Moroccan Journal Of Public Health Vol. 5, N° 1 (2023), 62-69 ISSN:2658-8099

ORIGINAL ARTICLE

The impact of serum glucose, total cholesterol and triglyceride levels on Breast Cancer risk: A retrospective study

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Article info

Received : June 2023
Accepted : June 2023
Online : July 2023

Keywords

Glucose;
Lipid profile;
Hyperlidemia;
Breast cancer;
Prognosis.

SUMMARY

This study aims to explore the relationship between serum glucose, triglyceride, and total cholesterol levels and breast cancer (BC).

We analyzed data from 100 women with confirmed BC and from the same number of age-matched disease-free controls. Cancer antigen 15-3 (CA15-3) and carcinoembryonic antigen (CEA) levels were determined using chemiluminescent microparticle immunoassay technology. Glucose, triglyceride, and total cholesterol levels were evaluated using the dry chemistry method.

In this study, no significant differences were found comparing glucose and total cholesterol levels in BC cases and controls. The adjusted ORs were 0.84 (95% CI: 0.48-1.49) and 0.62 (95% CI: 0.28-1.37) respectively. However, a significant inverse association between BC risk and increasing levels of triglycerides was observed, particularly at the postmenopausal stage (OR= 0.32, 95%CI: 0.14-0.77). Based on CEA and CA15-3 level measurements and BC duration, we showed that diabetes and lipid status did not influence the course of the malignancy.

Our study highlights the absence of the effects of diabetes and dyslipidemia on the risk and progression of BC. Further prospective investigations are required to confirm this important issue.

Introduction

Breast cancer (BC) continues to be a serious health concern worldwide, as it is considered to be the most commonly diagnosed cancer and the leading cause of cancer death among women. Indeed, BC was the second most commonly diagnosed malignancy, accounting for more than 11.6% of all female cancers, according to the status report on the GLOBOCAN (Bray F et al, 2018).

In Morocco, BC represents 34.3% of all female cancers (Greater Casablanca cancer registry report 2007, 2004; Bouchbika Z et al, 2013). Moreover, most cases are diagnosed in advanced stages: 44% at stage II, 24.4% at stage III, and only 13.5% at stage I (Mechita NB et al; 2016). BC is composed of distinct entities that differ in their capacity to spread cancer cells from the primary tumor to tissues and organs. The exact etiologies of this condition are still not fully known, although a number of BC susceptibility genes have been identified, the most important being BRCA1 and BRCA2 (Miki Y et al, 1994). However, lifestyle, environmental, and reproductive factors may influence BC issues (Boyd NF et al, 1990).

First and foremost, the implementation of the screening program for BC has contributed to reducing morbidity and mortality from disease and improving the quality of life for affected women. It has been postulated that early detection may increase BC incidence by up to 30% where organized programs have been implemented. In clinical practice, regular mammography and physical breast examinations are mostly used by trained health professionals for BC detection (Kawar LN et al, 2013; Mittra I et al, 2013; Smith RA et al, 2013). However, the benefit of early screening and monitoring BC with high sensitivity and specificity using tumor markers such as Cancer Antigen 15-3 (CA15-3) and Carcinoembryonic Antigen (CEA) has been widely demonstrated (O'Hanlon DM, et al, 1995; Uehara M et al, 2008).

Recently, it has been shown that the pathogenesis and prognosis of BC as is the case with many other cancers is associated with the metabolic syndrome defined as a series of metabolic abnormalities with components including obesity, hyperglycemia, hyperinsulinemia, dyslipidemia, and hypertension, which promote the development and progression of type 2 diabetes and cardiovascular diseases (Alexander CM et al, 2008). Due to ethnic differences and diagnostic criteria, its incidence varies widely from region to region. Over the last decade of the 20th century, numerous epidemiological studies in different ethnic groups have been dedicated to exploring the link between metabolic syndrome components and BC risk. However, the published data remain inconsistent (Høyer AP et al, 1992; Chang SJ et al, 2007; Shikata K et al, 2013; Gaard M et al,1994). The metabolic syndrome could increase the risk of worsening health status in cancer patients through alterations of several interdependent hormonal pathways, including those involving insulin, estrogen, cytokines, and growth factors (Xue F et al, 2007) Other possible mechanisms involve hyperinsulinemia and insulin resistance (Vona-Davis L et al, 2007)

To our knowledge, no in-depth research on the relationship between BC and the metabolic syndrome components has been conducted in a Moroccan population. Thus, in this study, we aimed to analyze the association between some biochemical components of metabolic syndrome and BC risk and prognosis among a population originated from an urban area.

Material and methods

Study population and data collection

This study was carried out in the Greater Casablanca area from January 2012 to December 2016. The case group was composed of 100 women with histopathologically confirmed and treated BC (median age 57 years, range 36–

74 years). As this study was retrospective in design, the recruitment of participants and data collection in this case group was done based on the available data from the laboratory registry. Inclusion criteria were age of over 18 years, having lived in the study area for at least 6 months, and historical onset of BC disease. Exclusion criteria included women with a history of other severe diseases. The control group was composed of 100 apparently healthy women (median age 55, range 37–75 years). Controls were matched to case groups based on age and the district of origin of admission. Women were classified as postmenopausal if they were over 47 years old, assuming that they did not report any menstrual bleeding at that age or later. The study was approved by the local ethical committee.

Analysis of plasma samples

Throughout the study, blood samples are collected from participants using appropriate collection tubes, then centrifuged, aliquoted, and stored according to laboratory-specific handling precautions. To ensure sample quality and minimize variation in results, grossly hemolyzed or icteric samples are routinely rejected. Serum glucose, triglyceride, and total cholesterol levels were measured using dry chemistry slides (Ortho Clinical Diagnostics, Johnson & Johnson, Inc.). Tumor marker CEA (normal range <5.0 ng/mL) and CA153 (normal range <31 U/mL) levels were measured using a chemiluminescent microparticle immunoassay technology (Abbott Laboratories, UK). All measurements were done according to the manufacturer's instructions.

Serum glucose, and serum lipid profiles cut-offs

In accordance with Alberti et al (Alberti KG et al, 2009), the cut-offs for laboratory measurements used for serum glucose, triglyceride, and total cholesterol determinations were ≥ 100 mg/dL, ≥ 150 mg/dL (1.7 mmol/L) and ≥ 200 mg/dL (5.6 mmol/L) respectively. The metabolic syndrome has been defined based on the combination of available registration information such as diabetes, treatment of diabetes, history of high blood pressure, and hyperlipidemia.

Statistical analysis

The data were analyzed using Graph Pad Prism 7 software (San Diego, USA). Continuous and dichotomous variables were presented as mean (standard deviation) and n (%) respectively. The statistical difference between means and proportions was assessed using the student t-test and chi-square test, respectively. The adjusted odds ratios (ORs) and 95% confidence intervals (95% Cis) were done using the presence of BC as a dependent variable and parameters of interest (age, menopausal status, fasting glucose, total cholesterol, and triglycerides) as independent variables.

Results

Table 1 highlights the clinical characteristics of BC cases divided into those with (n= 51) and without (n= 49) biochemical metabolic syndrome parameters. The majority of BC cases were more likely to be postmenopausal. The data showed no significant difference in age between the two subgroups of affected patients (p = 0.749). Similarly, the comparison of cancer duration (p = 0.379) did not show any significant differences in the two subgroups (Table 1).

Based on serum CEA and CA153 level measurements, no significant differences were detected in BC outcomes among the two sub-groups (Figure 1). As can be seen in Table 2, comparison of serum glucose, triglyceride, and total cholesterol between BC patients and controls revealed

similar mean levels in both groups (p = 0.509, p= 0.198 and p= 0.804, respectively).

Table 3 shows the distribution of BC cases and controls according to the available individual biochemical parameters involved in metabolic syndrome, and the corresponding ORs. In this study, we observed a significant inverse association between increasing triglyceride levels and the risk of BC among cases compared with controls (OR= 0.39, 95% CI: 0.18-0.88).

When we stratified our study population based on menopausal status, data showed a correlation between high triglyceride levels and the risk of BC in postmenopausal women compared to premenopausal women (OR= 0.32, 95% CI: 0.14-0.77 vs 0.72, 95% CI 0.68-7.80). However, we did not find any significant association between high serum glucose (OR= 0.84, 95% CI: 0.48-1.49) or total cholesterol levels (OR= 0.62, 95% CI: 0.28-1.37) and increased BC risk.

Table 1: Main characteristics of breast cancer cases according to glycemic and lipid status

Characteristics	With biochemical metabolic syndrome parameters (n=51)	Without biochemical metabolic syndrome parameters (n = 49)	*p*-value
Age*, (years)	56.9 (7.23)	57.4 (7.42)	0.749
Menopausal status			
Premenopausal (%)	11.76	12.24	0.941
Postmenopausal (%)	88.24	87.76	
Diabetes status			
Glucose** (mg/dL)	109 [78-405]	87 [66-98]	<0.0001
Lipid status			
Triglycerides ** (mg/dL)	131 [55-272]	94 [41-140]	0.007
Total Cholesterol** (mg/dL)	200 [146-366]	175 [138-212]	0.006
Duration of breast cancer* (years)	11.50 [3-22]	8 [1-16]	0.379

Mean ± standard deviation (SD) ; ** **Median [range]**

Table 2: mean serum glucose, triglyceride, and cholesterol levels in breast cancer patients and control

Parameter (mg/dL)	Reference ranges(mg/dL)	Cases (n=100)	Control (n=100)	*P* value
Age, years*		57.52 (7.16)	55.94 (9.58)	0.188
Serum glucose*	72-110	110.3 (52.6)	105.9 (38.6)	0.509
Serum triglycerides*	35-150	112.3 (55.9)	127.0 (58.3)	0.198
Serum total cholesterol*	116-220	199.7 (40.9)	197.9 (35.2)	0.804

*Mean ± standard deviation (SD)

Table 3: Odds ratio (ORs) for developing breast cancer related to serum triglycerides, total cholesterol and glucose

Characteristics	OR [95%CI]	p-value
	All recruited women	
High triglycerides	0.39 [0.18-0.88]	0.021
High total cholesterol	0.62 [0.28-1.37]	0.235
High glucose	0.84 [0.48-1.49]	0.564
	Postmenopausal women	
High triglycerides	0.32 [0.14-0.77]	0.008
High total cholesterol	0.56 [0.25-1.28]	0.168
High + glucose	0.62 [0.33-1.15]	0.132
	Premenopausal women	
High triglycerides	0.72 [0.68-7.80]	0.79
High total cholesterol	*	*
High glucose	2.5 [0.79-10.79]	0.213

Discussion

In this study, we found no significant difference in glucose levels between BC patients and controls. These results are consistent with our previous published data from a study carried out in the same location, indicating the absence of an association between diabetes status and prostate cancer (Ainahi A et al, 2018). Although some reported data from other investigations is in agreement with our findings (García-Esquinas E et al, 2016) several studies have shown that elevated glucose levels are associated with a high risk of many kinds of cancer, including BC (Agnoli C et al, 2015; Mink PJ et al, 2002 ; Lambe M et al, 2011; Ryu TY et al, 2014).

The lack of the association in our study may be attributed to the small sample size; it would be beneficial to highlight the importance of conducting larger studies in the future. A larger sample size can improve statistical power and increase the reliability of the results. Further, some misclassifications of BC cases, including factors like diagnostic accuracy, disease staging, or other relevant aspects, may have affected the results. Another explanation includes the use of oral glucose-lowering medication for a long period of time. These drugs, commonly used to maintain normal blood glucose levels, are known to inhibit the proliferation of breast cells (Dowling RJ et al, 2011) In the literature, the biological mechanisms involving the potential role of hyperglycemia on BC incidence are more likely related to alterations in circulating concentrations of insulin, insulin-like growth factor (IGF-I) and endogenous sex hormones. Insulin may promote cell proliferation in mammary epithelial cells and breast cancer cells by increasing the synthesis of IGF-I (Milazzo G et al, 1992; Sachdev D et al, 2007; Jung SY et al, 2017; Trinh T et al, 2015; Brown KA et al, 2012; Perks CM et al, 2011)-.

On the other hand, dyslipidemia, which is very often associated with a high fat diet and abdominal obesity, may play a significant role in carcinogenesis (Schreier LE et al, 1999). In the present study, we didn't observe higher total cholesterol levels in BC patients compared to controls. However, we have found a negative relationship between triglycerides and BC. These mixed results differ from other observational studies that have confirmed the positive connection between lipids and BC (Ray G et al, 2001; Geer EB et al, 2009; La Vecchia C et al, 1997; Key TJ et al, 2003). In the literature, several plausible mechanisms, including excess androgen, insulin (Brand JS et 2010), cytokines (Rose DP et al, 2007), or leptin (Siemińska L et al, 2006) may explain the positive association between BC risk and lipid status, especially in menopausal situations. Furthermore, a recent report found evidence of genome-wide genetic correlation between some lipid traits and BC and local genetic correlation at the ABO locus (Kho PF et al, 2021) Complementary analysis and data that support these findings are required to understand the mechanism underlying this causal relationship, with the goal of developing potential therapeutic strategies aimed at altering the cholesterol-mediated effect on BC risk.

Tumor markers such as CA153 and CEA are useful tools for diagnosing and monitoring BC outcomes. Based on serum CEA and CA153 levels and cancer duration as indicators of malignancy progression, no effect of serum glucose or lipid profile was observed. However, previous studies have shown that hyperglycemia may affect anticancer drug response during treatment and thus contribute to worsening BC (Peairs KS et al, 2011)

It should be noted that the design of our study has some limitations, such as the small sample size and the lack of detailed health characteristics (body mass index, obesity, duration of diabetes, intake of medications, and information on the exact age at menopause). In addition, we do not have sufficient data on high and low lipoprotein fractions to complete lipid profile alterations. Nevertheless, there is a good reason to believe that the results of the current report are very encouraging, considering that they

can be useful in understanding the interaction of individual biochemical metabolic syndrome components with the risk of BC in this specific population.

Conclusion

Our findings support the absence of an impact of high glucose and total cholesterol levels on BC risk and outcome among our local women's population. Moreover, our study highlights the unexpected protective effect of increasing triglyceride levels on BC risk. Given the discordant results between different investigations on the influence of diabetes and lipid profiles on BC, complementary studies on BC risk factors will be needed to elucidate this important relationship.

Conflicts of Interest

The authors declare no competing interests regarding the publication of this paper.

Funding Sources

None

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