RESEARCH ARTICLE

The Association Between the Serum Level of IGF-1 and IGFBP-3 and the Risk of Breast Cancer among Women in the Gaza Strip

Heba Mohammed Arafat[1]*, Julia Omar[1], Noorazliyana Shafii[1], Ihab Ali Naser[2], Nahed Ali Al Laham[3], Rosediani Muhamad[4], Tengku Ahmad Damitri Al-Astani[1]*, Ohood Mohammed Shamallakh[5], Kholoud Mohammed Shamallakh[5]

Abstract

Objective: The purpose of this research was to look at the relationship between insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3) levels and the risk for breast cancer (BC) among women in the Gaza Strip. **Methods:** This case-control study, which included 334 participants (112 women with BC as cases, and 222 women without BC as control), was conducted between January 2021 and August 2022. Research data for the cases were gathered at the Oncology Departments of the Gaza Strip's two hospitals, "Al- Shifa Hospital and Turkish Palestinian Friendship Hospital," as well as from the electronic records of the Screening Mammogram Unit at Al-Remal Clinic for controls. The information about the participants was gathered using a standardized questionnaire. The key variables related to BC were identified using multivariate logistic regression. **Results:** According to multivariate logistic regression, participants' age was associated with an increase in the risk of BC (OR= 1.03; 95%CI, 1.007-1.060). There was an association between serum concentrations of fasting blood glucose (FBG) (OR= 1.027; 95% CI, 1.013–1.042), IGF-1 (OR= 1.010; 95% CI, 1.006–1.015), and the risk of BC, while there was no link between IGFBP-3 and the risk of BC. In an analysis of the risk according to menopausal status, premenopausal women were associated with an approximate 0.5 time decrease in risk of BC compared to women in post-menopause (OR= 0.428, 95% CI, 0.258, 0.710). Dairy product was also related to a decreased risk of BC. **Conclusion:** The results suggest that age, lower physical activity, increased levels of FBG, and IGF- 1 increase the BC risk among females in the Gaza Strip. Meanwhile, premenopausal women and dairy products are linked to a reduction in the risk of BC. Furthermore, no link was found between IGFBP-3 and BC risk. Improving early BC detection rates in the Gaza Strip necessitates preventative interventions and screening for BC in the public and healthcare sectors.

Keywords: IGF-1- IGFBP- risk- breast cancer- women- Gaza Strip

Introduction

Breast cancer (BC) has now surpassed lung cancer as the most common form of cancer worldwide (World Health Organization, 2021). In Palestine, BC is regarded as a serious public health concern; in 2021, the incidence rate was 17.8 cases per 100,000 people overall, while it was 36.2 cases per 100,000 females. In the West Bank, 513 new BC cases were registered in 2021, which was 15.2% of all newly registered cancer cases, while in the Gaza Strip, 363 new cases were registered, amounting to 18.6% of all new cancer cases (Ministry of Health, 2022).

Insulin-like growth factor (IGF-1) and its binding proteins may have a major impact on the risk of various cancers (Rollison et al., 2006). IGF-1 and its primary binding protein (IGFBP-3) are known risk factors for BC due to their capacity to promote mitosis and prevent programmed cell death (Monson et al., 2020). The IGF-1 system, which includes IGF-1, IGF-binding proteins (IGFBPs), and the IGF-1 receptor (IGF-1R), is crucial for cellular proliferation and breast tissue development. The interaction of IGF-1 and IGF-1R promotes the phosphatidylinositol 3-kinase (PI3K) and mitogen activated protein kinase (MAPK) pathways, which are

*[1]Department of Chemical Pathology, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, Kubang Kerian 16150, Kelantan, Malaysia. [2]Department of Clinical Nutrition, Faculty of Applied Medical Sciences, Al- Azhar University- Gaza, Gaza City, Palestine. [3]Department of Laboratory Medicine, Al Azhar University-Gaza, Gaza City, Palestine. [4]Department of Family Medicine, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, Kubang Kerian 16150, Kelantan, Malaysia. [5]Department of Medical Laboratory Sciences, Faculty of Health Sciences, Islamic University of Gaza, Gaza City, Palestine. *For Correspondence: damitri@usm.my; hebaarafat4@student.usm.my*

two important signaling cascades for cell proliferation. Meanwhile, a family of IGF binding proteins (IGFBP-1 to IGFBP-6) can compete with IGF-1R to bind circulating IGF-1 with high affinity and specificity, modulating IGF bioavailability and half-life (Christopoulos et al., 2015; Tong et al., 2020).

According to studies, IGF-1 and IGFBP-3 levels in women are linked to both the development and recurrence of BC (Monson et al., 2020). Several studies have found that IGF-1 serum concentration is related to the risk of BC (Rodríguez-Valentín et al., 2022). Initial research found a link between high IGF-1 and IGFBP-3 plasma levels and an increased risk of BC in premenopausal women, but not in postmenopausal women. The European Prospective Investigation into Cancer and Nutrition research, on the other hand, found an elevated BC risk with rising IGF-1 and IGFBP-3 blood concentrations exclusively in older women (age at diagnosis >50y.o) (Papadakis et al., 2017).

A pooled analysis of 17 prospective epidemiologic studies found that circulating IGF-I was related with a 25% increased risk of BC in women ranging from the highest to the lowest quintile, and this relationship was not affected by menopausal status (Hada et al., 2019). The association between the serum concentration of IGFBP-3 and the risk of BC has been inconsistent. Some studies have reported positive associations, while others have shown inverse relationships (Rodríguez-Valentín et al., 2022). To our knowledge, no research has examined the link between serum levels of IGF-1 and IGFBP-3 and BC risk in the Gaza Strip. In this research, we looked at the association between the serum levels of IGF-1, IGFBP-3, and the risk of developing BC.

Materials and Methods

Study design and Setting

The study designed to be case-control study, carried out from January 2021 to August 2022. The participants in this research were selected from the newly diagnosed BC computerized medical records of women who attended the Oncology Department at Al-Shifa Hospital and Turkish Palestinian Friendship Hospital for cases and from the electronic records of the Screening Mammogram Unit at Al-Remal Clinic for controls.

Study Tool and Sampling

A questionnaire that conducted to fit the needs of the case and control groups was filled out during a face-to-face interview using the International Physical Activity Questionnaire (IPAQ), and biochemical analysis. The questionnaire was divided into two main parts: The first part covers socio-demographic variables including age, education level, anthropometric measurements, reproductive history variables, data on the medical records, as well as the family and personal history of cancer; the second part included data regarding lifestyle.

The sample size was determined using the Power and Sample Size Calculator (PS). After considering the 10% anticipated dropout rate, and a 1:2 ratio of the case to control. The total number of participants required in this study was 334 (112 women with BC as cases, and 222 women without BC as control).

Eligibility Criteria

The cases were newly diagnosed BC women confirmed on histopathology and not on any treatment (hormone therapy, chemotherapy, targeted therapy, radiotherapy, or alternative therapy), whereas, the controls were healthy women without BC whose screening mammography tested negative at Al-Remal Clinic. The cases and controls were frequency matched by age group, marital status, and governorate of residence. All individuals were subsequently recruited after providing written informed consent to participate.

Blood samples and biochemical analysis

The blood samples were collected at Al-Shifa Hospital, Turkish Palestinian Friendship Hospital, and Al-Remal Clinic. The samples were transferred under quality control and sterile conditions to Palestinian Medical Relief Society for biochemical analysis (IGF-1 and IGFBP-3). Under quality control and safety standards, venipuncture was used to obtain 5 ml of each participant's whole blood, then the whole blood was placed into redtop tubes, and centrifuged for ten minutes at 3,000 rpm. The serum was separated and analyzed for quantitative determination of FBG using analytical kit on Respons 920 fully auto analyzer (DiaSys, Germany), serum Growth Hormone (IGF-I and IGFBP-3) using analytical kits on the MAGLUMI 800 series fully auto-chemiluminescence immunoassay analyzer (Snibe, China).

Statistical analysis

Data collection, anthropometric measurements, and questionnaire results were reviewed before being incorporated into the Statistical Package for the Social Sciences (SPSS version 26). Pre- and postmenopausal women's data were evaluated independently. The socio-demographic characteristics were summarized using descriptive statistics. Numerical data like age of participant, waist circumference, body mass index (BMI), FBG, IGF-1 levels, and IGFBP-3, were presented as mean ±SD. Categorical information was shown as frequency (percentage). For the comparison of categorical data, the chi-square test was utilized. Using an independent t-test, quantitative data from two groups were analyzed.

To compare BC risk in women with high levels of IGF-1 and IGFBP-3 to those with lower levels, we utilized multiple logistic regressions on the 1:2 matched pairs of cases and controls. We adjusted for baseline factors such as menopausal status, gravidity, parity, BMI, smoking, past use of oral contraceptives (OC) and hormone replacement therapy (HRT), and dairy product intake. Two-sided testing was used to obtain each P-value, with a value (P ≤ 0.05) deemed a statistically significant test result.

Results

In accordance with the case-control status, Table 1 displays the participant baseline characteristics. We identified 112 BC cases and 222 controls. Cases were less likely to be educated, to be between the ages of 19

Table 1. Sociodemographic Features of the Study Participants

Sociodemographic variables		Cases n = 112 N (%)	Controls n = 222 N (%)	P value
Educational level	Illiterate	2 (1.8)	0 (0.0)	0.013
	Primary school	6 (5.4)	8 (3.6)	
	Middle school (preparatory)	18 (16.1)	30 (13.5)	
	High school certificate (secondary)	51 (45.5)	81 (36.5)	
	Intermediate post high school diploma	11 (9.8)	13 (5.9)	
	Graduation (Bachelor's) Professional degree	22 (19.6)	85 (38.3)	
	Master's and above	2 (1.8)	5 (2.3)	
Marital status	Single	10 (8.9)	16 (7.2)	0.694
	Married	97 (86.6)	191 (86.0)	
	Divorced	3 (2.7)	6 (2.7)	
	Widow	2 (1.8)	9 (4.1)	
Age at Menarche	9 years or younger	0 (0.0)	2 (0.9)	0.602
	10-14 years	91 (81.3)	179 (80.6)	
	More than 14 years	21 (18.8)	41 (18.5)	
Gravidity	None	16 (14.3)	31 (14.0)	0.815
	One	3 (2.7)	9 (4.1)	
	Two	5 (4.5)	15 (6.8)	
	Three	13 (11.6)	20 (9.0)	
	Four or more	75 (67.0)	147 (66.2)	
Parity	Nulliparous	20 (17.9)	33 (14.9)	0.863
	1-2	14 (12.5)	25 (11.3)	
	3-5	36 (32.1)	78 (35.1)	
	>5	42 (37.5)	86 (38.7)	
Age at first delivery	Never	13 (11.6)	28 (12.6)	0.047
	≤18	23 (20.5)	55 (24.8)	
	19-25	56 (50.0)	122 (55.0)	
	>25	20 (17.9)	17 (7.7)	
Menopausal status	Premenopausal	71 (63.4)	178 (80.2)	£ 0.001
	Postmenopausal	41 (36.6)	44 (19.8)	
OC use	No	86 (76.8)	173 (77.9)	0.813
	Yes, previously	26 (23.2)	49 (22.1)	
HRT use	No	106 (94.6)	210 (94.6)	0.985
	Yes, previously	6 (5.4)	12 (5.4)	
Cigarette smoking	Yes, current smoker	2 (1.8)	2 (0.9)	0.344
	Passive smoking	37 (33.0)	55 (24.8)	
	No	71 (63.4)	159 (71.6)	
	Nargileh	2 (1.8)	6 (2.7)	
First-degree relatives for BC	No	97 (86.6)	207 (93.2)	0.045
	Yes	15 (13.4)	15 (6.8)	
Physical activity	Low	66 (58.9)	99 (44.6)	0.014
	Moderate	45 (40.2)	111 (50.0)	
	High	1 (0.9)	12 (5.4)	
BMI category	Underweight	0 (0.0)	3 (1.4)	0.624
	Normal	22 (19.6)	54 (24.3)	
	Overweight	36 (32.1)	72 (32.4)	
	Obesity Class I	34 (30.4)	60 (27.0)	
	Obesity Class II	14 (12.5)	26 (11.7)	
	Obesity Class III	6 (5.4)	7 (3.2)	

N, Frequency; BC, Breast Cancer; OC, Oral contraceptives; HRT, Hormone replacement therapy; BMI, Body mass index; P ≤ 0.05, Significant.

Table 2. The Relationship between Serum Concentrations of IGF-1 and IGFBP-3 and BC Risk by Case-Control

Variables	Cases Mean (SD)	Controls Mean (SD)	P value
Age of participant	45.4 (10.5)	41.8 (8.9)	0.002
Waist Circumference (cm)	91.1 (7.6)	88.7 (11.6)	0.029
BMI	29.8 (5.6)	29.0 (5.6)	0.221
IGF-1 (ng/ml)	119.5 (59.0)	92.3 (48.8)	≤0.001
IGFBP-3 (µg/mL)	5.8 (22.4)	3.4 (1.4)	0.261

BC, Breast Cancer; SD,Standard deviation; BMI, Body mass index; IGF-1, Insulin-like Growth Factor-1; IGFBP-3, Insulin-like Growth Factor binding protein-3; P ≤ 0.05, Significant.

and 25 years, to be premenopausal, to have no first-degree relatives with BC, and to engage in less intense physical activity than control participants. Marital status, age at menarche, gravidity, parity, use of HRT and OC, cigarette smoking, and BMI did not statistically differ between the two groups.

The average age of the study population was 45.4 for the cases and 41.8 for the controls. Additionally, cases had statistically significant higher IGF-1 levels and waist circumference than controls (P≤ 0.001), while serum IGFBP-3 levels were not statistically significant in cases vs. controls (P=0.261) as shown in Table 2.

Table 3 explores the BC risk linked with socio-demographic data. The participants' ages were linked to an elevated risk of BC (OR= 1.03; 95% CI, 1.007–1.060), each year's increase in age participants was 1.03 times more likely to have BC risk. According to menopausal status, premenopausal women were associated with an approximate 0.5 time decrease in the BC risk than postmenopausal women. Consistent with the results, women who consume milk and dairy product have decreased risk of BC. In contrast to moderate or more vigorous physical activity, lower-intensity exercise was linked to an increased chance of developing BC. Additionally, there was an association between serum concentrations of FBG (OR= 1.027; 95% CI, 1.013-1.042), IGF-1 (OR= 1.010; 95% CI, 1.006-1.015), and the risk of BC, while, IGFBP-3 serum concentrations and BC risks were not related (data not shown).

Discussion

This study set out to explore whether there was an association between the serum levels of IGF-1 and IGFBP-3 and the risk of BC among Palestinian women in the Gaza Strip. In this research, we found that women with IGF-1 concentrations above the average had a statistically significant higher risk of developing BC.

Regarding the age of participants and BC risk, the findings of this research displayed that for every year's increase in age, participants were 1.03 times more likely to have BC among females in the Gaza Strip. Similar findings from earlier studies indicated that the incidence of BC increases with age and primarily affects older women (Butt et al., 2012; Pathy et al., 2011; Sandhu et al., 2010; Surakasula et al., 2014).

According to this study, women who exercise may have a decreased risk of BC than those who do not. Various research also indicated that exercise lowers the incidence of BC (Shuvo et al., 2017). Although there is less information on premenopausal women, more physical activity, especially recreational physical activity, was linked to lowering both pre-and postmenopausal women's risk of BC (Chan et al., 2019).

According to our research, women who consume milk and dairy products had a lower risk of BC. Our findings were similar to those of earlier researches, which indicated that consumption of milk and eggs was linked with a lower chance of developing BC, whereas consumption of all types of fish and meat was connected with a high risk (Bao et al., 2012; Shuvo et al., 2017). Additionally, dairy products include linoleic acid, a possible anticancer fat compound that can prevent the expansion and proliferation of cancer cells. These foods also contain vitamin D and calcium, which are known to have cancer-preventive properties. Meanwhile, a recent review published in the American Journal of Clinical Nutrition raises the possibility that intake of low-fat dairy products, including yogurt, cottage cheese, and skimmed milk may safeguard females from the condition (Rodríguez-Alcalá et al.,

Table 3. Multivariate Logistic Regression Model of Risk Factors and BC among Palestinian Females in the Gaza Strip.

Variables	OR	P-value	Confidence Interval 95%
Age of participant	1.03	0.012	(1.007, 1.060)
Low physical activity	7.31	0.06	(0.921, 58.005)
Moderate physical activity	4.538	0.153	(0.569, 36.201)
Milk and dairy product	0.972	0.037	(0.947, 0.998)
Menopausal status	0.428	≤0.001	(0.258, 0.710)
FBG (mg/dl)	1.027	≤ 0.001	(1.013, 1.042)
IGF-1 (ng/ml)	1.01	≤ 0.001	(1.006, 1.015)

FBG, Fasting blood glucose; IGF-1, Insulin-like Growth Factor-1; P ≤ 0.05, Significant.

2017).

According to the study's findings, BC is less likely to occur in females who have not yet reached menopause than it is in females who have (OR= 0.428, 95%CI, 0.258, 0.710). Similarly, Arafat et al., (2021) reported the same findings in a meta-analysis on BC risk from modifiable and non-modifiable risk factors in Palestinian women (Arafat et al., 2021). Additionally, Sangrajrang et al., (2013) found a statistically significant link between higher BC risk and postmenopausal women.

When compared to healthy controls, our research found that women with high FBG levels were overall 1.027 more likely to acquire BC. Similar findings were found in a study revealed that the fasting plasma glucose level was significantly increased in the BC patients (101.94±2.94 mg/dL) than the controls (90.75±2.02 mg/dL), p=0.002 (Osman et al., 2022).

Other studies (Alokail et al., 2009; Haseen et al., 2015; Kabat et al., 2009; Sieri et al., 2012) have also found higher FBG, in BC cases when compared to the control group, in accordance with our findings. Contrarily, research from Sweden and Korea revealed that the risk of BC was not correlated with blood glucose levels (Haseen et al., 2015; Jiralerspong et al., 2009). Also, neither premenopausal nor postmenopausal women in research by Manjer et al. showed any correlation between blood glucose levels and risk of BC (Haseen et al., 2015). High glucose levels are crucial for the growth and development of BC cells (Jiralerspong et al., 2009; Zhao et al., 2020). Additionally, high glucose concentrations promote the in vitro invasiveness of human breast cancer cell line MDA-MB-435 by altering the expression of matrix metalloproteinase MMP-9/MMP-2/E-cadherin (Hou et al., 2017).

According to research, IGF-1 controls fuel metabolism and is a crucial regulator of BC cell growth, proliferation, survival, differentiation, and transformation in many types of cancer, including BC. IGF-1 promotes downstream pathways involved in cancerous processes such as the PI3K/AKT, RAS/RAF/MAPK, and STAT cascades (Rodríguez-Valentín et al., 2022). There is evidence from numerous research that there is a link between elevated BC risk and IGF-1 levels (Baglietto et al., 2007; Rinaldi et al., 2006; Vatten et al., 2008; Zhu et al., 2020). Our results are in line with a meta-analysis of 17 epidemiological studies that found circulating IGF-1 to be positively linked with BC risk (OR= 1.28; 95%CI, 1·14–1·44; P < 0·0001) (Hormones et al., 2010). However, our finding is inconsistence with the study done by Abdulla et al, 2018 suggests that there is no evidence of an increased level of IGF-1 among Kurdish BC women (Abdulla et al.; Grønbaek et al., 2004).

Meanwhile, there is no evidence of elevated serum levels of IGFBP-3 among Palestinian BC women that is comparable to the findings from several but not all epidemiological studies. According to Schairer et al, 2010, there is no statistically significant association between IGFBP-3 levels and BC risk with OR of 1.01 (95% 0.86–1.18) (Schairer et al., 2010). In line with other studies' findings (Falk et al., 2006; Schernhammer et al.,

2006; Toniolo et al., 2000), IGFBP-3 concentrations and BC risk did not significantly correlate with one another. Contrary to our findings, Renehan et al., (2006) showed that levels of IGFBP-3 were positively linked to the risk of BC (OR= 1.96 (95%CI, 1.28- 2.99)) (Renehan et al., 2006). This might be a result of genetic and lifestyle factors in the risk of BC and other chronic illnesses.

This research has various strengths including a high case and control participation rate, an age-matched case-control study design, and the enrollment of healthy volunteers and patients with newly diagnosed, histologically confirmed malignant BC who had not received any therapy. Furthermore, this is the first epidemiological research in the Gaza Strip on the association between serum levels of IGF-1 and IGFBP-3 and BC risk.

In conclusion, this is the first study to look at the relationship between serum IGF-1 and IGFBP-3 levels and BC risk in Palestinian women in Gaza Strip. According to the study's findings, women in the Gaza Strip are at an increased risk of BC as they age, engage in lower physical activity, and develop an increased level of FBG, and IGF- 1. Premenopausal women and dairy product consumption, meanwhile, are linked to a lower incidence of BC. Additionally, there was no link between IGFBP-3 and the risk of BC.

Weight loss, increased physical activity, or pharmacological methods may all be used to lower FBG or circulating IGF-1 levels, hence decreasing the BC risk. Additionally, raising of early detection rate of BC in the Gaza Strip necessitates efforts to spread the concept of BC screening among the public and healthcare sectors to save women's lives and strengthen positive societal attitudes about breast health care. This includes support from family and friends.

List of abbreviations

BC, Breast Cancer; IGF-1, Insulin-like Growth Factor-1; IGFBP-3, Insulin-like Growth Factor Binding Protein-3; FBG, Fasting Blood Glucose; BMI, Body Mass Index; HRT, Hormone Replacement Therapy; OC, Oral Contraceptives; SD, Standard Deviation; CI, Confidence Interval; OR, Odds Ratio.

Author Contribution Statement

Conceptualization, H.M.A., J.O., I.A.N., O.M.SH., N.A.L., N.S., KH.M.SH., R.B.M., and T.A.D.A.; Methodology, H.M.A., and J.O.; Validation, H.M.A., O.M.SH., and KH.M.SH.; Data curation, H.M.A., J.O., I.A.N., O.M.SH., and N.S.; Writing—original draft preparation, H.M.A.; Writing—review and editing, H.M.A., I.A.N., J.O., O.M.SH., N.A.L., N.S., KH.M.SH., R.B.M., and T.A.D.A. All authors revised the manuscript and approved the final version to be submitted.

Acknowledgements

Hospital, and Al- Remal Clinic for permitting us to conduct the study in the Gaza Strip and to the laboratory staff at the Palestinian Medical Relief Society for their permission to conduct the laboratory tests and their great help, as well as the women who participated in our study.

Ethics approval

All participants in the research have provided informed consent for the use of questionnaire data and blood samples. Ethical approval was obtained from the Helsinki committee to conduct the research in the Gaza Strip, approval number PHRC/HC/699/20 at its meeting on 2020/02/03. Furthermore, ethical approval was obtained from the Human Research Ethics Committee, USM, JEPeM USM Code: (USM/JEPeM/20020122 on 13th January 2022).

Availability of data and materials

Upon a reasonable request, the corresponding author will disclose the datasets used and/or analyzed in the current study.

Conflict of Interests

The authors declare that they have no conflict of interest.

References

Abdulla PR, Ismael BO, Namiq KF, et al (2018). Insulin-Like Growth Factor-1 And Breast Cancer Risk In Kurdish Women. *Breast Cancer*, **3**, 5.

Alokail MS, Al-Daghri NM, Al-Attas OS, et al (2009). Combined effects of obesity and type 2 diabetes contribute to increased breast cancer risk in premenopausal women. *Cardiovasc Diabetol*, **8**, 1-7.

Arafat HM, Omar J, Muhamad R, et al (2021). Breast Cancer Risk From Modifiable and Non-Modifiable Risk Factors among Palestinian Women: A Systematic Review and Meta-Analysis. *Asian Pac J Cancer Prev*, **22**, 1987-95.

Baglietto L, English DR, Hopper JL, et al (2007). Circulating insulin-like growth factor-I and binding protein-3 and the risk of breast cancer. *Cancer Epidem Biomar*, **16**, 763-68.

Bao PP, Shu XO, Zheng Y, et al (2012). Fruit, vegetable, and animal food intake and breast cancer risk by hormone receptor status. *Nutr Cancer*, **64**, 806-19.

Butt Z, Haider SF, Arif S, et al (2012). Breast cancer risk factors: a comparison between pre-menopausal and post-menopausal women. *J Pak Med Assoc*, **62**, 120.

Chan DSM, Abar L, Cariolou M, et al (2019). World Cancer Research Fund International: Continuous Update Project-systematic literature review and meta-analysis of observational cohort studies on physical activity, sedentary behavior, adiposity, and weight change and breast cancer risk. *Cancer Causes Control*, **30**, 1183-200.

Christopoulos PF, Msaouel P, Koutsilieris M (2015). The role of the insulin-like growth factor-1 system in breast cancer. *Mol Cancer*, **14**, 1-14.

Falk RT, Brinton LA, Madigan MP, et al (2006). Interrelationships between serum leptin, IGF-1, IGFBP3, C-peptide and prolactin and breast cancer risk in young women. *Breast Cancer Res Treat*, **98**, 157-65.

Grønbaek H, Flyvbjerg A, Mellemkjaer L, et al (2004). Serum insulin-like growth factors, insulin-like growth factor binding proteins, and breast cancer risk in postmenopausal women. *Cancer Epidemiol Biomarkers Prev*, **13**, 1759-64.

Hada M, Oh H, Pfeiffer RM, et al (2019). Relationship of circulating insulin-like growth factor-I and binding proteins 1–7 with mammographic density among women undergoing image-guided diagnostic breast biopsy. *Breast Cancer Res*, **21**, 1-16.

Haseen SD, Khanam A, Sultan N, et al (2015). Elevated fasting blood glucose is associated with increased risk of breast cancer: outcome of case-control study conducted in Karachi, Pakistan. *Asian Pac J Cancer Prev*, **16**, 675-78.

Hormones TE, Group BCC (2010). Insulin-like growth factor 1 (IGF1), IGF binding protein 3 (IGFBP3), and breast cancer risk: pooled individual data analysis of 17 prospective studies. *Lancet Oncol*, **11**, 530-42.

Hou Y, Zhou M, Xie J, et al (2017). High glucose levels promote the proliferation of breast cancer cells through GTPases. Breast Cancer: *Targets Ther*, **9**, 429.

Jiralerspong S, Palla SL, Giordano SH, et al (2009). Metformin and pathologic complete responses to neoadjuvant chemotherapy in diabetic patients with breast cancer. *J Clin Oncol*, **27**, 3297.

Kabat GC, Kim M, Caan BJ, et al (2009). Repeated measures of serum glucose and insulin in relation to postmenopausal breast cancer. *Int J Cancer*, **125**, 2704-10.

Ministry of Health (2022). Health Annual Report Palestine 2021. Retrieved from https://site.moh.ps/index/Books/BookType/2/Language/ar.

Monson KR, Goldberg M, Wu HC, et al (2020). Circulating growth factor concentrations and breast cancer risk: a nested case-control study of IGF-1, IGFBP-3, and breast cancer in a family-based cohort. *Breast Cancer Res*, **22**, 1-5.

Osman HMA, Faggad AS (2022). Increased Fasting Plasma Glucose and Breast Cancer Risk in Sudanese Women: Association with Premenopausal Status and High Body Mass Index. *Asian Pac J Cancer Biol*, **7**, 289-95.

Papadakis GZ, Mavroudis D, Georgoulias V, et al (2017). Serum IGF-1, IGFBP-3 levels and circulating tumor cells (CTCs) in early breast cancer patients. *Growth Horm IGF Res*, **33**, 28-34.

Pathy NB, Yip CH, Taib NA, et al (2011). Breast cancer in a multi-ethnic Asian setting: results from the Singapore-Malaysia hospital-based breast cancer registry. *Breast J*, **20**, S75-80.

Renehan AG, Harvie M, Howell A (2006). Insulin-like growth factor (IGF)-I, IGF binding protein-3, and breast cancer risk: eight years on. *Endocr Relat Cancer*, **13**, 273-78.

Rinaldi S, Peeters PH, Berrino F, et al (2006). IGF-I, IGFBP-3 and breast cancer risk in women: The European Prospective Investigation into Cancer and Nutrition (EPIC). *Endocr Relat Cancer*, **13**, 593-605.

Rodríguez-Alcalá LM, Castro-Gómez MP, Pimentel LL, et al (2017). Milk fat components with potential anticancer activity-a review. *Biosci Rep*, **37**.

Rodríguez-Valentín R, Torres-Mejía G, Martínez-Matsushita L, et al (2022). Energy homeostasis genes modify the association between serum concentrations of IGF-1 and IGFBP-3 and breast cancer risk. *Sci Rep*, **12**, 1-11.

Rollison DE, Newschaffer CJ, Tao Y, et al (2006). Premenopausal levels of circulating insulin-like growth factor I and the risk of postmenopausal breast cancer. *Int J Cancer*, **118**, 1279-84.

Sandhu D, Sandhu S, Karwasra R, et al (2010). Profile of breast cancer patients at a tertiary care hospital in north India.

Indian J Cancer, **47**, 16.

Schairer C, McCarty CA, Isaacs C, et al (2010). Circulating insulin-like growth factor (IGF)-I and IGF binding protein (IGFBP)-3 levels and postmenopausal breast cancer risk in the prostate, lung, colorectal, and ovarian cancer screening trial (PLCO) cohort. *Horm Cancer*, **1**, 100-11.

Schernhammer ES, Holly JM, Hunter DJ, et al (2006). Insulin-like growth factor-I, its binding proteins (IGFBP-1 and IGFBP-3), and growth hormone and breast cancer risk in The Nurses Health Study II. *Endocr Relat Cancer*, **13**, 583-92.

Shuvo SD, Ahmad T, Paul DK, et al (2017). Dietary patterns and knowledge perception of breast cancer risk patients. *Nutr Food Sci*, **47**, 270-87.

Sieri S, Muti P, Claudia A, et al (2012). Prospective study on the role of glucose metabolism in breast cancer occurrence. *Int J Cancer*, **130**, 921-29.

Surakasula A, Nagarjunapu GC, Raghavaiah K (2014). A comparative study of pre-and post-menopausal breast cancer: Risk factors, presentation, characteristics and management. *J Res Pharm Pract*, **3**, 12.

Tong Y, Wu J, Huang O, et al (2020). IGF-1 interacted with obesity in prognosis prediction in HER2-positive breast cancer patients. *Front Oncol*, **10**, 550.

Toniolo P, Bruning PF, Akhmedkhanov A, et al (2000). Serum insulin-like growth factor-I and breast cancer. *Int J Cancer*, **88**, 828-32.

Vatten LJ, Holly JM, Gunnell D, et al (2008). Nested case-control study of the association of circulating levels of serum insulin-like growth factor I and insulin-like growth factor binding protein 3 with breast cancer in young women in Norway. *Cancer Epidemiol Biomarkers Prev*, **17**, 2097-100.

World Health Organization (2021). breast-cancer-now-most-common-form-of-cancer-who-taking-action. Retrieved from https://www.who.int/news/item/03-02-2021-breast-cancer-now-most-common-form-of-cancer-who-taking-action.

Zhao P, Xia N, Zhang H, et al (2020). The metabolic syndrome is a risk factor for breast cancer: a systematic review and meta-analysis. *Obes Facts*, **13**, 384-96.

Zhu Y, Wang T, Wu J, et al (2020). Biomarkers of Insulin and the Insulin-Like Growth Factor Axis in Relation to Breast Cancer Risk in Chinese Women. *Onco Targets Ther*, **13**, 8027.