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Original article

RISK ASSESSMENT IN CORRELATION WITH OBESITY AND LABORATORY MONITORING OF THE MOST COMMON FEMALE BREAST CANCERS IN SARAJEVO CANTON

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Abstract

Introduction: Breast cancer (BC) is a malignant disease that predominantly affects women, with known genetic components such as mutations in tumor suppressor genes BRCA1 and BRCA2. Other risk factors include unhealthy lifestyles, lack of physical activity, and consumption of alcohol and cigarettes. Aging also plays a role in BC development, with hormonal influences such as estrogen and progesterone promoting cancer growth.

Material and Methods: Research was conducted using data collection tools for risk factors and tumor markers from primary healthcare unit records. The sample comprised 200 women, divided into two groups based on BC diagnosis, with complete medical documentation. Male BC cases were excluded.

Results: Statistical significance was found between genetic components, family history, aging, obesity, alcohol and cigarette consumption, longer hormone exposure, and female BC development using the Chi-Square test, confirmed by Fisher's Exact test. Tumor markers CA 15-3, CEA, CA 19-9, and CA 125 were useful for BC screening and metastasis detection, as determined by the One Sample T-test. In Sarajevo Canton, invasive ductal BC was the most common type among women, while lobular carcinoma in situ was the least common.

Conclusion: Correlations between risk factors, including aging, unhealthy lifestyles, and hormone exposure, and increased BC risk were confirmed. Tumor markers CA 15-3, CEA, CA 19-9, and CA 125 were effective in diagnosis, screening, and metastasis detection in females, with sensitivity for regression detection at 81.8% and specificity at 100%.

Keywords: breast cancer, tumor markers, risk factors, lifestyles, genetics.

INTRODUCTION

According to data from the World Health Organization (WHO) in 2020, breast cancer (BC) stands as the most common cancer among women globally, and the second most common overall, with 2.3 million newly diagnosed cases among women worldwide, resulting in 685,000 deaths. Additionally, male BC accounts for approximately 0.5 to 1% of cases. Data from the Institute of Public Health FBiH revealed that malignant neoplasm of the breast (C50) ranked seventh among the leading causes of death in 2022, and first among the most common causes of death from malignancies. It was followed by malignant neoplasms of the bronchus and lungs (C34) and malignant neoplasm of the colon (C18).

Genetic components, including family history and carrying mutations of BRCA1 and BRCA2 genes, play significant roles in the development of BC. However, unhealthy lifestyles and environmental factors also exert a considerable influence.

Factors that increase the risk of developing BC include obesity due to an unhealthy lifestyle with a lack of physical activity after menopause, smoking, and consuming alcohol. Other risk factors include aging, nulliparity, having a first childbirth after the age of 30, never breastfeeding, early menarche, late menopause, use of hormonal replacement therapy and oral contraceptives, and exposure to thoracic radiotherapy before the age of 30. These factors will be further elaborated in this paper (1-4).

Early detection of BC enhances the chances of successful treatment. Therefore, it is crucial for every woman to take responsibility for her healthcare and conduct self-examinations if she is exposed to any of the previously mentioned risks. Screening programs for high-risk groups, including mammography and other examinations, are designed to prevent the disease. In cases of suspected disease, biopsies and tumor markers should be performed as laboratory screenings. Despite their limited sensitivity, tumor markers such as CA 15-3, CEA, CA 19-9, and CA 125 exhibit high specificity, particularly in detecting disease regression or the presence of metastases (5, 6).

The benefit of this research lies in identifying the exposure of women in Sarajevo Canton to BC risk factors. Based on this information, preventive examinations can be planned to detect BC long before it manifests symptoms, thereby reducing mortality rates from the disease and healthcare expenses. **The study aims** to motivate the healthcare sector to further investigate this issue and raise awareness among women about the risk factors associated with BC. One of the study's objectives is to examine the correlation between the rising obesity rates among women in Sarajevo due to depression and unhealthy lifestyles, which hinders physical activity. This correlation aligns with aging, the use of hormonal replacement therapy among postmenopausal women, and the increased risk of developing BC.

MATERIAL AND METHODS

A case-control study was conducted from July to September 2021 at The Public Institution Health Centre of Sarajevo Canton, specifically at the Organisational Unit Health Centre Novi Grad in the Primary healthcare unit located in the central facility. A sample of 200 women was included, consisting of 100 women with BC and 100 women without a BC diagnosis, serving as the control group. Data for the control group were collected from family medical records. A total of 200 family medical records with comprehensive medical documentation were randomly selected and examined. This method was chosen to minimize bias, ensuring the sample adequately represents the population, including all women with BC from Sarajevo Canton.

Inclusion criteria for the research were women diagnosed with BC and women without BC, residing in Sarajevo Canton, and possessing complete medical documentation. Exclusion criteria included men with BC, patients residing outside Sarajevo Canton, and patients lacking complete medical documentation. Data on tumor markers were extracted from family medical records and analyzed using analyzers such as ARCHITECT i2000SR, Vitros 5600, and Vitros ECIQ. Collected

risk factors included age, education, marital status, history of BC diagnosis, history of benign breast disease, and any family history of BC, including BRCA mutations. Additional data collected encompassed BMI, age of first menarche, number of pregnancies, breastfeeding history, menopausal status, potential use of hormonal replacement therapy or oral contraceptives, and history of ovariectomy. Lifestyle factors, such as smoking and alcohol consumption, were also recorded.

Statistical analysis was performed using IBM Statistics SPSS v 17.0 and MedCalc software, with results prepared and presented using Microsoft Word and Excel 2019. Prior to analysis, data distribution was tested using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Risk factor data exhibited non-normal distribution, necessitating the use of non-parametric tests including the Chi-Square test and Fisher's exact test. Tumor marker data demonstrated normal distribution allowing for the use of the parametric One Sample T-test. A significance level of $p < 0.05$ was considered statistically significant, with a confidence level of 95%.

RESULTS

For the total sample (N=200), we analyzed the ages of patients, noting that most women with BC were in the 65+ age group, followed by those in the 41-65 age group. This trend was consistent across both the BC group and the control group, each comprising 100% of the sample, as shown in Table 1 with statistical significance.

In our study, the majority of patients with breast cancer and those in the control group had secondary education. In terms of marital status, most patients, both with BC and in the control group, were married.

Furthermore, the majority of patients with BC and those in the control group did not have a history of benign breast disease. Analysis of family history of BC reveals that most patients with BC had a positive family history, including positive mutations of BRCA 1 and BRCA 2 genes, unlike the control group.

Additionally, most patients with BC were obese, contrasting with the control group. Furthermore, early menarche was more prevalent among patients with BC compared to the control group, where women mainly experienced menarche between the ages of 13 and 15.

Regarding the variable number of pregnancies, it is notable that the majority of patients with BC had given birth one or two times, mirroring the distribution seen in the control group. Additionally, most patients with BC who had given birth were also breastfeeding their babies, in contrast to the control group where a small proportion of women had never breastfed their children. Conversely, women in the control group were less likely to use oral contraceptives compared to women with BC, with approximately half of the latter group reporting usage for at least two months.

A significant portion of patients with BC were post-menopausal, whereas the control group was evenly split between pre-menopausal and post-menopausal women. Concerning the variable use of hormonal replacement therapy, most patients with BC reported using hormonal replacement therapy for at least two months, contrasting with the control group where usage was less common. Similarly, the majority of patients with BC and those in the control group had not undergone ovariectomy. Most patients with BC reported not smoking or consuming alcohol, a pattern also observed in the control group.

In this study, we monitored the tumor markers CA 15-3, CEA, CA 19-9, and CA 125. The reference ranges for these markers were as follows: <25 kIU/L for CA 15-3, <4.6 ng/mL for CEA in non-smokers and <10 ng/mL for smokers, <27 kIU/L for CA 19-9, and <35 IU/mL for CA 125.

Among our sample of patients with BC (N = 100), the most commonly utilized combination of tumor markers for follow-up and metastasis detection was CA 15-3 and CEA, comprising 78% of cases. This was followed by a combination of CA 15-3, CEA, CA 19-9, and CA 125, utilized in 13% of cases. The least utilized combination was CA 125, CA 15-3, and CEA, accounting for 9% of the total sample.

Comparison of our data for these tumor markers with data from the literature conducted using One Sample T-tests demonstrated statistical significance. Descriptive presentations of CA 125 values (Figure 1) and CEA values (Figure 2) according to our sample are provided in the accompanying figures.

Comparison of our data for tumor markers CA 15-3, specific for BC, and CA 19-9, specific for pancreatic cancer, with data from the literature, followed by One Sample T-tests, revealed statistical significance for their use in detecting BC. Descriptive presentations of CA 15-3 values (Figure 3) and CA 19-9 values (Figure 4) for our sample are provided below. The sensitivity

achieved for CA 15-3 in detecting regression was 81.8% with a specificity of 100% at a cutoff value of 19.55 kIU/L.

Among the group of women with BC from our study (N=100), the most prevalent type of BC in Sarajevo Canton was invasive ductal BC, accounting for 69 cases or 69% of the total sample. This was followed by ductal carcinoma in situ (DCIS) with 15 cases or 15%, and invasive lobular BC with 11 cases or 11% of the total sample. The least common type of BC observed among women in Sarajevo Canton was lobular carcinoma in situ (LCIS), comprising 5 cases or 5% of the total sample. Additionally, the correlation between the type of cancer and tumor markers is depicted in the figures below (Figure 5 and 6).

It is well-established that genetic components play a significant role in the development of BC, notably through mutations in tumor suppressor genes such as BRCA 1 and BRCA 2. In our sample, we gathered data on the presence of BRCA 1 and BRCA 2 mutations among patients with BC, the majority of whom had mutations, contrasting with controls without BC, who predominantly lacked mutations in these genes, as illustrated in Figure 7.

Because of the modern lifestyle, some women spend extended periods of time living a sedentary way of life. Coupled with reduced physical activity, this can contribute to obesity, as individuals may consume more food than necessary or can process. Our study revealed that obesity is more prevalent among postmenopausal women corroborating its status as a risk factor for developing BC, as depicted in Figure 8.

Significant statistical correlations were observed between obesity, menopausal status, and the use of hormonal replacement therapy as risk factors for developing BC as indicated in the accompanying table.

DISCUSSION

The findings from Wahidin et al.'s research in Indonesia align with our study, highlighting statistically significant correlations between several risk factors and BC development, including age, oral contraceptive use, early menarche, childbirth, breastfeeding, obesity, and history of benign breast tumors (7). In our sample, we also observed statistically significant associations for these risk factors. However, it's noteworthy that some of the results reported by Wahidin et al., such as non-significant associations for family history of BC and menopausal status, were not consistent with our findings. This variation may be attributed to differences in sample characteristics, methodology, or other contextual factors between the studies.

Similarly, research conducted by the Hong Kong BC Registry in Hong Kong identified significant associations between family history of BC, early menarche, childbirth, breastfeeding, smoking at a younger age, alcohol consumption, obesity, and oral contraceptive use. These findings are consistent with the results obtained from our analysis, as most of the risk factors were found to be statistically significant in both studies. However, unlike our findings, menopausal status and hormonal replacement therapy were not found to be statistically significant in the research conducted by the Hong Kong BC Registry. This discrepancy may stem from variations in sample characteristics, methodology, or other contextual factors between the studies (8).

In Malaysia, Kamarudin et al (9). found significant correlations between breastfeeding, obesity, and BC risk. However, they reported non-significant associations for variables such as marital status, education, menopausal status, childbirth, oral contraceptive use, hormonal replacement therapy, smoking status, and age. Our results, on the other hand, indicated that the aforementioned risk factors were statistically significant, which is not consistent with their findings. This inconsistency may be attributed to differences in sample characteristics, study design, or other contextual factors between the two studies (9).

Hing et al.(5) conducted a study in 2020, wherein tumor markers CEA and CA 15-3 were monitored for the diagnosis, follow-up, and detection of regression and metastasis of BC. They found that 23 patients (34%) with regression exhibited elevated levels of tumor markers, serving as the first indicator of disease regression before clinical symptoms appeared or were detected by any other diagnostic method. Specifically, the elevated level of CEA in patients with regression was found to be 10 ng/ml compared to 6 ng/ml in the control group. The sensitivity of elevated CA 15-3 alone was 71.6% with a specificity of 97%, while the sensitivity of CEA alone was 75% with a specificity of 92.5%. Moreover, the combination of elevated levels of CEA and CA 15-3 for monitoring regression showed a sensitivity of 93.9% with a specificity of 89.6%. Our study yielded consistent results with theirs, particularly regarding the sensitivity of CA 15-3 in detecting regression, which was 81.8% with a specificity of 100% (5).

In the study conducted by Li et al. (10) in 2019, they established statistical significance between women with low and high levels of carcinoembryonic antigen (CEA) and cancer antigen 125 (CA 125). Their findings suggest that CEA and CA 125 levels reflect different aspects of BC in young women. Specifically, groups with high and low CEA levels exhibited differences in tumor size, lymph node status, and HER-2 status, while groups with high and low CA 125 levels

showed significant differences in TNM stage, hormonal receptor status (ER and PR), molecular type of BC, and the use of endocrine therapy, all with p values < 0.05. Our results also demonstrated that CEA and CA 125 were useful in detecting BC and its metastases, consistent with their findings (10).

In the research conducted by Zalenski et al.(11), tumor markers including CEA, CA 15-3, CA 19-9, and CA 125 were analyzed using automatic immunoassays. They found that the best combination of tumor markers was CA 15-3 and CEA, with a sensitivity of 90% and specificity of 95%. However, their study did not demonstrate the usefulness of the combination of CA 125 and CEA in the early detection of BC and its metastases. Despite this difference, their study yielded results similar to our findings regarding the use of tumor markers, although they achieved higher sensitivity and specificity (11).

In the study conducted by Sun et al., it was demonstrated that approximately 16% of BC deaths in females in China were associated with excess weight and obesity, while 11.6% of BC deaths were attributed to physical inactivity. Our results similarly indicate a correlation between obesity and a higher risk of developing BC (12).

CONCLUSION

Based on our findings, we conclude that a correlation exists between various risk factors and an increased risk of developing female breast cancer (BC) in Sarajevo Canton. Furthermore, the tumor markers assessed in this study, namely CA 15-3, CEA, CA 19-9, and CA 125, demonstrated statistical significance, indicating their potential as a combined screening tool for detecting BC and its metastases. Invasive ductal BC was identified as the most prevalent type. The sensitivity for regression detection was found to be 81.8%, with a specificity of 100% at a cutoff value of 19.55 kIU/L.

Note: Artificial intelligence was not used as a tool in this study.

Authors contribution: BH: conceived the idea for the study, participated in writing the paper; **AK:** conceived the idea for the study**,** article writing; **LH:** designed the figures and contributed to the research implementation;**LI and VS:** verified the analytical methods and encouraged further

investigation into the correlation between obesity and BC; **MS:** verified the numerical results and supervised the project. All authors discussed the results and contributed to the final manuscript

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Sažetak

PROCENA RIZIKA U KORELACIJI SA GOJAZNOŠĆU I LABORATORIJSKIM MONITORINGOM NAJČEŠĆIH TIPOVA KARCINOMA DOJKE KOD ŽENA U KANTONU SARAJEVO

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Uvod: Karcinom dojke je maligno oboljenje, češće se javlja ženaa, a jedan od najpoznatijih uzroka je mutacija tumor supresorskih gena BRCA 1 i BRCA 2 što predstavlja genetičku komponentu. Drugi rizikofaktori uključuju nezdrave životne stilove uključujući manjak fizičke aktivnosti i konzumiranje alkohola i cigareta. Starenje također ima ulogu u razvoju karcinoma dojke sa uticajem hormona s obzirom da mnogi od ovih karcinoma za svoj rast koriste ženske hormone uključujući estrogen i progesteron.

Materijal i metode: Istraživanje je sprovedeno uz pomoć alata za prikupljanje podataka o rizikofaktorima i tumorskim markerima iz kartona porodične medicine. Naš uzorak je uključivao 200 žena koje su podeljene u dve grupe, jedna sa i druga bez dijagnoze karcinoma dojke sa potpunom medicinskom dokumentacijom. Muškarci sa karcinomom dojke su isključeni iz studije.

Rezultati: Sa Pirsonovim χ^2testom je dokazano da postoji statistička značajnost između genetičke komponente, porodične istorije, starenja, pretilosti, konzumiranja alkohola i cigareta i dužeg izlaganja ženskim hormonima i povećanog rizika za razvoj karcinoma dojke kod žena. Potvrdili smo rezultate sa Fisherovim egzaktnim testom. Za tumorske markere korišten je One Sample T-test i potvrđeno je da tumorski markeri CA 15-3, CEA, CA 19-9 i CA 125 su korisni u skriningu karcinoma dojke i njegovih metastaza. Najčešći tip karcinoma dojke kod žena u Kantonu Sarajevo je invazivni duktalni karcinom, dok najmanje zastupljen je lobularni karcinom in situ.

Zaključak: Korelacija između rizikofaktora uključujući: starenje, nezdrave životne stilove i duže izlaganje ženskim hormonima i povećan rizik za razvoj karcinoma dojke je dokazana. Tumorski markeri koji su korišteni uključujući CA 15-3, CEA, CA 19-9 i CA 125 su bili korisni u dijagnozi, skriningu i otkrivanju metastaza kod žena. Senzitivnost koju smo dobili za ove tumorske markere u otkrivanju recidiva je bila 81.8% sa specifičnošću koja je iznosila 100%.

Ključne reči: karcinom dojke, tumorski markeri, faktori rizika, životni stilovi, genetika.

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Table 1. Variables frequency distribution.

Variables	Cases (%)	Controls (%)	Chi-Square test value	p value / Fisher's exact test
Age (years)			31.977	0.000[1]
<30	0 (0)	9 (9)		
31-40	2 (2)	16 (16)		
41-65	23 (23)	34 (34)		
65+	75 (75)	41 (41)		
Total	100 (100)	100 (100)		
Education			7.230	0.027
Primary or less	10 (10)	3 (3)		
Secondary	65 (65)	58 (58)		
Tertiary	25 (25)	39 (39)		
Total	100 (100)	100 (100)		
Marital status			86.560	0.000
Married	65 (65)	63 (63)		
Divorced	22 (22)	22 (22)		
Never got married	13 (13)	15 (15)		
Total	100 (100)	100 (100)		
History of benign breast disease			14.174	0.000 / 0.000
Yes	27 (27)	7 (7)		
No	73 (73)	93 (93)		
Total	100 (100)	100 (100)		
Family history of BC			72.158	0.000 / 0.000
Yes	66 (66)	8 (8)		
No	34 (34)	92 (92)		

[1]The Fisher's exact test is displayed only for variables with a 2x2 format

Total	100 (100)	100 (100)		
Obesity (BMI ≥ 25 kg/m2)			24.921	0.000 / 0.000
Yes	74 (74)	39 (39)		
No	26 (26)	61 (61)		
Total	100 (100)	100 (100)		
Early menstrual cycle (<13 years)			41.747	0.000 / 0.000
Yes	53 (53)	11 (11)		
No	47 (47)	89 (89)		
Total	100 (100)	100 (100)		
Giving birth			132.280	0.000 / 0.000
Yes	86 (86)	77 (77)		
No	14 (14)	23 (23)		
Total	100 (100)	100 (100)		
Breastfeeding			3.854	0.037 / 0.037
Ever	86 (86)	75 (75)		
Never	14 (14)	25 (25)		
Total	100 (100)	100 (100)		
Oral contraceptives>2 months			17.887	0.000 / 0.000
Ever	42 (42)	15 (15)		
Never	58 (58)	85 (85)		
Total	100 (100)	100 (100)		
Menopausal status			35.143	0.000 / 0.000
Pre-menopausal	8 (8)	45 (45)		
Post-menopausal	92 (92)	55 (55)		
Total	100 (100)	100 (100)		
Hormonal replacement therapy>2 months			49.818	0.000 / 0.000
Ever	65 (65)	16 (16)		
Never	35 (35)	84 (84)		
Total	100 (100)	100 (100)		
Ovariectomy			147.920	0.000 / 0.000
Yes	6 (6)	8 (8)		
No	94 (94)	92 (92)		

Total	100 (100)	100 (100)		
Smoking (consuming at least 2 years)			30.420	0.000 / 0.000
Yes	32 (32)	29 (29)		
No	68 (68)	71 (71)		
Total	100 (100)	100 (100)		
Alcohol (>44g per day for at least 2 years)			131.220	0.000 / 0.000
Yes	8 (8)	11 (11)		
No	92 (92)	89 (89)		
Total	100 (100)	100 (100)		

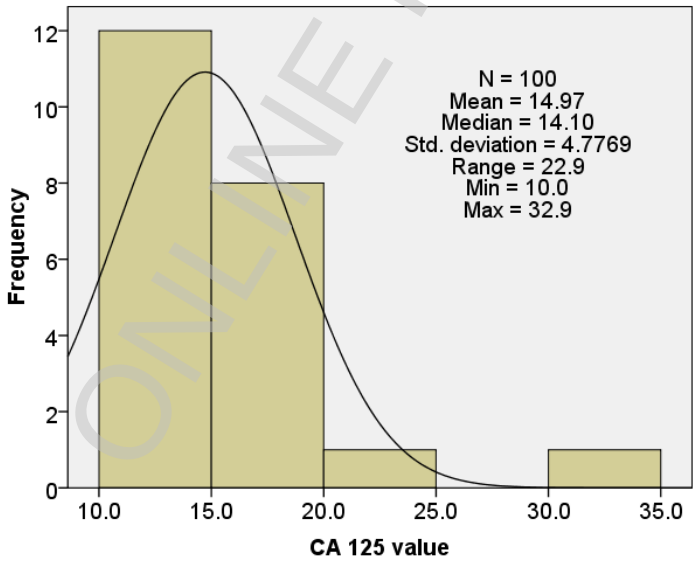

Figure 1. Histogram of distribution and descriptive presentation of CA 125 values.

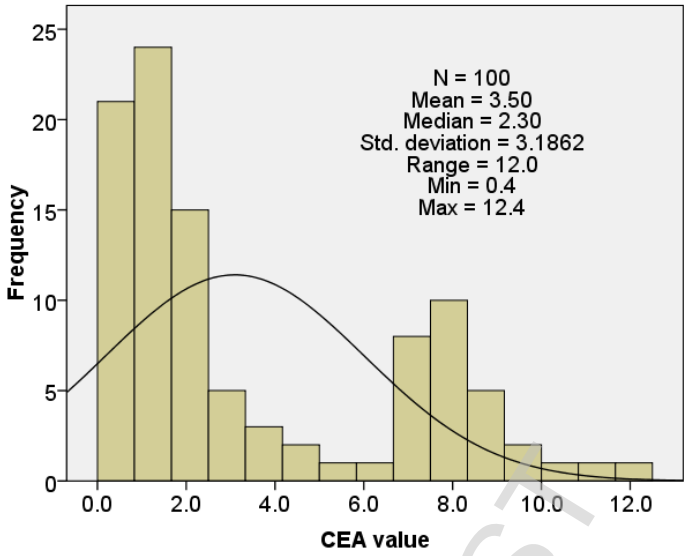

Figure 2. Histogram of distribution and descriptive presentation of CEA values.

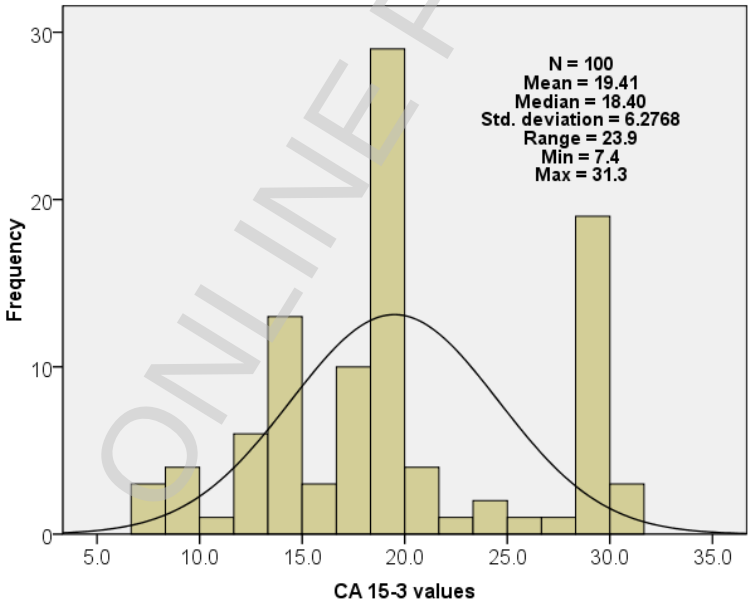

Figure 3. Histogram of distribution and descriptive presentation of CA 15-3 values.

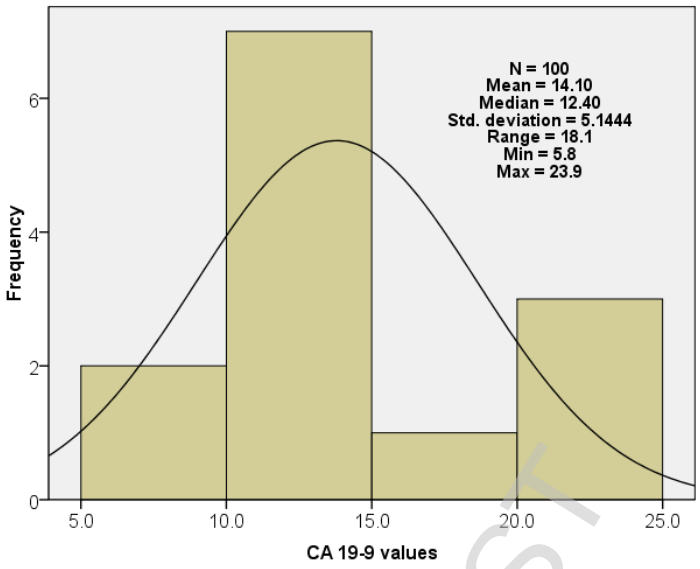

Figure 4. Histogram of distribution and descriptive presentation of CA 19-9 values.

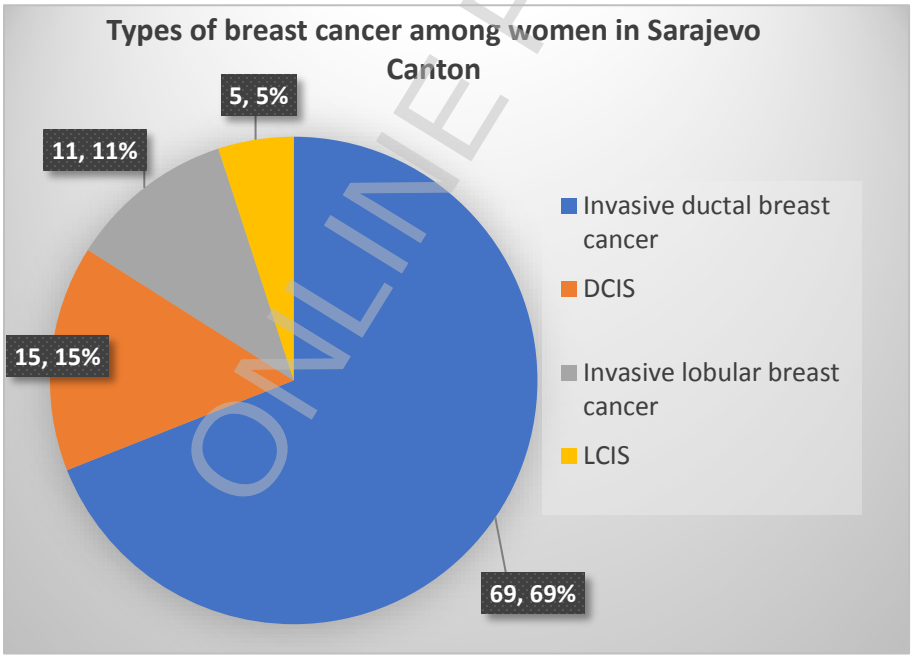

Figure 5. Types of BC among women in Sarajevo Canton.

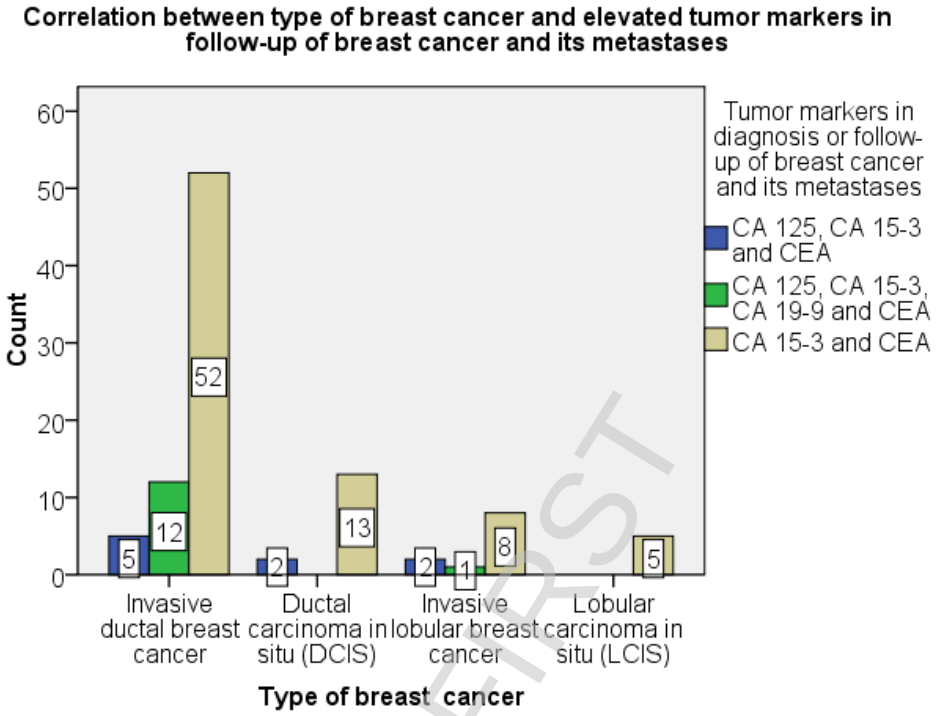

Figure 6. Correlation of type of breast cancer with tumor markers.

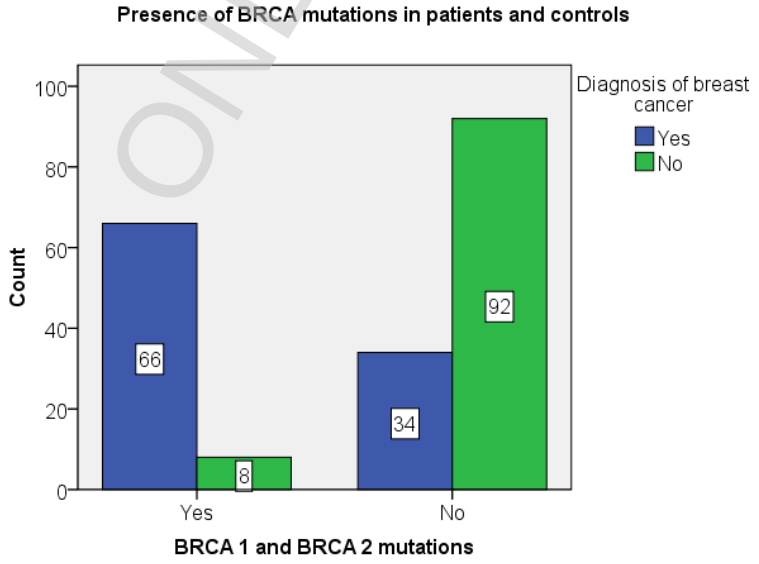

Figure 7. Presence of BRCA mutations in patients and controls.

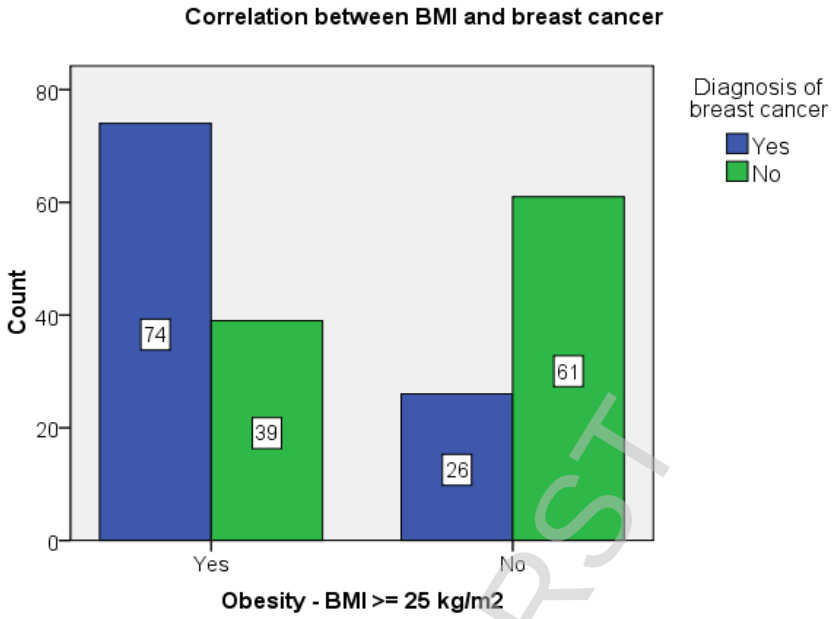

Figure 8. Correlation between obesity and BC.

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