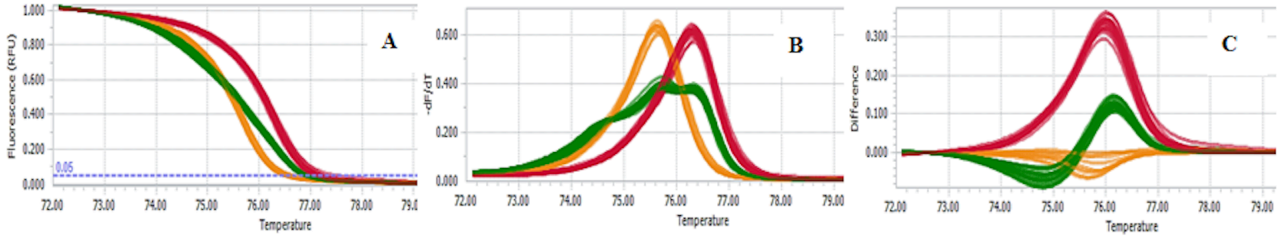

Figure 2. Three genotype groups of rs9485372 in melting curve (A), melting peak (B), different plot (C) analysis. The red, green and orange curve represented GG, GA and AA genotype, respectively.

Table 1. Allele and genotype frequency of SNP rs9485372 and HWE of sample sets

	Genotype (%)			Allele (%)		HWE P-value
	AA	GA	GG	A	G	
Case (111)	17 (15.32)	52 (46.85)	42 (37.84)	90 (38.74)	136 (61.26)	1
Control (109)	18 (16.51)	52 (47.71)	39 (35.78)	88 (40.37)	130 (59.63)	1
Total (220)						0.89

Association analysis

Based on allele and genotype frequency of the interested SNP, association analysis was then conducted by R version 3.3.2. Table 2 shows an association of SNP rs9485372 with breast cancer. OR per A allele was 0.93, revealing that the A

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allele may have a protective effect on risk of breast cancer. However, the Chi-squared test showed 0.73 of p-value for allele difference between case population and control population (P-value > 0.05) (Table 2). It suggested that SNP rs9485372 was not significantly associated with breast cancer risk in the Vietnamese population. In addition, genotypic association analysis revealed that the number of the minor allele in genotype also have an effect on reducing breast cancer risk. AA genotype with two A alleles is more protective ($OR_{AA\ vs.\ GG}$ = 0.88) than GA genotype which has only one A allele ($OR_{AG\ vs.\ GG)}$ = 0.93). It seems that A allele has a recessive effect on the disease. Nevertheless, the p-value for additive model, recessive model, and the dominant model was 0.94, 0.81 and 0.75, respectively, which is much higher than the threshold (P-value = 0.05) (Table 2). Therefore, there was a non-significant association between this SNP and breast cancer in the Vietnamese population.

Table 2. Association analysis of SNP rs9485372

Association analysis	Analysis model		OR	95% CI	P-value
Allelic analysis	**A vs G**		0.93	0.64 - 1.37	0.73
Genotypic analysis	**Additive**	AA vs GG	0.88	0.40 - 1.94	0.94
	Additive	GA vs GG	0.93	0.52 - 1.66	0.94
	Recessive	AA vs (GA+GG)	0.91	0.44 – 1.88	0.81
	Dominant	(AA+GA) vs GG	0.92	0.53 – 1.58	0.75

The power analysis

After identifying the association of SNP rs9485372 with breast cancer, the statistical power of our study was also computed to confirm the estimated association. With 220 samples including 109 controls and 111 cases, the power of this study was just 4.46%, which much lower than expectation (80%). The result revealed that non-significant association was not reliable. One reason for the low power of the study is small sample size. To raise the power up to 50% or more and have enough confidence to conclude the association between SNP rs9485372 with breast cancer in Vietnamese, a larger sample size needs to be investigated. Table 3 shows some predicted sample sizes that could be investigated to increase the power of the study. An estimated sample size of 12500 case/control will be investigated to reach 80% of power for this study (Table 3).

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Table 3. Predicting power, sample size for this study

Power (%)	4.46	50	60	70	80
Case/ Control	111/ 109	6105/ 6105	7785/ 7785	9808/ 9808	12472/ 12472

Discussion

Our study is the first study that investigated the association of SNP rs9485372 and breast cancer in Vietnamese population. In this case-control study, the frequency of a minor allele (A allele) was 40.37% in control and slightly decrease to 38.74% in case. In previous studies, the frequency of A allele in control in East Asian population ranged from 42% to 45.4%. Distribution of this allele in Vietnamese is roughly similar to its distribution in East Asian. It is possible that Vietnamese population and East Asian are in the same geographical distribution and may share the genetic variants through evolution. When the frequency of alleles similar with other populations in East Asia, the association between this SNP in Vietnamese is expected as seen in other studies (Long et al., 2012; Wen et al., 2016; Zheng et al., 2013). However, our study found that the $OR_{A\ vs.\ G}$ (95% CI) of this SNP was 0.93 (0.64-1.37) with an estimated 0.73 of P-value. It suggested that SNP rs9485372 might not be associated with breast cancer risk and the A allele does not affect the risk of breast cancer in Vietnamese.

A number of previous studies have shown a significant association of this SNP with breast cancer in East Asian population (Long et al., 2012; Wen et al., 2016; Zheng et al., 2013). In 2012, with approximately 40,000 cases and controls from Chinese, Korean, and Japanese population, Long et al. indicated SNP rs9485372 was strongly associated with breast cancer risk ($OR_{A\ vs.\ G}$ (95% CI) = 0.90 (0.87–0.92), P-value = $3.8x10^{-12}$) (Long et al., 2012). After that a replicated study of Zeng et al. (samples include 23 637 cases and 25 579 controls) suggested the same result ($OR_{A\ vs.\ G}$ (95% CI) = 0.90 (0.87–0.92), P-meta = 2.27×10^{-13}) (Zheng et al., 2013). Another study conducted in 2016 also suggested the association of this SNP with breast cancer in both ER negative and positive status ($OR_{G\ vs.\ A}$=1.15, one-side p=3.93x10-5 in ER-negative; $OR_{G\ vs.\ A}$=1.11 one-side p=2.72x10-5 in ER-positive population (Wen et al., 2016). With a large number of samples, these studies have shown a high power and the result is trustable. The positive association of SNP rs9485372 with breast cancer may be mediated through *TAB2* gene. SNP rs9485372 is located on intron region of *TAB2* gene and may have an effect on splicing of TAB2 mRNA. Hence, this SNP may affect expression and function of TAB2 and associate with breast cancer.

The non-significant association between the SNP rs9485372 with breast cancer in Vietnamese women (OR (95% CI) = 0.93 (0.64-1.37), P-value = 0.73) in our study is different from previous studies may due to a small sample size (109

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controls and 111 cases). However, our finding is consistent with some other studies. As seen in the study conducted in East Asian, Long et al. revealed that though this SNP was significantly associated with breast cancer in East Asian ($OR_{A\ vs.\ G}$ (95% CI) = 0.90 (0.87–0.92), P-value = 3.8x10-12, approximately 40,000 samples), but non-significant association was observed in Japanese population with roundly 2,000 samples ($OR_{GA\ vs.\ GG}$ (95% CI) and $OR_{AA\ vs.\ GG}$ were 0.93(0.76–1.13) and 0.84(0.66–1.07), respectively, P-value = 0.15) (Long et al., 2012). Another study in Indian population showed that this SNP was not significantly associated with breast cancer ($OR_{G\ vs.\ A}$ (95% CI) = 1.09 (0.94–1.25), P-value = 0.228, approximately 2,400 samples) (Nagrani et al., 2017). SNP rs9485372 was also indirectly evaluated association with breast cancer in African-American women by association of SNP rs9485370 which is in strong LD with rs9485372. With roundly 2,000 samples, this study showed that SNP rs9485372 had a non-significant association with breast cancer in African-American women (OR (95% CI) for heterozygote and homozygote were 1.13 (0.74-1.74) and 1.16 (0.77-1.76), respectively, P-value = 0.533) (Long et al., 2013).

According to previous studies, there are different conclusions about the association between SNP rs9485372 and breast cancer in different populations. It suggests that association of SNP rs9485372 with breast cancer depends on the ethnic group. Although this SNP is located on *TAB2* gene related to the development of breast cancer, the association of this SNP with breast cancer was not observed in Vietnamese women and other populations. The reason for this non-significant association is unclear but it may be due to epigenetic regulation that may play important role in expression and function of *TAB2* gene. Various environmental factors such as nutrition, behavior which occur during development of an individual can produce long-lasting epigenetic changes in the gene. It may regulate and affect the expression of *TAB2* gene (Faulk & Dolinoy, 2011). Therefore, the association of SNP rs9485372 with breast cancer was not consistent between populations.

With 109 controls and 111 cases, our study revealed that SNP rs9485372 is not significantly associated with breast cancer in Vietnamese ($OR_{A\ vs.\ G}$ (95% CI) = 0.93 (0.64-1.37), P-value = 0.73). Nevertheless, the power of this study is very low, roundly 4.46%. It may be due to a small sample size. Thus, a future study needs to be conducted with a larger sample size to confirm this finding.

Conclusion

In conclusion, our study is the primary research screening the association of SNP rs9485372 with breast cancer in Vietnamese women. With a quite small sample size including 109 controls and 111 cases, our study suggested that SNP rs9485372 was not significantly associated with breast cancer in Vietnamese women ($OR_{A\ vs.\ G}$ (95% CI) = 0.93 (0.64 - 1.37), P-value = 0.73), but the power of

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this study is very low, roundly 4.46%. Hence, the future study needs to be investigated with a larger sample size in order to confirm the result of our study.

Abbreviations

95% CI: 95% confidence interval
BC: breast cancer
GWAS: Genome Wide Association Study
HRM: High Resolution Melting
HWE: Hardy-Weinberg equilibrium
IKK: Inhibition Kappa B Kinase complex
NCBI: National Center for Biotechnology Information
NF-κB: Nuclear Factor- Kappa B
OR: Odd ratio
PCR: Polymerase Chain Reaction
SNP: Single nucleotide polymorphism
TAB2: TGF-beta activated kinase 1/MAP3K7 binding protein 2
TAK1: TGF-β-activated kinase 1
TGF: Transforming Growth Factor
TRAF: TNF receptor–associated factor 6
WHO: World Health Organization

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Author Contribution

Nguyen Thi Lan Huong contributed to acquisition, analysis, interpretation of data, drafting of manuscript. Nguyen Thi Ngoc Thanh reviewed and edited the manuscript for intellectual content. Nguyen Thi Hue oriented, gave important idea and revised the manuscript of this review. All authors gave final approval of the version to be published.

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Original Research

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The effect of laughter yoga exercises on anxiety and sleep quality in patients suffering from Parkinson's disease

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Abstract

Background: The aim of the present study is to evaluate the effects of laughter yoga exercises on anxiety and sleep quality in patients suffering from Parkinson's disease. **Methods:** In the study a semi-empirical and applied research design was used, which involved a pre-test and post-test, and appropriate control group. The study consisted of 24 patients suffering from Parkinson's disease who were referred and admitted to Hazarate Raoul Allah Hospital in Tehran, Iran. The patients ranged in age from 55 to 75 and met the study criteria prior to entering the research study. The patients were randomly divided into two groups – control or experimental (n=12 per group). After completing exercises (laughter yoga), post-evaluation of anxiety and sleep quality of patients in both groups were conducted using questionnaires. For normalization of research data, the Mann-Whitney nonparametric test was used. Statistical analyses were conducted using the SPSS software, with the statistically significant level set at $P<0.05$. **Results:** The Mann-Whitney tests indicated that there was a significant difference between the average stress change as well as sleep quality in patients suffering from Parkinson's disease (versus control subjects) following laughter yoga exercises. Indeed, regarding sleep quality laughter yoga was only effective on the subjective quality of sleep and latency in sleeping. There was no observation of a significant effect on the duration of sleep, sleep efficiency, sleep disturbances, use of sleeping pills, or daily functions of the patients. **Conclusion:** The results of the present study demonstrate that laughter yoga exercises can reduce anxiety and improve sleep quality in patients suffering from Parkinson's disease. As a result, laughter yoga exercises may be beneficial as a complementary therapy with standard treatment methods to reduce anxiety and improve sleep quality in patients with Parkinson's.

Keywords

Anxiety, laughter yoga, Parkinson's disease, sleep quality, yoga

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Introduction

Parkinson's disease is a chronic and progressive central nervous system disorder. It is classified among the motor system disorders (Yektamaram, 2010) which mostly affects elderly individuals (Yousefi, 2010) and is a common cause of disability in this age group (Afshar and Ghandehari, 2006). Movement disorders are neurological conditions which affect the control of movements. Activities such as walking or sipping a cup of tea may be difficult. In some cases, people cannot relax their bodies and some parts of their body remain in constant motion (Emsaki, 2010). British doctor James Parkinson was the first to describe the disease in 1817; he called the disease "shaking paralysis" and today it is known as Parkinson's disease (Abedzadeh, 2012).

In 1960, researchers found that the cause of this disease is a dysfunction in a particular area of the brain. Notably, the brain is unable to produce the chemical substance dopamine, a neurotransmitter which controls body muscle activities (Yaktamaram, 2009). Generally, Parkinson's disease occurs because of the reduction or loss of a major part of the nerve cells that produces dopamine in the region of the brain called the substantia nigra. Without dopamine, the brain cannot send motor messages (Yektamaram, 2010) leading to bradykinesia, tremors, mental deterioration and other dysfunctions of the automatic nervous system (Najarian, 2008).

Furthermore, psychological problems such as depression, anxiety, self-doubt, sleep disturbance, fear and shame can result from Parkinson's disease (Abedzadeh, 2012). Parkinson's disease has been seen in patients worldwide, affecting all ethnic groups and social classes (Moshfeghi, 2010). While many studies estimate the prevalence of the disease to be similar for men and women, some have reported it to be slightly more common (3:2 ratio) in men than women (Abargouei Azizi, 2011). The cause of this disease is still not fully understood but reports suggest an association with genetic factors (to a lesser extent) and environmental factors (to a greater extent), including agricultural jobs, drinking well water, village life and exposure to pesticides (Huang et al., 2014).

The main neuropathological sign of Parkinson's disease is destruction of dopamine-producing cells in the substantia nigra of the mid-brain. The decrease of dopamine levels and subsequent disruption of balance of dopamine and acetylcholine gives rise to a variety of movement disorders (Hartmann, 2005). In fact, clinical signs (e.g. movement disorders) of the disease are observable when loss of about 80% of dopamine-producing cells in the mid-brain occurs and when neurotransmission in the basal ganglia of the brain is disrupted. The most prominent movement dysfunctions of Parkinson's patients are reduced balance, loss of balance, lack of postural control and progressive reduction in the speed and range of motion (Morris, 2000). With an increased risk of falling, elderly patients with Parkinson's are prone to fractures, dislocations and serious soft

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tissue damages (Robinson et al., 2005). In terms of physiology, the "balance" referred to above is defined as the interaction between levels of control mechanisms of balance; with respect to biomechanics, the "balance" is defined as the ability to maintain and return the center of gravity of the body within a stability that is determined by the base of support (Bellew et al., 2003). Postural instability, thus, can occur as a result of decreased muscle strength and in combination with other complications which result from the destruction of dopamine-producing cells in the basal ganglia (Tinetti, 2003).

Researchers have suggested that the main cause of balance problems in Parkinson's patients is the impairment of excitation/inhibition in the basal ganglia (which also impacts downstream effects through direct and indirect means) (Shannon, 2004). On the other hand, being sick and/or elderly can increase the complications of this disease (Dibble et al., 2006). With the onset of old age, changes occur in the musculoskeletal system, vestibular system, sensory system and visual system. The changes in the metabolic and physiological systems involved in balance can put elderly individuals at risk for serious injuries related to lack of balance, including fractures and long-term disabilities.

Researchers have categorized factors which affect postural control deficits in older adults into two categories: external (foreign) and internal (domestic) factors. External factors can be uneven ground and use of inappropriate shoes. Internal factors include dysfunctions of the physiological systems of the body (e.g. decreased muscle strength, decreased range of motion, and/or reduction of visual, vestibular and proprioceptive senses) (Giroux, 2007; Lord, 2003). Thus, aging and inactivity may lead to enhanced aggravation of primary and secondary symptoms in patients. There is abundant evidence which show that the number of falls by Parkinson's patients is significantly higher than those for healthy, elderly individuals (Nelson et al., 2002).

At present, elderly people constitute 7% of the population. Within the next 20 years, this percentage will expected to double; in 30-40 years the majority of the population will be elderly people (Heydari et al., 2010). With the elderly population expected to rise dramatically worldwide, so too is the number of patients expected to suffer from Parkinson's disease (Giroux, 2007). Due to the progressive process of Parkinson's disease in the absence of controls, everyday problems of these patients will be increased and the tangible outcomes are movement disorders, psychological problems and economic problems for society (Abargouei Azizi, 2011; Morris, 2000).

Depression and anxiety are two times more likely to occur in individuals recently affected by Parkinson's disease than in healthy individuals. The tremors and movement disorders caused by Parkinson's are well-known, but the disease actually begins in the brain, affecting various chemical compounds which trigger, initially, sleep dysfunctions and mild forms of depression. In fact, sleep disorders are commonly seen in patients suffering from Parkinson's disease. Studies show that the prevalence of sleep disorders in Parkinson's disease is 60 to 98%

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(Covassin et al., 2012). This figure is higher than the prevalence of this disorder in people not suffering from Parkinson's disease in the same age and sex demographics (Scheller et al., 2008).

Parkinson's patients often experience sleep disturbances, excessive daytime sleeping, delay in falling asleep, and difficulty in maintaining sleep (Iranzo de RA, 2011). In addition, pulmonary disorders during sleeping, restless legs syndrome, mood and behavioral disorders, and rhythmic leg movements in sleep are common problems in the patients (Margis et al., 2009). Despite the obvious sleep disorders in these patients, studies have rarely addressed or evaluated them (Naismith et al., 2010). To date, various questionnaires have been prepared to assess the presence or absence of sleep disorders in order to provide treatment guidance. Indeed, treatment of non-motor disorders can improve the patient's quality of life (Najafi et al., 2012). The cause of insomnia in Parkinson's disease is multifactorial and includes older age, nocturnal motor symptoms, psychological disorders (including depression and hallucinations), and pharmacological effects.

The relationship between Parkinson's disease and severity of sleep disturbance has been studied and reported (Najafi et al., 2012). However, another study evaluating sleep quality in patients suffering from Parkinson's disease showed no significant correlation between the disease and duration or severity of sleep disturbance (Moshfeghi, 2010). In another study, sleep tests on patients with Parkinson's disease were conducted; the study conclusion was that the most common symptoms in these depressed patients were turmoil (43.2%), anxiety (43.3%), and irritability (40.1%) (Abedzadeh, 2012). Patients suffering from Parkinson's disease often experience feelings of anxiety or fear of attacks. Mood changes may also occur due to changes in drug levels (Soleimani, 2015). The most obvious manifestation of mental problems in patients suffering from Parkinson's disease is anxiety and depression, which are caused by physical symptoms and the resulting limitations associated with those. Tremors, slow movements and difficulty of movement can cause social isolation of the patient. Abnormal gait, trapped legs while walking, falling, problems with speech, and change in the patient's voice can all create a feeling of embarrassment in the patient, thereby reducing their motivation and willingness to participate in social activities (Pierce, 2008). Overall, these factors can affect the patient's quality of life. However, use of complementary therapies in combination with standard therapies may improve quality of life of individuals with Parkinson's.

In addition to drug therapy, exercise and physical activity can be used as complementary therapies (Keykhai Hosseinpour, 2013). Participation in sports is a beneficial means to achieve health and well-being. Engagement in exercise leads to physical, mental and social health. Indeed, physical activity/exercise is one of the main ways to prevent, delay or treat problems caused by the aging process, and has a profoundly positive impact on improving the quality of life of elderly people (Khorsand, 2016; Shaumway cook, 2007).

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Of the exercises, "laughter yoga" is a relatively new complementary therapy with beneficial effects. Laughter yoga was invented in 1995 by a Hindi physician named Madan Katarya. It combines the standard yoga breathing exercises with laughing exercises, and includes a variety of fun sports too (Pezeshki, 2012). Laughter is an emotional reaction that affects human life and social life in a positive manner, and has characteristics that distinguish it from other emotional reactions (Pezeshki, 2012).

Extensive research from the past two decades across various countries has proven that laughter has a positive effect on the body and is involved in strengthening the immune system. Scientists have also found that laughter has a preventive and therapeutic value (Kataria, 2004). Laughter yoga includes mind-body techniques and combines different methods of laughing with breathing exercises (Hasan and Hasan, 2009; Keykhai Hosseinpour, 2013). People who are regularly practicing laugh yoga exercises have experienced improvements in their health, mental outlook and energy level (Pezeshki, 2012).

Studies have shown that when someone pretends to laugh or be happy, the body produces chemicals (e.g. dopamine, serotonin, etc.) that induce a state of happiness (Kataria, 2004). Thus, the laughter is powerful in inducing physiological changes in the body. According to the principle "motion creates emotion", if one puts his/her body in a state of happiness, the mind will follow to a happy state (Kataria, 2004). Currently, the increase in population of elderly people (due to a reduction in birthrate, improvement of health and increased life expectancy) has garnered greater focus on the problems of the elderly (Abedzadeh, 2012).

Aging is a natural and inevitable process that affects all biological and psychological aspects of humans. Growth and maturity are the center point of childhood and youth hood. During adulthood, particularly during middle age and elderly age, most physical and mental functions decrease or atrophy due to aging. However, a sedentary lifestyle also accelerates the aging process. Physical, psychological, social and economic problems in old age often increase by 2-fold (Abedzadeh, 2012). Due to the growing elderly population in the world, according to estimates by the mid-21st century the number of the elderly is projected to reach 3.1 billion. Thus, it is critical to find solutions to health issues (e.g. Parkinson's disease) of this important age demographic.

Due to the close relationship between body and mind, it is clear that declining physical abilities along with increasing social/economic problems in old age can create a fertile ground for physical and mental illnesses. Parkinson's and Alzheimer's are among the most common diseases. Although the motor ability of patients is affected, they predominantly suffer from cognitive and behavioral impairment. Depression, dementia and mental disorders have a major impact on the quality of life for both patients and their families (Abedzadeh, 2012). Laughter yoga, through release of neurotransmitters from brain cells, can help induce feelings of happiness and potentially alleviate depression. According to

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modern medicine, disease originates from our minds (i.e. emotional thoughts and overall state of mind). Accordingly, it may be very beneficial to do laughter yoga exercise programs as a complementary step to treat the well-being of patients suffering from Parkinson's (Keykhai Hosseinpour, 2013).

Generally, the treatment of Parkinson's disease consists of three parts: surgery, medication and rehabilitation. Following selection of treatment plan, a detailed history of disease and clinical or para-clinical evaluations are conducted. Based on review of the literature on the role of treatment options for mental disorders in people with Parkinson's, the interventions/treatments are mainly pharmaceutical, nutritional and physiological; the role of physical activities and different sport activities in the treatment of Parkinson's have been less studied (Abedzadeh, 2012). As aforementioned, laughter exercises can impact organs and muscles, strengthen the immune system, induce blood biochemical changes, and affect oxygen; all of these play a significant role in the potential prevention and treatment of Parkinson's disease (Pezeshki, 2012). Therefore, we postulated that problems (e.g. depression, anxiety, loss of confidence, and sleep disorders) experienced by Parkinson's patients may be improved by laughter yoga exercises as a complementary treatment. We hypothesized that a course of laughter yoga exercises might improve anxiety and sleep quality of patients suffering from Parkinson's disease.

This study aimed to determine the effect of laughter yoga exercises on the severity of anxiety in patients with Parkinson's disease; and to determine the effect of laughter yoga exercises on sleep quality of patients with Parkinson's disease.

Materials-Methods

Methodology

This study was done with the purpose of studying a course of laughter yoga exercises on anxiety and sleep quality of patients suffering from Parkinson's.

Patients

For the present study there were initially 30 Parkinson's patients who were referred to Hazarate Raoul Allah hospital in Tehran, Iran. Patients ranged in age from 55 to 75 years old and each met the study requirements before entering into the research study.

Groups of investigation

Parkinson's disease is classified as Stage 1, 2 or 3, according to the Hoehn and Yahr Scale (H&Y). Parkinson's patients without chronic heart and respiratory disease, without open surgery in the inner region in the last six months, and

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without high blood pressure who voluntarily participated in this study were randomly divided into two groups of 15. One group was the experimental group (laughter yoga exercises) and the other was the control group (no laughter yoga exercises). From those individuals, 6 were removed from the study due to lack of continuous training, setting the machine Deep brain stimulation (DBS), and withdrawal for work purposes. After exclusion of these 6 patients, the final study consisted of 12 patients in the experimental group and 12 patients in the control group.

The voluntary participation of Parkinson's patients as subjects in the study was reviewed and approved by physicians. Notably, before the study was initiated subjects from both groups agreed by written consent to participate in the research study; those in the appropriate group(s) agreed to engage in laughter yoga classes. Also, before the start of the study, all executive items were approved by a committee of the University University Research Committee (Islamic Azad University of Karaj).

Laughter yoga exercises

Firstly, as a pre-test, the anxiety and sleep quality of patients suffering from Parkinson's disease in both the experimental and control groups, were measured by the anxiety inventory of Beck (1988) and the sleep quality inventory of Pitezbourg (1989) (PSQI), respectively. Then the treatment group, in addition to standard medical treatment, performed laugher yoga exercises under the supervision of a laughter yoga instructor for 8 weeks (2 sessions per week, 45 minutes per session). Meanwhile, patients in the control group received their standard medical treatment and continued their typical daily activities but did not practice any laughter yoga exercises.

Statistical analysis

After completing the laughter yoga exercises, as a post-test, the anxiety and sleep quality of the patients in both experimental and control groups were measured using questionnaires. To normalize the research data, the Mann-Whitney nonparametric test was used. As well, all the analyses was done at a significance level of ($P<0.05$) using SPSS software.

Results

The Table 1 shows the mean and standard deviation of all variables in the pre-test evaluation, post-test evaluation, and the corresponding difference of pre-test and post-test values for the practice (experimental) and control groups.

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Table 1. Mean and standard deviation of research variables of patients with Parkinson's disease

Variable	Group	Pre-test	Post-test	Difference of Pre-test & Post-test
Anxiety	Practice	21.5±7.4	1.86±6.6	-2.8±3.1
	Control	20.9±5.9	21.46.4±	0.50.79±
Sleep quality	Practice	9.414.6±	7.5±4.1	-1.9±1.3
	Control	8.5±4.1	9.25±5.1	0.75±1.2
Subjective quality of sleep	Practice	1.83±0.5	1.16±0.5	-0.66±0.4
	Control	1.330.4±	1.41±0.66	0.08±0.2
Delay in falling asleep	Practice	1.66±0.9	1.08±0.9	-0.580.5±
	Control	1.16±1.1	1.251.1±	0.080.28±
Sleep duration	Practice	1.58±1.1	1.51.08±	-0.08±0.2
	Control	1.41±1.08	1.51.1±	0.08±0.6
Amount of sleep efficiency	Practice	11.3±	0.75±1.2	-0.25±0.4
	Control	0.831.02±	0.911.08±	0.08±0.51
Sleep disorders	Practice	1.58±0.66	1.41±0.51	-0.16±0.3
	Control	1.5±0.52	1.83±0.71	0.330.4±
Use of sleep medications	Practice	0.58±1.1	0.581.1±	0
	Control	1.33±1.4	1.41±1.5	0.08±0.2
Daily functioning disorders	Practice	1.16±0.93	1±0.73	-0.16±0.5
	Control	0.91±1.1	0.91±1.1	0.00±0.4

Table 2 shows the relative frequency of gender; it can be seen that 58.3% of the participants were men and 41.7% were women. The Mann-Whitney test results in Table 3 show that there is a significant difference between the average change in anxiety of patients suffering from Parkinson's disease in the laughter yoga practice (experimental) group (M=-2.83) versus the control group (M=0.50) (U=136, Z=3.76, P=0.000). Thus, the null hypothesis is rejected; in other words, a course of laughter yoga exercises led to a significant decrease of anxiety in patients suffering with Parkinson's.

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Table 2. The relative frequency of gender in the study participants

Gender	Frequency	Relative frequency
Men	14	58.3
Women	10	41.7

Table 3. Results of Mann-Whitney test on anxiety

U	Z	Sig.
135	3.76	0.000

The Mann-Whitney test results depicted in **Table 4** show that there is a significant difference between the average change in sleep quality of patients suffering from Parkinson's disease in the laughter yoga practice (experimental) group (M=-1.91) versus the control group (M=0.75) (U=138, Z=3.88, P=0.000). Thus, the null hypothesis rejected; in other words, a course of laughter yoga exercises led to a significant increase of sleep quality in patients with Parkinson's. Note that on the basis of scoring, the lower the sleep quality scores the better the sleep quality.

Table 4. Mann-Whitney test results of sleep quality

U	Z	Sig.
138	3.88	0.000

Discussion

The Mann-Whitney test results in **Table 2** demonstrate that there is a significant difference between the average change in anxiety in patients with Parkinson's in the laughter yoga practice (experimental) group versus the control group. In other words, the course of laughter yoga exercises led to a significant reduction in the anxiety of patients suffering from Parkinson's disease. According to the literature, these results are consistent with study results of (Badr, 2014; Bagheri, 2011; Behzadi, 2010; Bennett et al., 2003; Eftekhari, 2004; Hassed, 2001; Hirosaki et al., 2013; Keykhai Hosseinpour, 2013; Kheirandish, 2014; Moshfeghi,

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2010; Shahidi, 2008; Sook and Hee, 2011). However, they differ from the study results of Omrani (2010).

As the results of our study are consistent with the aforementioned studies, it would seem that the predominant mechanism by which laughter influences anxiety is through its ability to establish and sustain a positive emotional state. During a state of anxiety, the adrenal gland frees corticosteroid hormones, which are converted to cortisol in the bloodstream. It is cortisol that increases in response to stress. Brouk (1998) believed that positive emotions such as laughter can reduce the ordinary stress response and as a moderator, amend sympathetic stimulation after stress (Shahidi, 2008). Keykhai Hosseinpour (2013) conducted a research on the impact of laughter yoga exercises on the motor and mental factors of patients suffering from Parkinson's (Keykhai Hosseinpour, 2013). The results of his study indicated that laughter yoga exercises have a positive impact on reducing depression, thereby improving the patient's quality of life and increasing motion performance, flexibility and pain reduction. His study concluded that Parkinson's patients, as they have a lack of dopamine and serotonin, can use laughter yoga which help secrete hormones that help to reduce depression.

Depression and anxiety are among the most common mental problems of patients suffering from Parkinson's. They arise due to the physical symptoms of the disease and also from the patient's disability. To combat this, laughter can be induced to provide benefits to the overall health status. Health benefits obtained of laughter yoga including physical, mental and emotional stress management. When stress decreases, the immune system automatically becomes stronger. Laughter also increases the oxygen supply to cells of the body and increases blood circulation, thereby creating a positive state of health.

Given that the body can be influenced by a series of hormonal and physical changes which cause damage to the patient, any strategy that regularly reduces the level of stress hormones in the blood helps to increase health. Moreover, laughter is known to be a good stress inhibitor. In fact, joking and laughing can reduce the neuroendocrine hormones (epinephrine and cortisol) that are secreted in response to stress, causing the person to be calm (Keykhai Hosseinpour, 2013). Laughter is one of the best, most cost-effective and easiest ways to relieve stress and relax the muscles of the body. Laughing dilates blood vessels and transmits more blood to the farthest muscles throughout the body. Furthermore, a good laugh from the heart reduces the secretion of stress hormones, epinephrine and cortisol.

When we are laughing there is no thought in our minds; all our senses seem to be synchronized for a brief moment. We feel joy, peace and comfort (Behzadi, 2010). Also, according to the theory of emotional discharge, laughter is a socially acceptable way to release tension and stress. Provin (2000) argued that laughter in social interactions can be used as a stress relief mechanism. Spencer (according to the theory of drain excitement) believed that the emotional and

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mental turmoil produce a kind of energy that somehow must be used. He suggested that nervous excitement tended to cause muscle tension and that laughter, as a kind of physical movement, can act as a stream of various forms of nervous energy. Moreover, Spencer created the idea of laughter to remove bad potential energy through the process of daily stress management, constantly stacking energy and release of excess energy by laughing after a stressful day (Provin, 2000).

Behzadi (2010) conducted a research study with the aim of evaluating the effectiveness of Katarya laughter therapy on increasing the general health of elderly residents in a nursing home of Shahid Hasheminejhad of Ray City (Behzadi, 2010). The results of that research data showed that Katarya laughter therapy was significantly effective in increasing public safety, improving physical symptoms, anxiety and insomnia, increasing social dysfunctions, and reducing depression. According to the findings of that study, it was concluded that Katarya Laughter therapy can improve the health of residents in nursing homes. Thus, this treatment method (laughter) may be used as replacement or supplement for improving overall health of elderly in nursing home.

Hased (2001) reviewed numerous clinical studies which all demonstrated that humor and laughter can reduce stress in all situations. Laughter can affect inflammatory disorders, asthma, cancer, and heart disease. In his article, he identified several psychological impacts, including reduction of stress and anxiety, and improvement of mood, self-esteem and coping skills. In addition, Hased described a positive psychological effect on pain and an increase in the safety of certain factors, e.g. immunoglobulin A and white blood cells.

Omrani (2010) conducted a research study on the effect of music therapy and laughter therapy to reduce anxiety in women prior to surgery. That study was a quasi-experimental study with pre-test and post-test assessments. In Omrani's study, the Katal anxiety test was used to measure stress; it was found that music therapy could reduce anxiety before surgery in women but that laughter did not have any therapeutic effect on anxiety of those women. In our study, however, laughter yoga exercises led to a significant increase in sleep quality of patients with Parkinson's disease (based on the scoring of the questionnaire on sleep quality). According to the literature, our study results are consistent with results of (Badr, 2014; Behzadi, 2010; Fotouhi, 2010).

As mentioned in Introduction, the quality of sleep of those afflicted with Parkinson's is influenced by factors such as anti-Parkinson's medications, Akintik pains, dystonia, restless legs syndrome, panic attacks, anxiety and depression, parasomnia, and sleep apnea. Laughter yoga is thought to impact all those factors, thereby improving sleep quality and ultimately alleviating the disorders. Akintik pains usually occur due to lack of mobility in these patients and often lead to sleep disorders. Extreme rigidity, fever, pain in muscles and joints, headaches, and occasional pain in all parts of the body are all typical symptoms (Soleimani, 2015).

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Laughter improves health by reportedly inducing the secretion of endorphins that reduce pain and promote the feeling of happiness (Martin, 2001). In fact, laughing increases the level of endorphins, also considered to be natural painkillers. The secreted endorphins have been shown to help reduce pain in people suffering from arthritis, inflammation of the spine, and muscle spasms (Kataria, 2004; Pezeshki, 2012). Indeed, laughter is regarded as a pain management technique that can be used for most incurable diseases. People who are regularly practicing laughter therapy can secrete endorphins with a simple smile. A few minutes of real laughing can induce the equivalent results as rowing or stationary biking for 10-15 minutes (Keykhai Hosseinpour, 2013). For the elderly who are not able to exercise, laughter is indeed a good secondary treatment option (Keykhai Hosseinpour, 2013).

In addition to Akintik pains, other problems such as dystonia (i.e. involuntary muscle contractions of legs, fingers, wrists, ankles and feet) can cause painful cramps for Parkinson's patients (Soleimani, 2015). In this regard, laughter yoga can improve muscles of the face, chest and abdomen. Indeed, muscle power is important and useful for hospitalized patients and elderly people who move around in a wheelchair. Kazines (1979) described laughter as running internal organs; that is, it is effective even for muscles of the digestive system and can help speed up the rate of digestion (Keykhai Hosseinpour, 2013).

Another important advantage of laughter is decrease of muscle tension. Stress keep muscles in a contracted state. People who learn muscle relaxation methods can reach peace psychologically. In muscle relaxation methods, the therapist asks the patient firstly to perform of series of muscle contractions on his body muscles and then relax to feel the relaxation in those muscles. Laughter has been reported to decrease tension in the neck, shoulder and abdomen muscles (Keykhai Hosseinpour, 2013). Joking and laughing reduce the hormones epinephrine and cortisol (which typically rise in response to stress), thereby leading to relaxation (Keykhai Hosseinpour, 2013). As in the theory of emotional discharge, Freud believed that the release of energy is an enjoyable experience that is expressed as a laugh, thereby reducing tension and stress (Shahidi, 2008).

Behzadi (2010) conducted a research with the aim of studying the effectiveness Katarya laughter therapy on the effect of general health of elderly residents of a nursing home in Hasheminejhad of Ray City (Behzadi, 2010). Results of study showed that Katarya laughter therapy significantly increases public safety, improves physical symptoms, reduces anxiety and insomnia, and alleviates social dysfunction and depression. According to the findings of that study, it can be concluded that the method of Katarya laughter therapy is advantageous in removing negative thoughts, changing beliefs, creating positive emotional states, and reducing the symptoms of Parkinson's disease. Overall, the general health of the senior home residents was markedly improved after laughter therapy.

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Among other activities which affect the quality of sleep in patients with Parkinson's disease is respiratory disorder. One of the benefits of laughter yoga is, thus, improvement of the respiratory system. Laughter provides exercise to the lungs and chest muscles, resulting in improved vital capacity and breathing. In normal breathing when person is relaxed, there is a balance between inhalation and exhalation. In the stress and disease states, not only does breathing become more shallow and slower but the level of oxygen becomes lowered too. There is a great amount of air that remains in the lungs. By keeping the air in the lungs, oxygen content decreases and water vapor and carbon dioxide levels increase. In this case, the more favorable conditions for bacterial growth and lung infections are created.

Laughter increases ventilation and removes mucous plugs to help maintain air exchange which increases oxygen levels in the blood. In fact, when we laugh the air is completely expelled from the lungs and following that, carbon dioxide and water vapor is also emitted and replaced with oxygen. The oxygen becomes available to blood cells. The effects of laughter can benefit middle-aged people with chronic respiratory diseases, such as emphysema, and reduce the risk of infection and inflammation of the lungs (Keykhai Hosseinpour, 2013). Therefore, laughter yoga can affect quality of sleep by improving the respiratory system.

Therefore, according to the benefits of laughter yoga, which include pain relief, muscle relaxation, reduced anxiety and depression, and improved respiratory system function, it can be concluded that laughter yoga does significantly improve sleep quality- either directly and indirectly- of patients with Parkinson's disease. The questionnaire (on sleep quality) by Peter Bourg evaluated 7 areas: sleep quality, sleep latency, sleep duration, sleep efficiency rate, sleep disturbances, use of sleeping pills, and daily functioning disorders.

Research limitations

All research studies have some limitations which are important to recognize and address for future insight. In this study, the limitations were as follows:

1. The number of individuals suffering from Parkinson’s, who are willing to cooperate in the study and participate in the laughter yoga exercises was very low; this was one of the greatest limitations of the study (contributing to a low sample size of experimental and control groups).

2. There was no possibility of taking advantage of the questionnaire for patients with Parkinson's disease due to the lack of standardized questionnaires in Iran. In the beginning, some steps were taken to standardize the questionnaires by translating it and having patients fill them out, but due to lack of time taking advantage of the questionnaire in this study was not feasible.

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3. Due to the lack of accredited and essential facilities, there was no possibility of holding meetings in the hospital; all meetings were held at a house.

4. Due to general limitations for holding laughter yoga classes in the houses of the neighborhood, and despite initial agreement on the presence of the patient at the house and same time for holding the classes for women and men, it was decided that classes be held flexibly and separately, as needed.

5. Due to the age requirements, specific issues of some Parkinson's patients and restrictions on the movements of these patients, not every patient could attend the regular meetings consistently.

Conclusion

In conclusion, laughter yoga significantly improves anxiety and sleep quality of Parkinson's patients and can serve as a beneficial complementary therapy to standard therapy.

Author contribution

AZ performed data acquisition, data analysis; AS performed designed the study, data analysis and manuscript preparation; SMB performed data acquisition, and manuscript preparation. All authors approved the manuscript.

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