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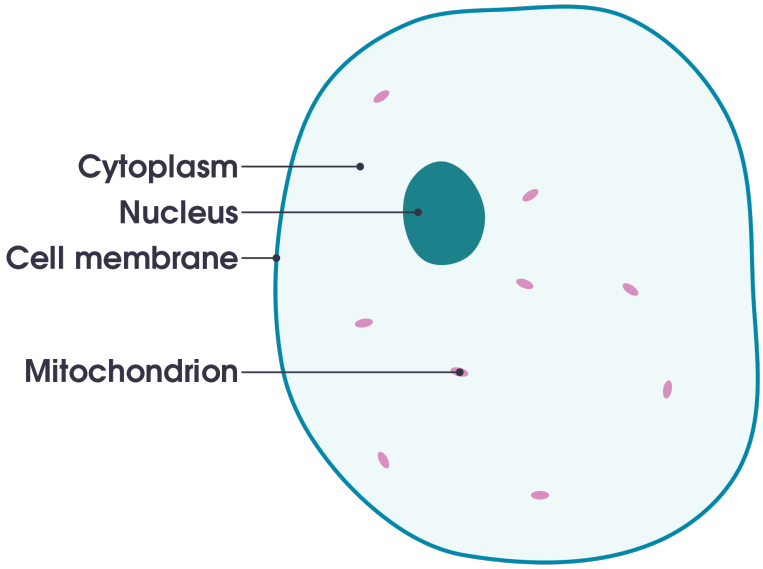

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Original Research

Dietary factors modify post-menopausal breast cancer risk: a case-control study from Turkish Cypriot population

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Abstract

Background: Being potentially modifiable risk factor of breast malignancy, the role of diet in the development of breast cancer (BC) is of great concern. As up to 40 % of cancers can be prevented through dietary strategies; therefore, this case-control study is conducted with the aim to investigate the effects of frequently used dietary factors and postmenopausal BC risk in Turkish Cypriot population. **Material and method:** Total 786 postmenopausal women including 401 histologically confirmed BC cases and 385 control, recruited from two hospitals i.e. Near East Hospital and Doctor Burhan Nalbantoglu State Hospital Nicosia, Turkish Republic of Northern Cyprus, between the month of July to December 2016. A standardized interview procedure is used and the information is collected using a structured questionnaire from participants after giving informed consent form. For data analysis, SPSS version 20 software is used. Age-adjusted odds ratios (OD) and 95% confidence interval (CI) were calculated by logistic regression before and after adjusting for potential confounding effects of other factors. **Results:** The multivariable adjusted model confirmed a 3-fold increased BC risk with daily oil use of ≥ 40 mL (OR = 3.22, 95%CI 2.01-5.17, p<0.001). And 4.1-fold increased risk was associated with 4 to 6 daily servings of sugar intake (OR = 4.19, 95%CI 1.79-9.80, p = 0.001), this risk increased to 7.5-folds (OR = 7.5, 95%CI 3.25-17.32, p<0.001) when the consumption of sugar was increased to > 6 servings per day.

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Daily 1 to 2-liter water intake was associated with 64% decreased BC risk (OR = 0.36, 95%CI 0.20-0.63, p = 0.001). While, no significant association were observed between consumption of full-fat dairy products (FFDP), olive oil, coffee intake and BC risk. Interestingly, daily 3 or more cups of tea intake were associated with 54% decreased risk of BC (OR = 0.46, 95% CI 0.22-0.98, p = 0.043). **Conclusion:** The study suggests that the risk of BC can be reduced by limiting the consumption of oil and sugar and increasing daily water intake more than a liter.

Keywords

Breast cancer, Dietary factors, Odds ratio, North Cyprus

Introduction

Breast cancer is the most prevalent malignancy in Turkish Cypriot women (Pervaiz et al., 2017). There are various established risk factors for BC worldwide including, exogenous and endogenous hormonal exposure, various reproductive factors (early menarche, late menopause, late pregnancy, not breastfeed, and being non-parous) and lifestyle factors (smoking, alcohol and exercise) in addition to high penetrant gene variants i.e. BRCA1&2, ATM, PALB2, and CHEK2) (Rudolph et al., 2016).

The role of diet in the aetiology of BC is also noteworthy as large international variations exist in BC incidence rates (Horn-Ross et al., 2002). These variations might be ascribed to the antioxidant properties of certain selected nutrients that influencing DNA mutation, DNA repair, growth factors stimulations. These nutrients may also have some anti-estrogenic effects and metabolic detoxification (Potter and Potter, 1997).

Recently, a randomized control trial among women at high risk of cardiovascular disease has provided the first evidence about the reduction of BC incidence by diet intervention. Women were randomly assigned to Mediterranean diet patron which is generally rich in plant food, fish and olive oil. About half of these women were as likely to develop invasive BC as those who were only assigned to a diet with only reduce fat intake (Toledo et al., 2015).

Dietary factors have been thought to be the main modifiable risk factors for cancer and it is estimated that up to 40% of cancers could be prevented through dietary strategies (Surh, 2003). The risk of BC is supposed to increase with

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various food nutrients that increase the circulation level of oestrogens and growth factors including insulin-like growth factors I (Potter and Potter, 1997).

In TRNC population, The Mediterranean dietary patron is increasingly changing to the western dietary patron, leading to the rise of diseases incidence including cancer. As to enhance general health and reduce the risk of BC, women can alter their diet successfully. Therefore, the purpose of this case- control study is to assess the strength of association between the consumption of various commonly used diet factors including oil, sugar, water, dairy products, olive oil, alcohol, coffee and black tea and BC risk in this part of the island. To the extent of our knowledge, this is the first epidemiological investigation on BC risk and dietary factors in this population.

Materials - Methods

Study Subjects

This case-control study was carried out in connection with our previous study on BC risk factors in North Cyprus population. The analysis comprised of total 786 menopausal women; 401 BC cases and 385 control healthy women without any malignancy. Both cases and control were recruited from two hospitals of the island i.e. Near East Hospital Nicosia and Doctor Burhan Nalbantoglu State Hospital Nicosia, TRNC between the month of July to December 2016.

Data collection

A standardized interview procedure was used for both cases and control and information regarding sociodemographic factors and the various commonly used dietary factors were collected on a detailed questionnaire after giving informed consent form. From control, questions about diet intake in the previous year were asked, while from cases in the previous year before diagnosis were asked. Furthermore, age at the time of interview of control women is noted and for cases, age at the time of diagnosis is noted.

In addition to the questions about the quantity of specific dietary factors consumption i.e. oil or fat, sugar, olive oil, water, full fats dairy products (FFDP), coffee and tea intake, questions about age, weight, height, education, income status, marital status, family history of BC, age at menarche and menopause, parity, age at first full-term pregnancy (FFP), number of children, breastfeeding (at least 1 month), oral contraceptive and HRT use, smoking status and exercise were included in the questionnaire. All information was self-reported except BMI which was based on actual measurement. The exercise was considered a 30 minutes' walk or physical activity for at least four times a week. Smoking was considered one cigarette a day for at least 6 months. A gestation period of 24 weeks or more is considered pregnancy, oral contraceptive used and HRT was

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considered the use for at least one month. Sugar consumption was considered as anything containing added sugar i.e. jam, jelly, syrup, frozen desserts, non-frozen desserts, candies, chocolate and soft drinks etc. for a serving size of 1 teaspoon (5-7grammes) and one glass of soft drink (250-300 grammes) was indicated. For FFDP i.e. butter, cheese, full-fat milk etc. serving size of 100 grammes is considered. Only frequency and not the quantity of olive oil use were asked in the food frequency questionnaire.

Analysis

The difference between socio-demographic characteristics, dietary factors and cases and control were first assessed by cross-tabulation and chi-square test. In order to assess the degree of association of potential risk from dietary factors and BC, unconditional logistic regression model before and after adjusting for potential confounders are used. The fit of the model is assessed on the basis of Pearson chi-square or Hosmer-Lemeshow goodness-of-fit statistics. Age group is not used as a potential risk for BC but is used as a confounder in the uni- and multivariable regression models. The statistical analysis was performed using SPSS statistical software version 20.

Results

The analysis confirmed that more cases than control were obese (BMI ≥ 30), single, with family history of BC, with earlier menarche, late menopause, with no parity, with no or ≤ 2 children, never breastfeed, used HRT, were smokers, physically inactive, and consumed more fatty food, more sugar and less water, less FFDP, and more likely to use alcohol. But, no significant difference was reported for education, income status, age at FFP, oral contraceptive used, olive oil used, daily coffee and black tea intakes in cases and control (**Table 1**).

In the multivariable adjusted logistic regression model, more than 3–fold increased risk of BC were reported for daily oil consumption of ≥ 40ml (OR = 3.22, 95%CI 2.01-5.17, p<0.001). A 4.1-fold increased risk were associated with 4 to 6 daily serving of sugar (OR = 4.19, 95%CI 1.79-9.80, p = 0.001), this risk increased to more than 7-folds (OR = 7.5, 95%CI 3.25-17.32, p<0.001) when daily sweets consumption was increased to > 6 servings. However, daily 1 to 2-liter water intake were found to associated with 64% decreased BC risk (OR = 0.36, 95%CI 0.20-0.63, p = 0.001) in multivariable logistic regression model. While, no significant association were observed between consumption of FFDP, olive oil, coffee intake and BC risk. Interestingly, daily 3 or more cups of tea intake were associated with 54% decreased risk of BC (OR = 0.46, 95% CI 0.22-0.98, p = 0.043) (**Table 2, Fig. 1**).

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Table 1. Socio-demographic features and potential risk factors among cases and control

Variable	Cases (n = 401)		Control (n = 385)		P-value[1] for chi-square
	n	%	n	%	
Age group					**P= 0.377**
45-54	149	37.2%	161	41.8%	
55-65	193	48.1%	170	44.2%	
≥65	59	14.7%	54	15%	
Education					**P= 0.231**
Primary	104	25.9%	110	28.6%	
Secondary	183	45.6%	178	46.2%	
Tertiary	65	16.2%	58	15.1%	
University	49	12.2%	39	10.1%	
BMI					**P< 0.001**
<25	37	9.2%	59	15.3%	
25-29.9	152	37.9%	190	49.4%	
≥ 30	212	52.9%	136	35.3%	
Income status					**P= 0.174**
< 5000TL	157	39.2%	163	42.3%	
5000-10,000 TL	226	56.4%	213	55.3%	
> 10,000TL	18	4.5%	9	2.3%	
Marital status					
Single (widow divorced)	77	10.6%	41	10.6%	**P= 0.001**
Married	324	80.8%	344	89.4%	
Family History					
No	174	43.4%	260	67.5%	**P< 0.001**
Yes	227	56.6%	125	32.5%	
Menarche Age					
12 or less	322	80.3%	166	43.1%	**P< 0.001**
> 12	79	19.7%	219	56.9%	
Age at Menopause					

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≤ 50	193	48.1%	246	63.9%	**p< 0.001**
> 50	208	51.9%	139	36.1%	
Full term pregnancy					
No	165	41.1%	83	21.6%	**p< 0.001**
Yes	236	58.9%	302	78.4%	
Age at 1st pregnancy (FFP)					
≥30 years	77	19.2%	25	6.5%	**P= 0.133**
<30 years	159	39.7%	277	71.9%	
Nil	165	41.1%	83	21.6%	
No. of Children					
No children	166	41.4%	84	21.8%	**p< 0.001**
Up to 2	128	31.9%	112	29.1%	
More than 2	107	26.7%	189	49.1%	
Breast Feeding					
Never	229	57.1%	133	34.5%	**p< 0.001**
Yes	172	42.9%	252	65.5%	
Oral Contraceptive use					
No	189	47.1%	201	52.2%	**P= 0.155**
Yes	212	52.9%	184	47.8%	
HRT					
No	244	60.8%	280	72.7%	**p< 0.001**
Yes	157	39.2%	105	27.3%	
Smoking					
No	170	42.4%	229	59.5%	**P< 0.001**
Yes	231	57.6%	156	40.5%	
Exercise					
No	233	58.1%	162	42.1%	**P< 0.001**
Yes	168	41.9%	223	57.9%	
Oil/fats consumption/day					
< 20ml	88	21.9%	123	31.9%	**P< 0.001**
20-40 ml	121	30.2%	173	44.9%	

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> 40ml	192	47.9%	89	23.1%	
Sugar consumption, servings/day					
≤ 3	11	2.7%	52	13.5%	**P< 0.001**
4-6	137	34.2%	170	44.2%	
> 6	253	63.1%	163	42.3%	
Water consumption/day					
<1 litre	89	22.2%	39	10.1%	**P= 0.010**
1-2 litre	148	36.9%	168	43.6%	
> 2 litre	164	40.9%	178	46.2%	
FFDP* use/day					
Never	30	7.5%	25	6.5%	**P= 0.031**
1-3 servings	309	77.1%	275	71.4%	
≥4	62	15.5%	85	22.1%	
Olive oil use/day					
Never	49	12.2%	44	11.4%	**P= 0.959**
Some time	179	44.6%	177	46.0%	
Daily	173	43.1%	164	42.6%	
Alcohol consumption/day					
Never	274	68.3%	314	81.6%	**P< 0.001**
≤ 300 ml	44	11.0%	27	7.0%	
> 300 ml	83	20.7%	44	11.4%	
Daily Coffee consumption/day					
Never	34	8.5%	29	7.5%	**P= 0.829**
1-2 cups	218	54.4%	213	55.3%	
≥3 cups	149	37.2%	143	37.1%	
Daily black tea consumption /day					
Never	40	10.0%	26	6.8%	**P = 0.209**
1-2 cups	236	58.9%	231	60.0%	
≥3 cups	125	31.2%	128	33.2%	

Notes: 1. *P-value of the chi-square test for independence.*
** Full fats dairy Products.*

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Table 2. Uni- and multivariable logistic regression and adjusted odds ratios with 95% CI.

Variables	Univariable		p-value[2]	Multivariable		p-value[2]
	OR1	(95% CI)		OR3	(95% CI)	
Oil/fats consumption/day						
(≤ 20ml)	1					
(21-40 ml)	0.99	(0.69-1.42)		0.98	(0.62-1.54)	0.83
(> 40ml)	3.08	(2.12-4.48)	<0.001	3.22	(2.01-5.17)	<0.001
Sugar consumption, servings/day						
≤ 3	1					
4-6	3.92	(1.96-7.81)		4.19	(1.79-9.80)	0.001
> 6	7.60	(3.84-15.03)	<0.001	7.50	(3.25-17.32)	<0.001
Water consumption/day						
<1 litre	1					
1-2 litre	0.38	(0.24-0.58)		0.36	(0.20-0.63)	
> 2 litre	0.39	(0.25-0.61)	<0.001	0.37	(0.21-0.64)	0.001
FFDP* use/day						
Never	1					
1-3 servings	0.94	(0.54-1.64)		0.94	(0.47-1.89)	0.86
≥4	0.61	(0.32-1.14)	0.06	0.53	(0.24-1.17)	0.119
Olive oil use/day						
Never	1					
Some time	0.90	(0.57-1.42)		1.13	(0.62-2.06)	0.67
Daily	0.78	(0.59-1.48)	0.89	1.37	(0.75-2.51)	0.30
Daily Coffee intake						
Never	1					
1-2 cups	0.87	(0.51-1.49)		0.67	(0.34-1.36)	0.27
≥3 cups	0.90	(0.52-1.55)	0.89	0.61	(0.29-1.26)	0.18
Daily black tea intake						

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Never	1					
1-2 cups	0.67	(0.40-1.14)		0.51	(0.25-1.01)	0.057
≥3 cups	0.65	(0.37-1.14)	0.30	0.46	(0.22-0.98)	0.043

***Note: 1**. Univariable odds ratios adjusted for age. 2. P values for the difference between binary variables or p value for linear trend across ordinal categorical variables. 3. Multivariable odds ratios adjusted for age, BMI, family history, menarche age, age at menopause, parity, Breast feeding, smoking, exercise and HRT. * Full fats dairy Products.*

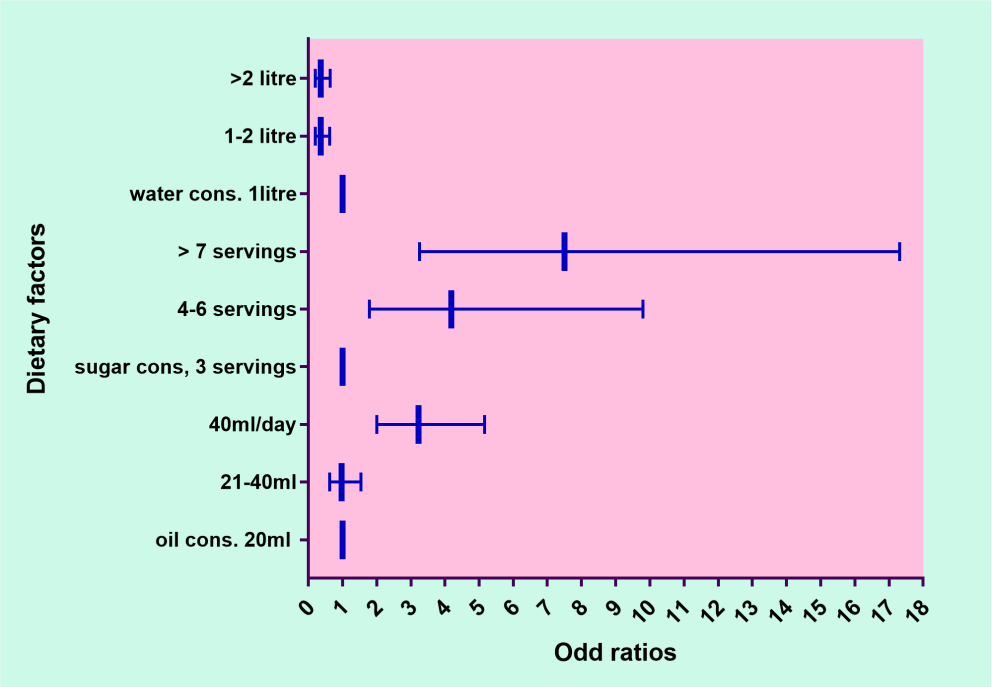

Figure 1. Odds ratios and 95% Wald confidence interval for BC risk.

Discussion

The key purpose of the present study was to evaluate the strength of association of various commonly used dietary factors and BC risk in TRNC. Only post-menopausal cases and control women were included in the study since diet has been indicated to have a different influence on pre and post-menopausal BC (Psaltopoulou et al., 2011). It is to be noted that all the factors used here are self-reported excluding BMI. Of the studied dietary factors, we found that consumption of excess oil/fats and sugar were associated with increased BC risk.

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Also, daily water intake of more than one liter was associated with reduced BC risk.

Our results are in consistence with other studies. For instance, a prospective study on a large heterogeneous population of European women has shown the high fats diet to increase BC risk, particularly high saturated fat intake increases the risk of receptor-positive BC (Sieri et al., 2014). However prospective observational studies on association between fat consumption and BC risk have inconsistent findings, but many studies have confirmed that this association may be due to unspecific quantification of fat intake (Prentice et al., 2013) despite the fact that, other comprehensive study did not confirm this (Key et al., 2011), the cause of inconsistencies may be due to the fact that specific type of fat (not of the total fat) is linked only to some BC types. In nested case-control study within the French EPIC cohort, it is shown that trans fatty acids increase the risk of BC (Chajès et al., 2008). Evidence supports that the high fats intake increases the concentration of bio-available serum sex hormones (Parry et al., 2011), which is the main risk factor for BC. It also enhancing reabsorption in the intestine and increasing blood fatty acid level that may increase free estrogenic concentration in blood serum (Rock et al., 2004). The role of dietary fats in cancer tumor formation are given in a recent study in Nature. The study has shown the effects of high fats diet on the intestinal stem cells lineage and has established a mechanism by which progenitor cell when exposed to high fats diet become more stem cells like and prone to oncogenic transformation (Beyaz et al., 2016). Same is the case of dilatory sugar intake. Recently, in a multiple mouse model study, the impacts of dietary sugar on mammary gland tumor development and the mechanism involve were investigated, and found that sucrose intake comparable to the amount of western diet led to increasing tumor growth and metastasis by inducing 12-lipoxygenase signaling, when compared with non-sugar starch diet (Jiang et al., 2016). Furthermore, our study showed that daily 1-2 liter water intake decreased the risk up to 64%, an only small increase of 1% were observed with further increased water intake. Malignancies mostly studied in connection with water include bladder and colorectal cancers and only rarely with BC (Michaud et al., 1999). Conversely, a hospital-based study on diet and beverage consumption and BC risk by Stookey et al observed that water intake is significantly associated with 69% reduced BC risk (adjusted odds ratio of 0.31, 95%CI, 0.13-0.72) (Stookey et al., 1997).

No significant association between BC risk and consumption of FFDP and olive oil were reported. In contrast, the majority of case-control studies carried out in Mediterranean countries consistently concluded an inverse association of BC risk and olive oil consumption (Sieri et al., 2014). It is reported that the hydrocarbon squalene compound in olive oil, exerts a beneficial effect on oxidative stress and DNA damage in mammary epithelial cells (Warleta et al., 2010), polyphenols from olive oil may have a possible role in the prevention of BC (Casaburi et al., 2013). Being a part of Mediterranean island, olive oil and dairy products consumption are frequent in TRNC. Therefore, large follow-up study may

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provide an appropriate finding of the effect of olive oil and FFDP use on BC risk in this population.

Although coffee and tea consumption showed no significant association with BC risk in this study, it is reported that a daily 3 or more cups of black tea were found to associated significantly with decreased BC risk in the adjusted model. This association was not significant in the uni-variable model. As one of the most commonly proposed pathways leading to carcinogenesis is oxidative DNA damage which is strongly determined by body iron storage (Toyokuni, 2009), coffee and tea are supposed to inhibit iron absorption in the small intestine, and subsequently decreasing oxidative stress through reducing stored iron in the body (Morck et al., 1983). Recently it has been confirmed that coffee and not tea was associated with lower level of oxidative DNA damage and low body iron storage in women (Hori et al., 2014). There is inconsistency in the association of BC risk and intake of coffee and tea, in the published literature (Harris et al., 2012). Furthermore, a large meta-analysis indicated no association of black tea intake and BC risk (Nie et al., 2014).

Conclusion

It is concluded that there is a strong association between consumption of fats, sugar and BC risk. Water intake has beneficial effects on the primary prevention of BC. The most appropriate approach against cancer is the preventive strategies. To the best of our knowledge, this is the first report to validate an association of BC risk and dietary factors in this part of the island. Hopefully, these findings will give new insights in BC epidemiology. Nevertheless, these results need confirmation by long-term prospective studies.

Abbreviations

BC: Breast cancer

BMI: Body Mass index

CI: Confidence interval

FFDP: Full-fat dairy products

HRT: Hormonal replacement therapy

OD: Odds ratios

SPSS: Statistical Package for Social Sciences

TRNC: Turkish Republic of Northern Cyprus

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Author contribution

RP participated in the conception of the study, data acquisition, interpretation and drafting the manuscript. ÖT participated in the statistical analysis and revising the article. HB participated in the design of the study and revising the article. NS participated in the conception of the study and critically revising the article for important intellectual content.

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Original Research

Assessment the association between liver cancer incidence and mortality rate with human development index in the European countries in 2012

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Abstract

Background: Liver Cancer (LC) is one of the most common cancers in the worldwide. This cancer is considered as the fifth most common cancer in male and the ninth most common cancer in female. However, socioeconomic factors and morbidity and mortality of cancer are linked by sophisticated and flexible pathways. We were investigated the association between incidence and mortality of LC with the Human Development Index (HDI) in European countries in 2012. **Methods:** This study was an ecologic study in European countries for assessment the correlation between Age-Specific Incidence Rate (ASIR) and Age-Specific Mortality Rate (ASMR) of LC with HDI and its details including: Life expectancy at birth, Mean years of schooling and Gross National Income (GNI) per capita. We used of Pearson correlation method for appraisement the association between HDI and its components with ASIR and ASMR. Data of study was analyzed by SPSS15 statistical analysis software; the significance level of the tests was considered P<0.05. **Results:** Generally in 2012, European countries have recorded 63,462 new cases of LC, crude rate was 8.6 and ASIR was 4.3 per 100,000. On the other hand in Europe countries in 2012, 62,191 cases of deaths were occurred due to LC, crude rate was 8.4 and ASMR was 3.9 per 100,000. Strong positive Correlation was observed between ASIR and ASMR ($r = 0.848$; $P \leq 0.001$). HDI have weak negative correlation with ASIR of LC ($r = - 0.194$; $P = 0.230$), and strong negative correlation with ASMR of LC($r= - 0.515$; $P = 0.001$). **Conclusion:** Increase in the human development index was associated with reduce in incidence and mortality of LC.

Keywords

Liver Cancer, HDI, Incidence, Mortality, Europe

Introduction

Liver cancer (LC) is one of the most common cancers in the worldwide (Wei et al., 2014). This cancer is considered as the fifth most common cancer in male and the ninth most common cancer in female (Hall and Wild, 2003). Estimates from the year 2012 indicate that 782,451 new cases of LC occurred worldwide, including 554,369 cases in male and 228,082 cases in female. Also in this year, 745533 case of death of LC were observed in worldwide, including 521,041 cases in male and 224,492 cases in female (Ferlay et al., 2014). This tumor accounted for 5.6% of all human cancers (7.5% among male and 3.5% among female) in (Ferlay et al., 2001).

In the worldwide, the areas with high Age Standardized Incidence Rate (ASIR per 100,000) of LC are located in Eastern Asia (ASIR= 20.9) , Intermediate rates

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happen in Africa (ASIR= 8.9) and Middle Africa America (ASIR= 8) and the lowest rates are in South-Central Asia (ASIR= 2.9) and Northern Europe (ASIR= 3.1) (Ferlay et al., 2014).

In the Europe, ASIR for LC in 2012 was equal to 4.3 per 100,000, with ranges from a relatively low rate in the Netherlands (ASIR=1.6) to the high rates in Republic of Moldova (ASIR=8.5). Also, Age Standardized Mortality Rate (ASMR per 100,000) for this cancer in the Europe in 2012 was 3.9 per 100,000, with ranges from a relatively low rate in Norway (ASMR=1.7) to the high rates in Republic of Moldova (ASMR=9.5) (Mohammadian et al., 2015). LC is ordinarily a problem of the less developed countries (Ferlay et al., 2014). Extra than 85% of LC new cases take place in developing countries which do not have suitable detection and treatment services (Ferlay et al., 2010). LC is the second most common cause of mortality from cancer in worldwide, estimated to be responsible for closely 746,000 deaths in 2012 (9.1% of the whole death of cancer). The prognosis for LC is very low, so general ratio of LC mortality to incidence is around 0.95 (Ferlay et al., 2014).

Socioeconomic factors are connected with cancer incidence and mortality by intricate and variable pathways. One of the most important known meters of socioeconomic factors is Human Development Index (HDI). According to HDI, countries are assigned into four categories: countries with low HDI (HDI≤0.5), countries with Medium HDI (0.8> HDI>0.5), countries with high HDI (HDI≥0.8) and countries with very high HDI (HDI≥0.9) (Bray et al., 2012).

In the study that conducted in Asian countries about relationship of incidence and mortality of LC with HDI, negative correlation was observed between ASIR and ASMR with HDI, But this relationships wasn't significant (Mohammadian et al., 2015). Similarly, relationship of HDI and incidence and mortality from other cancers were examined in other studies (Ghoncheh et al., 2015; Hassanipour-Azgomi et al., 2016; Mohammadian et al., 2015; Pakzad et al., 2015a, b; Pakzad et al., 2016; Pakzad et al., 2015c; Rafiemanesh et al., 2015). However, according to our information, no study has been done still regarding the association between the ASIR and ASMR of LC with HDI in European countries; therefore in this study we investigate the association between incidence and mortality of LC with HDI in European countries in 2012.

Materials - Methods

This study was an ecologic study in European countries for appraisal the relationship among Age-Specific Incidence Rate (ASIR) and Age-Specific Mortality Rate (ASMR) with Human Development Index (HDI) and its details including: Life expectancy at birth, average years of schooling and Gross National Income (GNI) per capita. Data about the ASIR and ASMR for every European countries for year 2012 had gathered from GLOBOCAN project that is

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available in (http://globocan.iarc.fr/Default. aspx) (Ferlay et al., 2015). Also data about Human Development Index had extracted from Human Development Report 2013 (Malik, 2013).

Details of Methods for estimate the Age-specific incidence rate (ASIR) and Age-specific mortality rate (ASMR) in GLOBOCAN project have been provided in previous reports (Ferlay et al., 2010; Ferlay et al., 2015; Foulkes and Cooney, 2010; Pakzad et al., 2015b; Pakzad et al., 2016).

Statistical analysis

In current report, we used of Pearson correlation method for assessment of correlation between Age-specific incidence rate and Age-specific mortality rate of LC by human development index and its details. All reported ASIR and ASMR were per 100,000. Statistical significance was considered as $P<0.05$. All P-values reported in study are two-sided. Also, Statistical analyses were performed using SPSS (Version 16.0, SPSS Inc.).

Results

Overall, European countries have recorded 63,462 cases of LC, Crude Rate was 8.6 and ASIR was 4.3 per 100,000. The five countries with the highest ASIR of the LC were Republic of Moldova (ASIR=8.5), Italy (ASIR=7.1), Luxembourg (ASIR=6.7), France (ASIR=6.6), and Spain (ASIR=5.9), respectively. Also, five countries with the lowest ASIR of the LC were The Netherlands (ASIR=1.6), Iceland (ASIR=1.7), Norway (ASIR=2.1), Belarus (ASIR=2.1), and Ukraine (ASIR=2.1), respectively.

On the other hand in Europe countries in 2012, 62,191 cases of deaths occurred due to LC, Crude Rate was 8.4 and ASMR was 3.9 per 100,000. The five countries with the highest ASMR of the LC were Republic of Moldova (ASMR=9.5), Romania (ASMR=7.2), Montenegro (ASMR=6.6), Luxembourg (ASMR=6.3) and Bosnia Herzegovina (ASMR=6.2), respectively. Similarly, lowest ASMR of the LC were in Norway (ASMR=1.7), Belarus (ASMR=1.9). The Netherlands (ASMR=1.9), Iceland (ASMR=2), and Ukraine (ASMR=2.2), respectively. The countries with the highest and lowest ASIR and ASMR in both sexes are observable in **Table 1**.

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Table 1. ASIR and ASMR of LC and HDI in Europe

Country	ASIR of LC			ASMR of LC			HDI and its details			
	Total	Male	Female	Total	Male	Female	HDI	Life expectancy at birth	Mean years of schooling	GNI
Albania	4	5.1	2.9	5.7	7.2	4.2	0.749	77.1	10.4	7822
Austria	5.2	8.1	2.8	4.7	7.2	2.6	0.895	81	10.8	36438
Belarus	2.1	3.4	1.2	1.9	3.2	1	0.793	70.6	11.51	13385
Belgium	3.1	4.7	1.7	2.9	4.2	1.8	0.897	80	10.9	33429
Bosnia Herzegovina	4.6	5.8	3.7	6.2	8.1	4.7	0.735	75.8	8.3	7713
Bulgaria	4.2	6.4	2.4	5.5	8	3.5	0.782	73.6	10.6	11474
Croatia	4.7	8.1	2	4.5	7.1	2.4	0.805	76.8	9.8	15419
Cyprus	2.7	3.8	1.7	2.4	3.5	1.4	0.848	79.8	9.8	23825
Czech Republic	4.3	6.4	2.6	3.1	4.7	1.9	0.873	77.8	12.3	22067
Denmark	2.9	4.5	1.4	2.6	4.3	1	0.901	79	11.4	33518
Estonia	2.3	3.4	1.6	3	4.7	2	0.846	75	12	17402
Finland	4.9	7.4	2.7	3.5	5	2.2	0.892	80.1	10.3	32510
France	6.6	11.3	2.5	5.7	9.6	2.3	0.893	81.7	10.6	30277
FYR Macedonia	4.1	5.7	2.6	5.5	7.5	3.8	0.59	69.6	5.6	3557
Germany	4.6	7.2	2.3	3.6	5.4	2	0.92	80.6	12.2	35431
Greece	3.4	5.3	1.8	4.5	6.9	2.5	0.86	80	10.1	20511
Hungary	3.3	5.6	1.5	3.1	5.2	1.5	0.831	74.6	11.7	16088
Iceland	1.7	2.1	1.3	2	2.6	1.5	0.906	81.9	10.4	29176
Ireland	3.3	4.5	2.2	3	3.8	2.3	0.916	80.7	11.6	28671
Italy	7.1	11	3.6	5.3	8.3	2.8	0.881	82	10.1	26158
Latvia	3.3	5.6	1.8	2.7	4.3	1.6	0.814	73.6	11.5	14724
Lithuania	2.7	4.7	1.3	2.7	4.5	1.6	0.818	72.5	10.9	16858
Luxembourg	6.7	10.3	3.4	6.3	9.3	3.6	0.875	80.1	10.1	48285
Malta	2.3	3.6	1	2.4	3.8	1.2	0.847	79.8	9.9	21184
Montenegro	5.2	7	3.6	6.6	8.8	4.8	0.791	74.8	10.5	10471
Norway	2.1	2.9	1.4	1.7	2.1	1.3	0.955	81.3	12.6	48

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Poland	2.8	3.8	2	2.8	3.7	2	0.821	76.3	10	17776
Portugal	5	8.6	1.7	3.8	6.5	1.6	0.816	79.7	7.7	19907
Republic of Moldova	8.5	12.5	5.4	9.5	14.1	5.9	0.66	69.6	9.7	3319
Romania	5.8	9.2	3.1	7.2	11	4.2	0.786	74.2	10.4	11011
Russian Federation	2.9	4.4	1.9	3.5	5.5	2.2	0.788	69.1	11.7	14461
Serbia	4.5	6.6	2.7	4.7	6.7	3	0.769	74.7	10.2	9533
Slovakia	4.3	6.8	2.4	3.6	5.6	2.2	0.84	75.6	11.6	19696
Slovenia	4.9	8.4	2	4.1	6.8	1.9	0.892	79.5	11.7	23999
Spain	5.9	9.9	2.4	4.3	6.9	2.1	0.885	81.6	10.4	25947
Sweden	2.5	3.4	1.6	2.7	3.7	1.7	0.916	81.6	11.7	36143
Switzerland	5.2	8.7	2	4	6.7	1.7	0.913	82.5	11	40527
The Netherlands	1.6	2.4	0.9	1.9	2.6	1.2	0.921	80.8	11.6	37282
Ukraine	2.1	3	1.4	2.2	3.2	1.5	0.74	68.8	11.3	6428
United Kingdom	3.2	4.6	1.9	2.9	4.1	1.9	0.875	80.1	9.4	32538

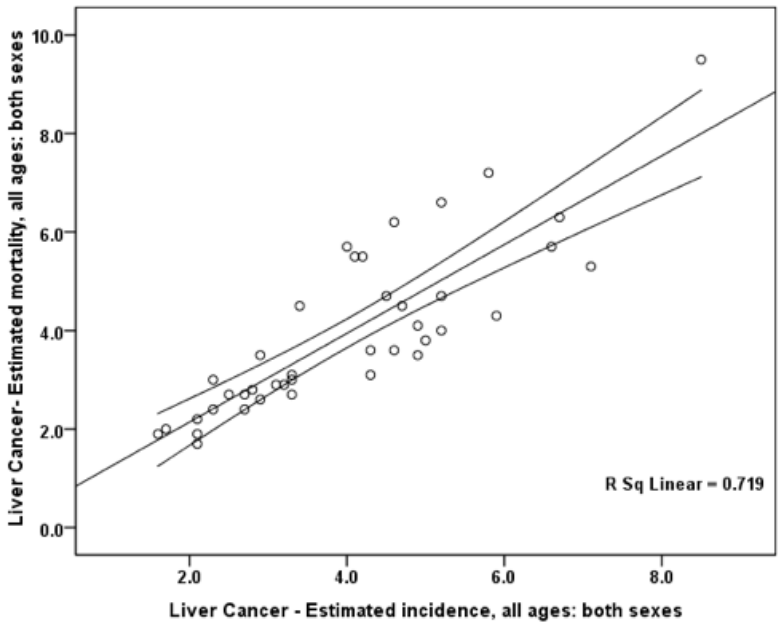

Figure 1. Correlation between ASIR and ASMR of LC in Europe in 2012.

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ASIR and ASMR

Between the Age-Specific Incidence Rate (ASIR) and Age-Specific Mortality Rate (ASMR) of LC, strong positive significant correlation was observed (r = 0.848; P ≤ 0.001).Also, in males and females, strong positive significant correlation was observed between ASIR and ASMR of LC (r =0.850; p ≤ 0.001) and (r =0.897; P ≤ 0.001), respectively (Fig. 1).

ASIR and HDI

The weak negative correlation was observed between the HDI and ASIR of LC(r=-0.194; P=0.230). Also, ASIR have weak negative correlation with life expectancy at birth (r=-0.064; P=0.695), mean years of schooling (r=-0.290; P=0.070), and GNI (r=0.059; P=0.718) (Fig. 2).

In male, a weak negative correlation was observed between the ASIR of LC and HDI (r=-0.114; P=0.482). Also, ASIR have weak positive correlation with life expectancy at birth (r=0.10; P=0.537), weak negative correlation with mean years of schooling (r=-0.235; P=0.144), and weak positive correlation with GNI (r=0.116; P=0.474).

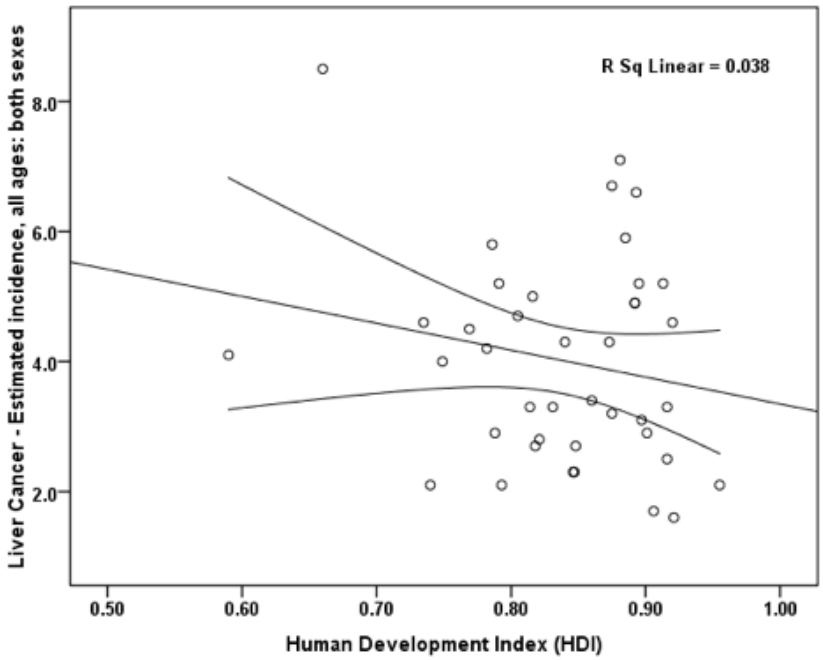

Figure 2. Correlation between HDI and ASIR of LC in Europe in 2012.

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In female, a strong negative correlation was observed between the ASIR of LC and HDI (r=-0.420; P=0.007). Also, ASIR have weak negative correlation with life expectancy at birth (r=-0.164; P=0.312), and GNI (r=-0.187; P=0.248), but has strong negative correlation with mean years of schooling (r=-0.316; P=0.047).

ASMR and HDI

The strong negative significant correlation was observed between the ASMR of LC and HDI (r=-0.515; P =0.001). Also, ASIR have weak negative correlation with life expectancy at birth (r=-0.221; P=0.171), and GNI (r=- 0.236; P=0.143), but has strong negative significant correlation with mean years of schooling (r=-0.421; P=0.007), and (Fig. 3).

In male, a strong negative significant correlation was observed between the ASMR of LC and HDI (r=-0.456; P=0.003). Also, ASIR have weak negative correlation with life expectancy at birth (r=-0.196; P=0.225), and GNI (r=-0.176 ;P=0.276),but has strong negative correlation with mean years of schooling (r=-0.380; P=0.016).

In female, a strong negative significant correlation was observed between the ASIR of LC and HDI (r=-0.613; P≤0.001). Also, ASMR have strong negative significant correlation with life expectancy at birth (r=-0.331, P=0.037), mean years of schooling (r=-0.430; P=0.006), and GNI (r=-0.381; P=0.015).

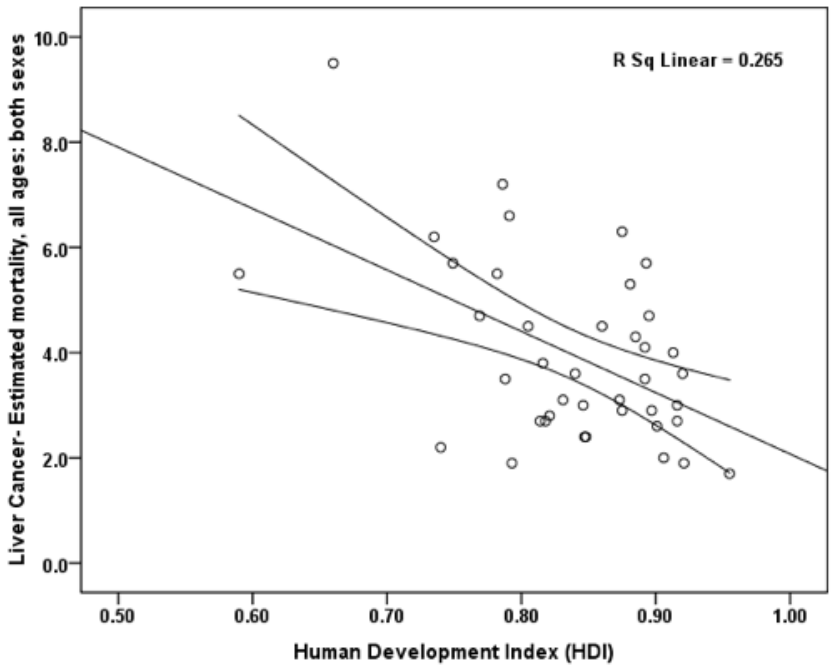

Figure 3. Correlation between HDI and ASMR of LC in Europe in 2012.

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Discussion

Overall in 2012, European countries have recorded 63,462 cases of LC, Crude Rate was 8.6 and ASIR was 4.3 per 100,000. On the other hand in Europe countries in 2012, 62,191 cases of deaths occurred due to LC, Crude Rate was 8.4 and ASMR was 3.9 per 100,000. Correlation between ASIR and ASMR was 0.848 ($P \leq 0.001$), that was statistically significant. In this study between HDI and ASIR of LC a negative correlation was seen about 0.194 (P=0.230), also between HDI and ASMR of LC was a negative correlation about 0.515 (P =0.001).

In European countries, Republic of Moldova (ASIR=8.5), Italy (ASIR=7.1), Luxembourg (ASIR=6.7), France (ASIR=6.6, and Spain (ASIR =5.9), had the maximum ASIR of LC. Four of these countries were in very high level of HDI, but Republic of Moldova was in Medium HDI level. In contrast, five countries with the lowest ASIR of the LC were The Netherlands (ASIR= 1.6), Iceland (ASIR= 1.7), Norway (ASIR=2.1), Belarus (ASIR=2.1), and Ukraine (ASIR=2.1), respectively (Ferlay et al., 2015). The HDI in three countries were in very high level of HDI, but in two countries were in high level of HDI (Malik, 2013).The results of study that conducted with Chang and et al,. displayed that hepatocellular carcinoma by reason of chronic hepatitis B infection was common in countries with low and medium level of HDI, mostly in Asian and African countries (Chang et al., 1997). However, the increased incidence of hepatocellular carcinoma in developed countries was mainly due to increase the prevalence of alcohol use and hepatitis C infection. It seems that the rise of HCC in western countries that have a higher HDI, has been due to hepatitis C infection and alcohol consumption (Liver, 2012). However, ASIR of LC in Europe in 2012 was 6.8 per 100,000 that was less than observed ASIR in the world (ASIR=15.3), Africa (ASIR=12.4), Asia (ASIR =20) and Oceania (ASIR=7.8) (Ferlay et al., 2015). In developing parts of the world, especially in Asian countries, cancer is becoming one of the most severe health problems. So that in some of these countries, such as Japan and South Korea, cancer is known as one of the most common causes of deaths. It is expected that if current management strategies and programs do not modified, the number of deaths from cancer by 2020 in these areas will reach 7.1 million cases per year (Mackay, 2006).

The distribution of cancers in different parts of the world in terms of human development index is very different, so in regions with very high, high, medium and low HDI, various cancers are classified as the most common cancer. cancer of the lung, breast, colorectal and prostate in areas with very high and high HDI are considered as the most common cancers that almost include half of new cancer cases in this region. Also, in regions with medium and low HDI, in addition to breast, colorectal and lung cancer, cervical cancer, liver and stomach cancer classified as cancers with high incidence and mortality. However, in regions with low HDI, cancers due to infectious agents included a large part of incidence and mortality of cancer (Bray et al., 2012; Franceschi and Wild, 2013).

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The results of this study presented that the ASMR of LC in Europe varies from 1.7 in Norway to 9.5 in Republic of Moldova. The highest ASMR of LC occurred in Republic of Moldova (ASMR=9.5), Romania (ASMR=7.2), Montenegro (ASMR=6.6), Luxembourg (ASMR=6.3) and Bosnia Herzegovina (ASMR=6.2). In these countries only Luxembourg was in very high level of HDI. Similarly, five countries with lowest ASMR of LC were Norway (ASMR=1.7), Belarus (ASMR=1.9), The Netherlands (ASMR=1.9), Iceland (ASMR=2), and Ukraine with (ASMR=2.2) that were in very high and high level of HDI.

This study is an ecological study and its results can be interpreted only at the population level and attribution of the results of this study to individual levels lead to occurrence of ecological fallacy. This study also has some advantages. The first advantage is that we studied all European countries. So the data have perfect integrity. The second advantage is the novelty of findings because we couldn't find a study that shows relationship between the ASIR and ASMR of LC with HDI and its components in European countries. Therefore, it is proposed that similar studies in other parts of the word should be done, so that the relationship hypothesis between the incidence and mortality rate of LC and HDI in these regions can be examined.

Conclusion

Correlation between ASIR and ASMR was statistically significant. Also, we were observed a negative correlation between HDI and the ASIR of LC, but between the HDI and ASMR of LC significant correlation was observed. Therefore, increase in the human development index was associated with reduce in incidence and mortality of LC.

Abbreviations

ASIR: Age-specific incidence rate

ASMR: Age-specific mortality rate

HDI: Human Development Index

LC: Liver Cancer

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Author contribution

All authors contributed to the design of the research. MS, SIF, SK and HS collected the data. HS, SK and AMH conducted analysis and interpretation of data. All authors drafted the first version. MM, MA, PB, FAB and AMH edited the first draft. All authors reviewed and commented on final draft.

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Original Research

The effect of peer support group on self-transcendence in patients undergoing haemodialysis

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Abstract

Introduction: Self-transcendence helps patients undergoing haemodialysis to organize the variety of challenges caused by the disease in order to make them feel well. This study was conducted to determine the effect of counterpart group on improving self-transcendence level in patients undergoing haemodialysis. **Materials and Methods:** This clinical trial was conducted with two groups of intervention and control, with 55 patients undergoing hemodialysis. The samples were divided in 2 groups of intervention and control through block randomization. Two-hour counterpart group sessions were held for eight weeks for intervention group. The session's topics were based on the patients' needs and interests. Research tools were questionnaire, demographic information and "Reed's Self-Transcendence Scale (STS)". The descriptive and inferential statistics were used for data analysis using the SPSS v18. **Results**: There was a significant difference between self-transcendence scores in two groups of intervention and control ($P<0.05$). A significant increase in the level of self-transcendence in both groups was seen at the end of the study compared to basal status ($P<0.05$).

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Conclusions: According to the study results, attending the counterpart groups improved self-transcendence in patients undergoing haemodialysis. The results can be used in nursing education and management. Training Self-transcendence evaluation is recommended for other chronic diseases with the emphasize on participating in counterpart groups for assessing its efficiency.

Keywords

Counterpart group, Haemodialysis, Self-transcendence

Introduction

End stage renal disease is one of the significant reasons of death and disability all around the world (Smeltzer et al., 2012). Prevalence of the end stage renal disease is increasing in the world. The number of End stage renal disease (ESRD) patients undergoing treatment in 2009 was 2.456.000 among which 1,895,000 were under dialysis (Fresenius-Medical-Care, 2009). It is estimated that the dialysis population will reach 3,500,000 by 2020 (Davids, 2007). Haemodialysis is the most common therapy for ESRD (Aliloo et al., 2011). By starting therapy, the patient's overall health will improve and finally their life span will be increased. However, haemodialysis therapy may provide some side effects as well (Phipps et al., 1999). The patients that undergo haemodialysis are exposed to a large rank of physical, psychological and social problems (Tayyebi et al., 2010) and the psycho-social disorders caused by disease such as changes in imaginations, behavioral changes and etc. and causes exposure of patients to daily tensions (Rafiee et al., 2011). These patients are often worried about their unpredictable future and suffer from depression and death fear because of their chronic disease (Eslami et al., 2014; Kirby, 2013).

The life quality level of dialysis treated patients is lower than the other people in society (Lindqvist and Sjoden, 1998). The chronic and weakening nature of disease, the long-lasting and dynamic therapy and patients' actual and potential problems (Rahimi et al., 2006) show their need to support (Tayyebi et al., 2010). The findings indicated that self-transcendence will effect increase of self-care and the life quality of chronic patients (Jadid-Milani et al., 2014). The word self-transcendence refers to spiritual facts and is adopted from Reed's Self Transcendence Theory (Reed, 2009). Self-transcendence is a nursing descriptive theory designed by Palma J. Reed in 1991 and it's aim is understanding the health status of the people who are vulnerable or close to death (Reed, 2008). Self-transcendence theory was first developed on mental health and welfare in the elderly and then many researches have been done on this field and other

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fields (Kausch and Amer, 2007). This theory has been used in all age groups from childhood to adulthood in all cultures from America to Asia during the past years (Reed, 2008).

Self-transcendence is defined as the expansion of self-boundaries in the following dimensions:

1. Inner: self-acceptance and goal discovery

2. Outer: communicating with others and environment and considering other's welfare

3. Temporally: Your past and future develops your presence through this dimension and you are attached to a higher dimension by this one

Therefore, self-transcendence is the expansion of self-boundaries and being aware of the dimensions beyond self. It is formed as a developmental talent (or maybe a survival mechanism) from a person's experiences of health and illness (Reed, 2008).

As a person transcends, he feels that the around boundaries are without any physical or temporal limitations (Coward and Kahn, 2005). Self-transcendence is gained by helping others (Gulliver, 2007). It helps a person to organize the challenges caused by illness inside some meaningful systems to make person feel better (Jafarzadeh et al., 2015) and accept death as a part of life and find spiritual meanings in life (Reed, 2009). Nursing interferences can be a facilitator of patient's internal sources and others support to reach self-transcendence and a higher level of health (Reed, 2008). Interpersonal approaches like face to face contact, phone and internet that focus on people's communication with others, can facilitate self-transcendence. Consultation with counterparts and other supportive groups are among the approaches that a nurse can provide for patients (Reed, 2009). Supportive groups are often one of the effective communicating ways for those who have difficult situations in their lives. The supportive groups gather people with the same experiences and facilitate group member's communication, sharing experiences, transferring information about strategies of compliance with problems, and making a situation to help each other in order to reach self-transcendence (Kausch and Amer, 2007; Messmer Uccelli et al., 2004; Nichols and Jenkinson, 2006).

Researches showed that supportive groups increased self-transcendence level in patients undergoing prostate cancer (Chin and Fernsler, 1998) and MS (Jadid-Milani et al., 2014). However, the study on improving the self-transcendence level and positive attitude to take care of the elderly in nursing students showed that the self-transcendence level had no meaningful changes before and after intervention (Chen and Walsh, 2009; Lamet et al., 2011). The studies showed that self-transcendence has a significant effect on increasing self-care in patients (Mellors et al., 1997; Upchurch and Mueller, 2005), having goals in life (Nygren et al., 2005), and life quality in patients with incurable diseases (Jadid-Milani, 2012).

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Therefore, considering the controversies about the quality and quantity of nursing intervention on self-transcendence level in studies, this study was conducted to determine the effect of supportive counterparts group on improving self-transcendence of patients undergoing hemodialysis.

Materials - Methods

This randomized clinical trial was approved by the Ethics Committee of the Sabzevar University of Medical Sciences. This research was conducted on end-stage renal disease patients referring to the hospital under the supervision of the Sabzevar University of Medical Sciences in 2013. Among 110 qualified patients (having at least 6 months haemodialysis therapy and aged over 18), 64 patients were selected randomly regarding the sample volume with the confidence coefficient of 95. Patients were divided into two groups of intervention and control group using the block randomizations.

Foursome blocks were used so that "**A**" was defined as control group and "**B**" as intervention group. Different forms that can be used for forming tertiary groups was written as below: **AABB**, **ABBA**, **BAAB**, **ABAB** and then each block was written in a paper and was thrown inside a dish and the first block was chosen randomly and it was continued so for all the samples.

On the first day of the study, the objectives, data collection methods and regulations of the study were explained to participants and informed written consent was obtained from all participants. The 26 ethics codes were also accomplished. For control group, routine care of dialysis department was done and the counter parts group was designed for intervention in the intervention group. The most appropriate group size for health changes is 8 to 12 (Jadid-Milani, 2012). So the sessions were held on 3 groups according to sample volume. About 10 to 12 individuals were selected for each group, then if there was sample withdraw, there would remain at least 8 individuals in each group. As well as 10 individuals remained in group 1, 10 individuals in group 2, and 12 individuals in group 3. The groups' wrappings were due to patient's haemodialysis program. In order to prevent bias, the intervention and control groups were arranged in separate shifts for dialysis in order that they do not meet each other. Group sessions were scheduled for 8 sessions in 8 weeks (Mohr et al., 2005; Uccelli et al., 2004) and each session was 2 hours per week. Those who were absent followed the topics by calling the researcher or from other members of the group. While, more than 2 sessions absence, meant person's data omission The formation and management was the same for all counterpart groups and cultural and ideological issues were noticed in the classes. Also, a transportation company was coordinated for patient's communication to the sessions place All three counterpart groups discussed topics were gained by health problems that were asked from patients based on their need and interest . The other seven session topics were chosen based on priority of

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patients at the first session. Discussed topics were determined based on Reed's self-transcendence scale (STS). According to Reed theory, the items in STS can be used as a guidance for education and spiritual attitude in the members of counterpart groups (Smith and Liehr, 2013). While talking about mental and physical disorders in each session, approaches such as adapting with physical changes and its difficulties, adapting with the present situation, building new concept of life and using others'' experiences and opinions were emphasized. To observe ethics, at the end of the study after completing the questionnaire, the items that were taught in the sessions for intervention group, were given as pamphlets to the group.

The study tools include demographic questionnaires and self-transcendence scale (STS). The tools designed by Reed (STS1986) consists of 15 items and it gains 15 to 60 scores according to Likert scale. Higher score means higher self-transcendence. The Cronbach alpha coefficient has been 0.72 to 0.93 in the recent studies and has been localized and translated into Persian at Milani et al new study (Jadid-Milani, 2012). In this study, the test-retest method was used for determining the reliability of self-transcendence scale, the tool was given to patients during one week interval and the correlation coefficient was 0.81 for self-transcendence scale which indicates the scale's reliability. The tools were completed at baseline and end of the intervention by patients themselves in both groups (intervention and control group). the questionnaire was done by the researcher for illiterate patients. .

During the sessions, three participants were omitted due to renal transplantation, four participants because of absence more than two sessions, and two participants because of refusal to continuing. Finally, the data of 28 participants of intervention group and 27 ones of control group were analyzed. The SPSS version 18 software and descriptive and inferential statistics were used for data analysis, the independent T test was used for self-transcendence comparison between two groups at the end of study, paired T test was used for internal test and the ANOVA was used for analyzing the contextual variables effect. Significant stage equaled confidence interval of 0.95% ($p<0.05$).

Results

The demographic information of the results of the study on 55 patients in two groups (28 intervention and 27 control group) has been shown in **Table 1**. According to **Table 2**, the means score of self-transcendence developed in intervention group after intervention. Statistically, there was a significant difference between baseline and post intervention ($p<0.0001$). The self-transcendence score was also increased at the end of the study in control group and this was statistically significant in before and after the intervention status

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(p=0.006). There was a significant difference between control group and intervention group at the end of the intervention (p<0.0001).

Table 1. The relative frequency of research units based on demographic characteristics

Demographic information	Groups		P values
	Intervention	Control	
Age (Mean,SD) (Year)	47.04±13.29	48.04±13.20	**0.65**
Sex			
Men	25%	22.2%	**0.80**
Women	75%	78.8%	
Marital status (%)			
Single	82.1%	85.2%	
Married	14.3%	7.4%	
Widow	0	7.4%	**0.42%**
Divorced	3.6%	0	
Education (%)			
Illiterate	7.1%	11.1%	
Primary school	35.7%	33.3%	
Secondary school	39.3%	37%	**1**
High school	17.9%	14.8%	
University	0	3.7%	
Employment status (%)			
Worker	25%	14.8%	
Employer	7.1%	7.4%	
Housewife	21.4%	25.9%	**0.95**
Self employed	14.3%	14.8%	
Unemployed	25%	29.6%	
Retired	3.6%	7.4%	
Student	3.6%	0	
Income (%)			
Good	3.6%	7.4%	**0.67**
Average	39.3%	29.6%	

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Weak	57.1%	0.63%	
Dialysis history (Years)	2.08±2.6	1.25±2.3	**0.98**

Table 2. Comparison and distribution of self-transcendence before and after participating in counterpart group, in intervention group, and in control group in patients undergoing haemodialysis

Study variables	Research time groups				T-test results btw. two groups
	Before intervention Mean ± SD	After intervention Mean ± SD	Before intervention Mean ± SD	After intervention Mean ± SD	
Self-transcendence	43.18±5.3	48.64±3.09	42.7±3.31	43.18±3.16	p <0.0001
T test results	p<0.0001		p=0.006		

Moreover, in ANOVA analysis, it was found that participating in counterpart group will increase the self-transcendence mean score of haemodialysis patients up to 4.33 units which is significant in range of confidence interval of 0.95 ($p<0.0001$). The self-transcendence mean score is also significant according to the age ($p<0.05$) and increases 0.76 units by aging. Other contextual variables did not have any significant effect on predicting self-transcendence score ($p>0.05$).

Discussion

The result of recent study showed that the mean score of the self-transcendence was promoted after participating in counterpart groups in the intervention group and there was a statistically significant difference after and before the intervention. Few studies have been performed interventionally about self-transcendence and Reed's theory, or at least they have not been available. But the available studies show that the results of this study are consistent with the new study of Milani et al (2014) performed on patients with Multiple Sclerosis (Jadid-Milani et al., 2014). It is similar to the studies of Femsler and Chin-A-Loy (1998) (Chin and Fernsler, 1998). However, the study was inconsistent with the study of Chen and Walsh (2009) that examined the effects of nursing interventions in development of self-transcendence and positive perspective towards elderly care in the nursing students in the University of USA and

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showed that the nursing intervention didn't improve self-transcendence level of the students significantly (Chen and Walsh, 2009). Also in Lamet et al. study which assessed the intervention effect for developing perspective of nursing students in elderly care, there was no significant different before and after the intervention in self-transcendence (Lamet et al., 2011) and this differences can be related to the target group of Reed's theory that was the nursing students. Nursing students experience situations of taking care of the elderly during their education repeatedly that can be the reason of the lack of student's self-transcendence increasing level, but in this study and Jadid-Milani's et al. study, there were patients who had more vulnerability because of their chronic diseases and they felt more self-transcendence to reach higher life quality (Jadid-Milani et al., 2014). Self-transcendence improving in this study can be a reflection of community's activities, sharing problem and solving it in counterpart group. Counterpart group sessions helped participants to develop individual boundaries by contemplating themselves and accepting their own situation.

Having a sense of responsibility and concern about others during the period and using others' experiences and hope to the future helped them to improve their situation.

The mean score of self-transcendence changed in control group and showed statistically significant difference before and after the intervention (p=0.006). The significant increase of self-transcendence was less in control group which is similar to Coward's study (2005) in the USA performed on women with breast cancer. In their study, eight weeks after counterpart group formation, the self-transcendence score, the cognitive welfare and physical performance increased in both groups of intervention and control, but no significant differences was seen between these three variables (Coward and Kahn, 2005). Moreover, in Daineer's study (2003) with the aim of determining the personal narration effect during illness on self-transcendence in patients with chronic disease, no significant difference was seen in self-transcendence of control group after intervention (Diener, 2003). The cause of self-transcendence increase in control group in our study can be related to two months of disease experience and dealing with its hardships. The difference in self-transcendence score of two groups is because individuals in intervention group can reach to a better result by using each other's experiences in shorter time and with less costs. Therefore, their health problems are less as well and the significant difference in two groups indicates that.

The results indicate that there was a significant difference between self-transcendence of intervention and control groups at the end of the intervention. Based on the results, it is shown that the self-transcendence score of haemodialysis patients increases by participating in counterpart group. Patients find out their situation, will notice other's welfare by communication with others, and would share their experiences by adapting others' experiences with their own experience and concern about the future and also they will improve their

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situation. On the other hand, finding an acceptable feeling by other group members would improve self-transcendence in patients (Nguyen et al., 2009).

According to the results of the present study, the contextual variables had no role in predicting patient's self-transcendence changes undergoing haemodialysis before and after intervention. The contextual variables had also no role in predicting self-transcendence difference in patients with MS in Jadid Milani's study (2012). however participating in counterpart group improved self-transcendence in patients (Jadid-Milani, 2012). The results of this study confirmed the effect of counterpart group on self-transcendence level. The results has some finding which can be useful for education and management field in nursing, but using these findings is not useful without managers' support. Also, the findings of the present study can be used in in-service training curriculum for nurses by nursing managers for designing nursing process for patients and with other critical conditions with the focus on self-transcendence. Forming counterpart groups by nurses (which is one of their responsibilities) for haemodialysis patients and other chronic patients in community, can be effective on promoting self-transcendence level. On the other hand, forming counterpart group for patients' families causes better understanding of families about the patient status, and reduces their tiredness at home.

Limitation

The possibility exchanging information in the intervention and control groups during dialysis. In order to prevent errors, the intervention and control groups were arranged in separate shifts for dialysis to ensure that they don't meet.

Conclusion

The nursing interventions will effect individuals internal sources for self-transcendence without cost and high clinical services by forming counterparts group and self-transcendence makes new concepts for patients undergoing haemodialysis and the patients will learn how to cope with disease from other peers and by raising their knowledge about the diseases and its symptom's controlling ways and treating manners and mixing them with their own experiences, they can deal better with their concern about the disease and this knowledge improvement would change patients attitudes and as well the health status will also promote. So, the nurse can form interventions for developing patients undergoing haemodialysis conditions by self-transcendence theory.

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Author contribution

MJM and AKK contributed to the design of the research. MJM,PA and MV collected the data. HS and AMK conducted analysis and interpretation of data. All authors drafted the first version. MJM, HS and AMK edited the first draft. All authors reviewed and commented on final draft.

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Review

Molecular basis of glaucoma and its therapeutical analysis in Pakistan: an overview

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Abstract

The human eye is an organ of vision. It plays a prime role in life, gives us the sense of sight, and enables to understand about the world around us. Visualization and interpretation of colors, shapes and dimensions of numerous objects is made possible by eye. Inherited eye diseases comprise 1/3 of all reported human genetic disorders. This review will focus on Glaucoma which comprises a predictable visual illnesses concerning optic nerve deterioration and if remains without any cure can result in failure in eyesight. The optical nerve injure comprises deterioration of the retinal ganglion cells (RGCs). Glaucoma represents a heterogeneous group of optic neuropathies with a complex genetic basis. These neuropathies gradually reduce vision without warning and often without symptoms. Different forms of glaucoma share some common clinical manifestations that usually include specific abnormal appearance of the optic nerve head, characteristic loss of visual field and chronic painless progression. Glaucoma is a progressive optical neuropathy considered by optical disc changes, nerve fiber film break, and visual field defects. Present-day treatment preferences predominantly targeting at reducing IOP by making use of pharmaceutical means, laser treatment and surgical procedure. Developed conducts target neuroprotection with vaccines, the hang-up of NO synthesis and apoptosis. Attaining a better appreciative of the pathogenesis can support in the improvement of novel handling options and, perhaps, even a remedy for glaucoma. There are more than 1.8million glaucoma patients in Pakistan and almost half of them have already lost their eyesight, permanently, due to delay in diagnosis and treatment. About 90% population in the country has no awareness about this disease, resultantly; more and more people are becoming permanently blind in Pakistan due to untreated glaucoma.

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Keywords

Eye, glaucoma, diagnosis, treatment, Pakistan

Introduction

The term "glaucoma" covers a quantity of diverse eye disorders, all of which encompass impairment to the optic nerve (Janssen et al., 2013). One common reason is that there is too much pressure inside the eye. The situation tends to be hereditary and may not display up until later in life. The improved pressure, called intra-ocular pressure, can harm the optic nerve, which communicates images to the brain. Intra-ocular pressure is produced by a fluid termed as aqueous humor formed by the eye themselves in the compartments of the eye in the middle of the cornea and the lens (Fatt and Weissman, 2013). Generally, this liquid, called aqueous humor, runs out of the eye through a mesh-like network. If this network becomes jammed, fluid forms up, triggering glaucoma. Glaucoma typically occurs when intra-ocular pressure upsurges. This take place when the fluid stress in the eye's anterior cavity, the area in the middle of the cornea and the iris, rises.

If the aqueous humor is prevented from draining appropriately, it twitches to accumulates pressure inside the eye builds up (Gupta et al., 2014). This presses alongside the optic nerve and there is a threat that nerve cells perish. Whether the amplified intra-ocular pressure does cause loss depends on, amid other things, how well the optic nerve can struggle this pressure. Glaucoma will cause loss of vision. Readings between 10 and 21 mm Hg are considered normal. Someone who has glaucoma does not always have above-average intra-ocular pressure.

Glaucoma sufferings roughly 70 million people around the globe, of whom around 10 % are supposed to be bilaterally unsighted (Lawrence, 2014). Estimation that is put forward in 2010 nearly 60.5 million individuals were affected by glaucoma and around 8.4 million were visionless from the sickness and it is expected that by the year 2020, this amount would rise to nearby 79.6 million. Statistics gather round by the World Health Organization (WHO) indicated that glaucoma is the second foremost reason of blindness worldwide, after cataract (Bourne et al., 2016). It is expected that glaucoma affects 12 million individuals accounting for 12.8% of the republics blindness and by 2020; this is estimated to be 16 million. Glaucoma is accountable for 10% of blindness worldwide. Glaucoma denotes to a group of disorders categorized by distinctive variations to the retinal nerve fiber layer and optical nerve head ensuing in compact optical field compassion. Its massive social and cost-effective impact

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can be cherished by the fact that it leftovers a principal cause of sightlessness around the globe (Quigley and Broman, 2006). Glaucoma is a progressive optical neuropathy considered by optical disc changes, nerve fiber film break, and visual field defects (Pascolini et al., 2009; Resnikoff et al., 2004). This situation is known as glaucomatous optic neuropathy (GON) causing failure of visual field and ultimately to a state of irretrievable blindness (Alguire, 1990; Quigley, 1996). Glaucoma is the second principal reason of permanent blindness worldwide, thinking to influence 60 million inhabitants (Kelliher et al., 2006; Quigley and Broman, 2006). A convincing 70 million citizens suffer from glaucoma, and Asian ethnic minorities are extra susceptible to this visual ailment (Zhong et al., 2012). Linkage examinations have recognized 23 loci (the GLC1A, .GLC1L, the GLC3A-GLC3B, 2p14, 2q33.-q34, 5q22.1-q32, 10p12-p13, 14q11, 14q21-q22, 17p13, 17q25, and 19q12-q14) (Gemenetzi et al., 2012; Stone et al., 1997) for dissimilar kinds of glaucoma. Conversely, merely 4 genes (MYOC/TIGR, CYP1B1, optineurin [OPTN], and WD recap domain 36 (WDR36) (Monemi et al., 2005) have been recognized so far.

Currently, the only confirmed treatment for glaucoma is to reduce intra-ocular stress (IOP) with the aim of preventing supplementary glaucomatous optic nerve smash up (Heijl et al., 2002). Whilst many patients can be controlled with medications, patient devotion and optical toxicity are key issues in the residential globe, and lifetime outlay and ease of access to medications are issues in growing regions (Lemij et al., 2015).

Glaucoma is a composite peculiarity, in utmost condition have not pursue a straightforward heritage shape, and has inconsistent penetrance, subtle advancement, and habitually a later on commencement. Linkage examination have recognized 23 loci (the GLC1A, GLC1L, the GLC3A-GLC3B, 2p14, 2q33-q34, 5q22.1-q32, 10p12-p13, 14q11, 14q21-q22, 17p13, 17q25, and 19q12-q14) (Gemenetzi et al., 2012; Stone et al., 1997) for dissimilar kinds of glaucoma. Conversely, merely 4 genes (MYOC/TIGR, CYP1B1, optineurin [OPTN], and WD recap domain 36 (WDR36) (Monemi et al., 2005) have been recognized so far.

Classification of Glaucoma

Glaucoma is categorized conferring for the cause (primary VS secondary), composition of the frontal compartment (open angle VS closed angle) and stage of beginning (juvenile VS adult) (Sarfarazi, 1997). Glaucoma can categorized as primary once it happen with not any identified etiology or secondary wherever an earlier damage or illness is contributing. In broad-spectrum, glaucoma can be classified into 3 main kinds:

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Primary open-angle glaucoma (POAG)

"Open-angle" means that the angle where the iris meets the cornea is as wide and open as it should be. It is also called chronic glaucoma and is the most common form, accounting for at least 90% of all glaucoma cases. The most general type of glaucoma is primary open angle glaucoma (POAG), disturbing over 33 million persons wide-reaching (Quigley, 1996). It is produced by the slow impediment of the drainage channels, causing in improved eye pressure. Primary open-angle glaucoma (POAG), in which the iridocorneal angle and frontal eye organizations emerge ordinary in gonioscopy inspection. It is the supreme ordinary form analyzed in all populaces investigated and is particularly predominant (~4.2%) in individuals with African lineage. Genetic line of attack make to know that primary open angle glaucoma may be innate either as a general, multifaceted trait with fully developed onset or, fewer commonly, as a conventional Mendelian or monogenic sickness that inclines to have an premature onset (Wiggs, 2007). Hereditary link studies of complex relations, frequently of European lineage, have acknowledged at smallest amount twenty one loci (GLC) for Mendelian arrangements of POAG (Fan and Wiggs, 2010).

Juvenile onset of open angle glaucoma (JOAG) is an alternative of primary open angle glaucoma (POAG). JOAG is diagnosed prior before the age of 40 and universally described as an artifact of autosomal dominant inheritance (Alward et al., 1998). The manner of inheritance in POAG is inconclusive (Nemesure et al., 2001). Furthermore, greater than 90 point alterations have been recognized universally in numerous racial groups. These kinds of mutations report for three to five percent of POAG cases and a higher percentage of Juvenile-onset of open angle glaucoma cases (just about six to thirty six %) (Challa, 2008; Gemenetzi et al., 2012). Primary open angle glaucoma (44.7 million cases wide-reaching) is measured more communal than primary angle closure glaucoma (15.7 million).

Primary Congenital Glaucoma (PCG)

Primary congenital glaucoma (PCG) is the supreme recurrent babyhood glaucoma and can lead to sightlessness during neonatal or early infantile period. Primary congenital glaucoma is the common term used for a glaucoma diagnosed in infancy or early childhood and is caused by abnormal intra-ocular fluid drainage from the eye as a result of a blocked or defective trabecular meshwork (the mesh- like drainage canals in the eye) (Ghate and Wang, 2015). It may also be due to a hereditary defect or abnormal development during pregnancy. In other cases, an abnormal drainage system may be the result of some other disease in the eye which results in secondary glaucoma. In these cases, the glaucoma may be associated with recognizable iris (the colored part of the eye), corneal, or other eye problems. Molecular genetic studies conducted during the last numerous years have established that PCG is an autosomal recessive trait. At present, four chromosomal loci have been concerned in PCG on GLC3A harboring the cytochrome P4501B1 (CYP1B1)

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gene (Stoilov et al., 1997). Congenital glaucoma is a type of blinding eye illness that ruthlessly affects the improvement of visual acuity amongst children, infants and teenagers. It is caused by the hindrance of the aqueous outflow by the mal-development of the frontal chamber angle and the trabecular meshwork of the eye for the period of the embryonic development phase (Maul et al., 1980). PC Glaucoma is autosomal recessive eye disarray observed in intermittent and familial cases. The Primary Congenital Glaucoma is universal in North Africa and at hand in a more harsh form than in the western world (Helmy, 2016). The pervasiveness of pediatric glaucoma in the Middle East is 1:2500, while in consanguineous Slovakian children, it is 1out of 1250. The incidence ranges between 1out of 10,000 to 1out of 12,500 in western countries (Helmy, 2016).

The popularity of Primary congenital glaucoma differs permitting to the topographical position and civilization. The occurrence is 1/10,000 in Western motherlands, 1 out of 2,500 in Arabic people, and uppermost in the Gypsy inhabitants of Slovakia, wherever its prevalence is 1 in every 1,250 living births outstanding to an elevation speed of cousin marriages in these republics (Bejjani et al., 2000; Sarfarazi et al., 2003). The predominance of Primary congenital glaucoma in south Indian is estimated to be 1 in 3,300 and result 4.2 percent of infancy loss of sight (Dandona et al., 1998). 3 loci have been recognized: the GLC3A (2p21) (Sarfarazi et al., 1995), the GLC3B (1p36) (Akarsu et al., 1996) and GLC3C (14q24.3) (Stoilov et al., 2002).

Primary angle Closure Glaucoma (PACG)

It is caused by clogged drainage channels, causing in a sudden increase in intra-ocular pressure 12-21. It is also called acute glaucoma or narrow-angle glaucoma. Unlike open-angle glaucoma, angle-closure glaucoma is a result of the angle between the iris and cornea closing. It is relatively a less common form of glaucoma. Primary angle closure glaucoma (PACG) is the supreme widespread type of glaucoma universally (Kuehn et al., 2011). Nevertheless, primary angle closure glaucoma (PACG) is thought to be the most familiar reason of bilateral glaucoma sightlessness cosmopolitantly (Quigley et al., 2001). This is a sub kind of glaucoma, and can be defined as an anatomic disarray of the frontal cavity, through which the drainage position is obstructed by the frontal development of the iris (Lin et al., 1997). Primary angle closure glaucoma leftovers a main reason of unalterable blindness, predominantly in Asian countries such as China (Foster et al., 2000), Mongolia (Foster et al., 1996), Singapore (Foster et al., 2000), and India (Dandona et al., 2000) with up to 80% of the predictable 15 million citizens afflicted with PACG inhabitant in Asia (Quigley and Broman, 2006). The figure of patients with PACG is probable to rise by roughly 5 million people from 16 million over the next decade (Quigley and Broman, 2006). Quite a lot of anatomic hazard issues for the improvement of Primary angle closure glaucoma has been famous together with a narrow frontal chamber deepness and petite axial distance. Pretended replica organizations have providing the facts that the occurrence of equally amplified lens curving and a undersized zonule-iris space add to a pupil block in angle closure glaucoma (Huang and Barocas, 2004).

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PACG patients have been found to have exacting anatomic biometric skin tone together with shallow anterior chambers (Lin et al., 1997), lens breadth and position (Foster et al., 1996), constricted iridio-trabecular drainage angles, dumpy axial lengths (Abu-Amero et al., 2007), and hyperopic refractive fault (Congdon et al., 1996). The infection is accompanying with grownup stage, womanly masculinity and rivalry (anterior compartment angle is thinner in Eskimos and Asians (Salmon, 1999).

Numerous studies have exposed that genetic factors take part in an chief role in the development of PACG (Alsbirk, 1975; Amerasinghe et al., 2011). Although a sum of susceptible loci and genetic factor have been investigated for PACG, the accurate genes underlying PACG have not been recognized (Cong et al., 2009).

Most frequently glaucoma genes reported in Pakistan

Novel CYP1B1 mutations in consanguineous Pakistani families with primary congenital glaucoma identified an innovative cyp1b1 mutation in consanguineous Pakistani families with primary congenital glaucoma. The disease-causing alterations could be identified in ~31% of PCG affected families from Pakistani population (Firasat et al., 2008). This frequency estimation of CYP1B1 mutations in our population may be imprecise because of a small number of PCG families studied. Nonetheless, it connotes the prominence of CYP1B1 in PCG pathogenesis. Homozygosity mapping in consanguineous Pakistani family revealed one 11-Mb homozygous area incorporating the CYP1B1 gene (Micheal et al., 2015b). A homozygous CYP1B1 missense mutation (p. Arg390His) was recognized in this family. Sequence analysis of CYP1B1 in 39 supplementary families revealed one known and three fresh homozygous mutations in PCG (p.Ala288Pro, p.Asp242Ala, p.Arg355* and p.Arg290Profs*37). In POAG, one novel heterozygous missense mutation (p.Asp316Val) was recognized in one family and a beforehand reported mutation (p.Glu229Lys) was identified in three families. CYP1B1 mutations are the prime cause of primary congenital glaucoma in Pakistani patients (Rauf et al., 2016). Also recounted a family from Pakistan in which participants have inherited JOAG and PCG due to a known homozygous mutation in CYP1B1 (Bashir et al., 2015).

LTBP2 is the succeeding gene concerned in PCG to date. identification of homozygous null mutations in LTBP2 as a basis of PCG in human patients (Khan, 2011). These results might have insinuations for the clinical supervision of infancy sightlessness and give new intuitions into the development of the anterior organizations of the eye, implying that LTBP2 may have an critical structural role in keeping the shape of the ciliary body and its neighboring structures.

Another homozygous null mutation in LTBP2 as a trigger of PCG reported in Pakistani as well as Gypsy patients (Ali et al., 2009). Micheal et al.,

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(2015) revealed that variants in ASB10 were found to be significantly associated with sporadic POAG in the Pakistani population (Micheal et al., 2015a).

First described MYOC correlated glaucoma from Pakistan isolating as autosomal dominant peculiarity in large family detected with JOAG (Waryah et al., 2013). Identification of innovative disease producing allele in MYOC suggests hereditary heterogeneity of the populace. Association of novel disarray allele indicates genetic heterogeneity of the populace. Linkage scrutiny revealed an autosomal dominant allele at GLC1A1 locus, co-segregating with disorder phenotype in a huge consanguineous household, enrolled from inner of Sindh area. Succeeding sequencing of MYOC gene in all patients, recognized a heterozygous c.1130 CNG variation in exon 3, substituting Threonine to Arginine at codon 377 of Myocilin. Preponderance of MYOC mutations (97%) has been discovered in exon 3 of the gene, which code a functionally essential Olfactomedin domain. The data indicate that Threonine residue at 377 codon of MYOC is functionally essential and its changeover with Arginine bases hard-hitting form of glaucoma.

Present-Day Treatment Preferences in Pakistan

Glaucoma is a lineage of chronic disorders due to the worsening of the optic nerve; its onset is asymptomatic in early phases and leads to sightlessness if left untouched. It is the next supreme usual cause of blindness globally with an predictable worldwide occurrence of about 67 million (Consoli and Ramlogan, 2015). The causes behindhand glaucoma and the manner in which it spearheads to loss of eyesight have not been clearly acknowledged; glaucomatous loss can be decelerated down but not reversed, and no particular precautionary measures exist. To date the maximum important regions of enhancements distresses the cataloguing of different forms have the disorder as well as cleansing clinically and pharmacological involvements for very specific conclusions. Glaucoma creates a thought-provoking case analysis in that the obstinacy of a specific framing which is now solidly considered by the ophthalmology medical society as only somewhat correct at source of much misdiagnosis and fairly unsuccessful clinical reaction.

The objective of remedying glaucoma lies predominantly on checking or postponing the loss of optical field (Brubaker, 2003). Since neuronal cell fatality is irretrievable, no treatment exists once the visual field is disappeared. Though, since IOP is the principal risk source causing the loss of RGCs, the approaches of handling mostly involve lessening IOP (Brubaker, 2003). Other essential factors such as cost, suitability and well-being should also be measured (Fechtner and Realini, 2004). Undercurrent treatments for glaucoma involve medication, laser usage and operation.

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With early analysis and appropriate medication and cure, glaucoma can be controlled. Conversely, sight loss causing from glaucoma cannot be renovated. At the present-day, there is no remedy. Once perceived, glaucoma usually needs continuing, long-standing care.

But beforehand the cure recognizing is important. Diagnosing glaucoma is not continually stress-free. The most principal anxiety is defending eyesight. Physician aspects at many aspects before making decisions about treatment.

Glaucoma Diagnosing

Tonometry

In tonometry, eye drops are used to emotionless the eye. Afterward a physician or technician uses a stratagem called a tonometer to measure the inner stress of the eye.A small aggregate of pressure is pertained to the eye by a minute device. The normal range for eye pressure is 12–22 mm Hg. The level of eye pressure by which glaucoma progresses is not the same for everybody and some individuals can get glaucoma even if their pressures are in the normal range.

Ophthalmoscopy

This investigative route aids the doctor scrutinize optic nerve for glaucoma impairment. Eye drops are used to expand the pupil so that the physician sees throughout eye with a particular lens in direction to observe the form and color of the optic nerve.

Perimetry

Perimetry (or a ophthalmic field assessment) creates a map of field of visualization. This analysis helps a specialist to regulate whether a individual vision has been disturbed by glaucoma.

Gonioscopy

This is a investigative exam that supports to regulate whether the position wherever the iris gathers the cornea is open, thin, or closed. Through the examination, eye droplets are used to distress the eye and a distinct hand-held contact lens is smoothly positioned on the eye for a few minutes.

Pachymetry

It measures the wideness of the cornea, the well-defined opening at the anterior of the eye. Corneal thickness has likely to effect eye pressure interpretations. Uncertainty a cornea is thicker than normal, pressure evaluations with a

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tonometer may be sophisticated. This contributes your eye physician surplus evidence for glaucoma analysis.

Medications

Glaucoma is characteristically cured with the use of medications that either helps the unsolidified drain healthier or lessening the quantity of fluid built by the eye. In Most incidents, prescription can securely control eye pressure for several years.

Medications encompass hindering the incursion of aqueous humor, improving the outlay of aqueous humor, shielding the optical nerves (Woodward and Gil, 2004) and biasing the osmotic pressure concerning plasma and the eyes (Kwon et al., 2009). α2 adrenoreceptor agonists and β1 receptor antagonists depress IOP by impeding the inflow of aqueous humor to the eye. Timolol, which is the supreme recommended drug, and betaxolol, which has the littlest universal side effects, are together β1 receptor blockers (Woodward and Gil, 2004). A third kind of drug that restrains the inflow of humor is carbonic anhydrase inhibitors, such as acetazolamide and dorzolamide. Such medications are regularly prepared jointly as in Cosopt (dorzolamide hydrochloride and Timolol maleate) (Fechtner and Realini, 2004). Alternative approach of decreasing IOP is by boosting the outflow of humor from the eyes over the use of muscarinic acetylcholine receptor agonists (Schwartz and Budenz, 2004; Woodward and Gil, 2004). This method is unintended, but encompasses a muscarinic acetylcholine receptor (M3)-mediated narrowing of the ciliary muscle (Woodward and Gil, 2004). The shrinkage triggers the broadening of the gaps in the trabecular meshwork. The latest class of drugs using this approach is the prostaglandin F2α byproducts which boost the uveoscleral outflow (Khaw et al., 2004). Bimatoprost falls underneath this classification and is considered the furthermost successful anti-glaucoma drug (Woodward and Gil, 2004).

Laser and Operation

A subordinate choice for cure of glaucoma is the use of laser treatment. The principal scheme encompasses "burning" holes in several spaces inside the eyes incorporating the ciliary and the pigmented trabecular meshwork cells (Schwartz and Budenz, 2004). The profits contain being noninvasive, demanding fewer patient observance and decreasing the likelihood of infectivity or hemorrhage. The IOP of most patients can cutback approximately 20-30%, but the treatment result wears off 5-10% each year. In addition with timolol, the two year IOP decreasing attainment ratio is 70%, likened with the laser isolated (44%) and timolol alone (30%) (Schwartz and Budenz, 2004).

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A everyday practice of operation is trabeculectomy, which generates a secured channel permitting aqueous humor to run from the fore chamber inside the eye to sub-Tenon's and sub conjunctival area (Khaw et al., 2004; Schwartz and Budenz, 2004). The benefits of operation involve alleviating IOP and avoiding the necessities for exacting patient passivity and constant drug expenditures (Schwartz and Budenz, 2004). Surgery is well-thought-out as the last remedy as failure of operation can outcome in instantaneous blindness due to impediments such as choroidal outflow, hypotonic maculopathy, suprachoroidal bleeding and optical nerve dowsing (Schwartz and Budenz, 2004).

Alternative Surgical Treatments

Looking for to moderate difficulties accompanying with established glaucoma operation, alternate surgical possibilities have been established.

- The Ex-Press tiny glaucoma shunt is used with established trabeculectomy methods to systematize the procedure and conceivably decrease the possibilities of the eye pressure becoming excessively low in the immediate post-operative stage, which is infrequently a problematic with established methodologies.

- Canaloplasty is a technique that implicates magnifying the surviving fluid outflows passageway (the Schlemm's canal) in supplement to generating a novel fluid outflow alleyway within the eye wall.

Gentler sorts of laser Cyclophotocoagulation

These innovative methodologies to glaucoma operation show potential for improved protection. As with all novel practices, time and continuation conclusions are compulsory to see which medical measures will persist advantageous for relieving glaucoma patients durable.

Forthcoming Treatment Possibilities for treatment of glaucoma in Pakistan

Based on latest information gotten from research on the pathology of neuronal apoptosis, there are numerous practices of new treatments that can be helpful for diagnosis of glaucoma in Pakistani population. Some of them are discussed here.

Minimally Invasive Glaucoma Surgery (MIGS)

In this technique, contrasting conventional glaucoma operation, there is minimum maneuvering of the sclera and the conjunctiva. Whilst these practices

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lessen the frequency of hitches, some quantity of efficacy is also transacted for the better protection.

- Miniaturized forms of trabeculectomy; operating tiny, microscopic sized ducts that can be injected into the eye and trench fluid from the internal of the eye to beneath the conjunctiva, these innovative procedures are aimed to create the trabeculectomy process securer.

- Complete internal or suprachoroidal shunts; by Using teeny tubes with very slight internal openings, the front of the eye is connected to the suprachoroidal space between the retina and the wall of the eye to intensify the drainage of fluid from the eye.

- Trabecular Operation; the trabecular meshwork can be detached or evaded.

Neuro defensive Vaccines

Subsequently resistance to elevated intra ocular Pressure is immune related, T-cell provoked neuro-protection may immunize the retinal ganglion cells from apoptosis. For instance, copolymer-1 could be used as a vaccine as it is an antigen that cross responds with a widespread array of T-cells, and can provoke a defensive immune reaction to shield retinal ganglion cells from cell mortality initiated by toxins or improved Intra ocular Pressure (Bakalash et al., 2003). A fundamental concern for planning neuro-defensive vaccines is the position of protection. Some recommended that the focus should be in the retinal ganglion cells and not in the optical nerves because in the initial glaucomatous phase cell fatality stimulated by higher intra ocular pressure that arises in the retinal ganglion cells, not in the optical nerve (Bakalash et al., 2003). R16, a peptide derivative from the retinal ganglion cell, is one paradigm of a neuro-protecting vaccine. Though R16 can instigate slight retinal ganglion cell death for those deprived of glaucoma, the advantage from this treatment extremely surpassed the mutilation from untreated glaucoma situations (Bakalash et al., 2003).

NMDA Receptor Antagonists

Memantine is a NMDA receptor opponent that chunks unnecessary NMDA receptor action. This medication has been accepted for medical use in Europe for the healing of Alzheimer's disease and vascular dementia, although its efficiency in preventing glaucomatous retinal ganglion cell disintegration is still undetermined (Lipton, 2003).

INOS-2 Inhibitors

Subsequently the up regulation of iNOS-2 is injurious to neurons, its inhibition could have a neuro-defensive outcome. An inhibitor like amino guanidine can inhibit the mortality of around 75% of retinal ganglion cells during six months of

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provoked higher intra ocular pressure and help to prevent additional damage of retinal ganglion cells (Neufeld, 2004).

Nutritive Complements

A thought-provoking alternate to amino guanidine is *Ginkgo biloba* extract (EGb 761). *Ginkgo biloba* is used as a nourishing complement for the decline of platelet accumulation, vasodilation and lessening of blood viscidness (Bartlett and Eperjesi, 2004). This comprises 24 percent flavonoid glycosides and 6 percent terpenoids, which might prevent toxicity and NO free radical accretion by impeding iNOS (Hirooka et al., 2004). In experimentations when intra ocular pressure is raised in rats by cautery of episcleral vessels, nurturing the rats 30 mg of EGb 761/day for about five months reduced retinal ganglion cell damage from 29.9% to 4.6% (Hirooka et al., 2004). Additional research scrutinizing the alteration of NO in reaction to EGb 761 treatment might deliver insight into its neuro-defensive method.

Calcium Channel Blockers

Utmost apoptotic means comprise increasing intracellular calcium stages. Flunarizine, a calcium network blocker, has been indicated to expressively increase retinal ganglion cells existence in rat and rabbit mockups by decreasing intra ocular pressure (Osborne et al., 2002). Nevertheless, the accurate method of this and further calcium channel blockers desires to be explained.

STAT-3 Initiation

Alternative objective is the signal transducers and activators of transcription protein 3 (STAT-3). They play an significant role in cell development and discrimination and are of significance due to the messenger RNA of this protein is upbeat regulated in rats with glaucoma (Thanos and Naskar, 2004). The initiation of STAT-3 passageway could impede apoptosis by suppressing caspase-3. One molecule that has been examined is ciliary neurotropic factor (CNTF), which is an interleukin-6 cytokine. The insertion of CNTF into rat eyes with enlarged intra ocular pressure decreases apoptosis, phosphorylates STAT-3, and downgrades the action of caspase-3 (Adamus et al., 2003). Interleukin-10 also has neuro protecting action through the STAT-3 passageway (Boyd et al., 2003).

Caspase Inhibitors

Inhibitors of apoptosis protein (IAP) can correspondingly decrease apoptosis by impeding Caspase. Baculoviral IAP repeat-containing protein-4 (BIRC-4) is a direct inhibitor of Caspase 3, 7 and 9. BIRC-4, transducted into the eye, can obstruct apoptosis of optical nerve axons (McKinnon et al., 2002). A pharmacological methodology for apoptosis inhibition is the usage of minocycline, which could inhibit caspase-3-induced apoptosis (Baptiste et al.,

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2004). It proliferate the persistence rate of retinal ganglion cells visible to the damaging results of glutamate. Moreover, it can act synergistically with MK-801, an opponent to NMDA receptors, to escalate retinal ganglion cells existence percentage.

Heat Shock Proteins

Geranylgeranylacetone (GGA) is an acyclic polyisoprenoid presently used in Japan as an anti-ulcer remedy. The neuro defensive effects of the medication are accelerated through the use of heat shock proteins. Specifically, Heat Shock Protein 72 looks to act as an opposing apoptotic chaperone protein that inhibits with various phases in the apoptotic passageway. Systematically, the drug is assumed to stimulate Heat Shock Factor 1 (HSF-1), a transcription element for heat shock protein, which oligomerizes in the cytosol and transfer into the nucleus once visible to stressors (Sohn et al., 2013).

CONCLUSION

There is no medication for glaucoma still, and vision loss is irretrievable, consequently molecular diagnostics for predictive assessment and early interference is essential to decrease the influence of visual mutilation and eventually blindness. To accomplish this goal, the requirement is to exemplify all subtypes of glaucoma at molecular level and recognize loci/genes contributing to this ophthalmic disorder in diverse populaces.

Abbreviations

PCG: Primary Congenital glaucoma

POAG: Primary Open Angle Glaucoma

PACG: Primary angle Closure Glaucoma

RGCs: Retinal ganglion cells

IOP: Intra Ocular Pressure

CYP1B: Cytochrome P450 1B1

LTBP2: Latent Transforming Growth Factor-Beta-Binding Protein 2

Author Contribution

LK collected data and wrote the manuscript. MA, MQ participated in the design and editing of the manuscript. FJ, and BH edited the first draft.

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