

Obesity, Metabolic Syndrome & Breast Cancer – short review

Nadia Islam¹

¹Genetics and Bioengineering, International University of Sarajevo, Bosnia and Herzegovina

*Corresponding author: 170301126@student.ius.edu.ba

© The Author
2021.
Published by
ARDA.

Abstract

Breast cancer is the leading cause of death among women and the second largest cause of mortality in the entire population worldwide. This review investigated how breast cancer is patho-physiologically associated with obesity which is defined by body mass index ≥ 30 kg/m² and metabolic syndrome which leads to type 2 diabetes in pre and postmenopausal women. It also addressed the controversy relating the definition of BMI. The biological markers in breast cancer currently in use are ER, PR, HER2, uPA, and PAI-1. This study looked into future of predictive and prognostic biomarkers, such as exosome by altering interaction of distant cancer cells in the tumor microenvironment and the breast cancer progress.

Keywords: Obesity; BMI; Breast Cancer; Metabolic Syndrome

1. Introduction

The rate of obesity is a major public health issue worldwide. Obesity is usually defined as those with a body mass index (BMI) ≥ 30 kg/m² as a phenotype marker by the World Health Organization (WHO) and The Centers for Disease Control and Prevention (CDC) and said to have direct link with type 2 diabetes (T2D), metabolic syndrome (MetS) [1-2] and cancer, including colon, rectal, kidney, endometrial and adenocarcinoma [3]–[5]. It is specifically associated with a higher risk of developing breast cancer among women [6], particularly post-menstrual women by creating an obese tumor microenvironment with signaling pathways [7] and the consequences are said to have negatively effect on the prognosis [8]. Epidemiological data have shown that the prevalence of breast cancer increases its occurrence by 30-50% [8] in post-menstrual women, whereas meta-analyses have reported an ~30% increased danger of reappearance or mortality in obese versus regular weight women diagnosed with breast cancer [3]. The prevalence, however is highly specific for “gender, site, geographical population, histological subtype and molecular phenotype” [9] and studies have shown that being underweight (BMI < 18.5 kg/m²) is associated with increased risk of breast cancer mortality in non-Latina whites whereas morbid obesity (BMI ≥ 40 kg/m²) is only suggestive of increased risk. In addition, no BMI–mortality connections are to be seen in African Americans and Asian Americans [10].

1.1 Definition of Obesity

According to WHO and CDC, one in five adults will be obese worldwide by the year 2025 [11]. Obesity was thought to be a disease of wealthy people in the past [12]. In the recent years, it has been proven to be a consequence of poverty and malnutrition [4]. It is defined as BMI ≥ 30 kg/m² or waist/hip ratio (WHR) of ≥ 0.85 and a waist circumference of ≥ 88 [13].

By defining obesity according to BMI has shown that postmenopausal women at pre-diagnosis and at the most recent measurement were 1.50 and 1.56 times more likely to develop breast cancer respectively, in the multivariate analysis [6].

Although BMI is the most used measure in this context, there are questions whether it can be used appropriately as a phenotypic marker of adiposity or not across populations of different race and ethnicity [4]. The major shortcomings of using BMI include measuring of excess weight, not excess fat [14] and therefore it is highly susceptible to label someone from African-American ethnicity as obese who simply has higher muscle mass when comparing to someone from Asian or Hispanic background. Secondly, when considering the risk of T2D and breast cancer, the BMI data are also inconsistent in different races and ethnicity [10]. Thirdly, factors such as age and smoking status that could modify BMI–cancer associations [15] and finally, BMI is said to be inadequate in measuring stature dependency of adiposity [16] meaning short and tall people with same BMIs will not have similar distribution of adipose tissue throughout their bodies, since major anatomical compartments of importance (brain, liver, bones etc.) also contribute to how weight scales to height.

Despite the controversy regarding the definition of BMI dependent obesity, it is said to be one of the integral factors related to the risk of breast cancer [15].

1.2 Definition of Metabolic Syndrome

MetS is defined by WHO as co-occurrence of several known cardiovascular risk factors and pathologic condition characterized by abdominal and visceral adiposity, insulin resistance, hypertension, low-serum, high-density lipoprotein cholesterol, hypertriglyceridemia, hypertension and hyperlipidemia [17], [18]. According to WHO 1999 definition, presence of insulin resistance or glucose > 6.1 mmol/L (110 mg/dl), 2 h glucose > 7.8 mmol (140 mg/dl) (required) along with any two or more of the following can be characterized as MetS: HDL cholesterol < 0.9 mmol/L (35 mg/dl) in men, < 1.0 mmol/L (40 mg/dl) in women, and/or Triglycerides > 1.7 mmol/L (150 mg/dl), and/or Waist/hip ratio > 0.9 (men) or > 0.85 (women) and/or BMI > 30 kg/m² and/or Blood pressure $> 140/90$ mmHg [19].

MetS is associated with 17% increase in the risk of developing breast cancer, three-fold recurrence and two-fold increase in breast cancer–specific mortality [18], [20], [21].

1.3 Risk Factors of Breast Cancer

Apart from the BMI, the general hormonal and nonhormonal risk factors include age, blood type, menstruation history, infertility, age of first fulltime pregnancy, duration of lactation, smoking, age of menopause, oral contraceptive use, an inherited mutation in the BRCA-1 or BRCA-2 genes and usage of hormones (estrogen and or progesterin) in postmenopausal stage [22], [23].

1.3.1 Bio-Markers, Genetic and Epigenetic Factors associating Breast Cancer

The genetic markers for the breast cancer are breast cancer susceptibility genes BRCA-1 and BRCA-2, which are said to be playing a small role (5–10%) in transferring the disease from either one of the parents [24] when comparing with other epigenetic factors. However, mutation in genetic level of these two genes increase 40–80% chance of developing the cancer [22].

There are 13 types of tumor markers of breast cancer are measured, and 6 out of 13 are novel for the guideline [24]. The exosomes [25], serum markers (Ca 15-3, Ca 27.29, CA 549, BR 27.29, MCA, carcinoembryonic antigen (CEA), oncoproteins (e.g. HER2/c-erbB-2), and cytokeratins (e.g. tissue polypeptide antigen and tissue polypeptide-specific antigen)), tissue markers (hormone receptors, human epidermal growth factor-2 (HeR-2 antigen), urokinase plasminogen activator (uPA), plasminogen activator inhibitor (PAI-1), tumor suppressor gene (p53) and cathepsin D) [22], positive estrogen receptor (ER) subtype, the expression of

progesterone, and triple-negative (TN) receptors in postmenopausal women and pre-diagnostic obesity according to BMI are the major bio-markers for breast cancer [6].

Studies have shown that higher BMI helps tumor cell growth and cell survival through upregulation of leptin and insulin-like growth factors [26]. When the body reduces and stops producing estrogen in pre and postmenopausal women, the adipose tissue stored in obese women start synthesizing estrogen and oestrone to bring back the homeostasis. This overproduction of hormones eventually result in increasing the risk factor in breast cancer [27].

Table 1. Association of BMI and WC with Clinico-photological variable among postmenopausal breast cancer. Brazil, 2017, source: [6]

	ER Status		PR Status		HeR-2 Status		TN	
	Negative	Positive	Negative	Positive	Negative	Positive	Yes	No
	n (%)	n (%)	n (%)	n (%)				
Prediagnosis BMI (kg/m ²)								
<30	13 (31.7)	28 (68.3)	15 (37.5)	25 (62.5)	9 (28.1)	23 (71.9)	6 (18.8)	26 (81.3)
≥30	1 (4.8)	20 (95.2)	3 (14.3)	18 (85.7)	6 (35.3)	11 (64.7)	0 (0.0)	17 (100.0)
p value	0.01*		0.05*		0.60		0.06*	
Current BMI (kg/m ²)								
<30	6 (15.4)	33 (84.6)	10 (26.3)	28 (73.7)	9 (31.0)	20 (69.0)	27 (93.1)	2 (6.9)
≥30	8 (34.8)	15 (65.2)	8 (34.8)	15 (65.2)	6 (30.0)	14 (70.0)	16 (80.0)	4 (20.0)
p value	0.07		0.48		0.93		0.17*	
BMI at age 20 years (kg/m ²)								
<30	13 (21.3)	48 (78.7)	17 (28.3)	43 (71.7)	15 (31.3)	33 (68.8)	6 (12.5)	42 (87.5)
≥30	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	1 (100.0)
p value	0.22*		0.29*		0.69*		0.87*	
Waist circumference (cm)								
<80	1 (20.0)	4 (80.0)	1 (20.0)	4 (80.0)	2 (40.0)	3 (60.0)	1 (20.0)	4 (80.0)
≥80	13 (22.8)	44 (77.2)	17 (30.4)	39 (69.6)	13 (29.5)	31 (70.5)	5 (11.4)	39 (88.6)
p value	0.68*		0.53*		0.48*		0.49*	

1.4 Types of Breast Cancer

Breast cancers can be divided into invasive and non-invasive types according to the site. On the other hand, molecular classification of the breast cancer provides four distinctive subtypes: Luminal A, Luminal B, HER 2+ and basal like [28].

1.4.1 Non-invasive Breast Cancer

1.4.1.1 Lobular Carcinoma In Situ (LCIS): is a non-obligate precursor of breast carcinoma, meaning non-invasive form of breast cancer [29] which extends exterior to the lobules into the breast tissue [30], shows loss of E-cadherin and diffuse cytoplasmic staining for p120 catenin [29], [31].

1.4.1.2 Ductal Carcinoma In Situ (DCIS): is the most general kind a non-invasive form of breast cancer, and contributes towards 20-25% of all breast cancers if not treated at this stage [32], and tends to show micro-calcifications more commonly than other forms [33].

1.4.2 Invasive Breast Cancer

1.4.2.1 Invasive Lobular Carcinoma (ILC): is correlated with older age, greater counts of positive lymph nodes and ER or PR positive nodes [34].

1.4.2.2 Invasive Ductal Carcinoma (IDC): originates in the milk ducts [24], the proportion of bone metastasis is lower and its cohort has advantages over the ILC group when considering disease-specific survival [34]

1.4.2.3 Medullary Breast Carcinoma: creates a discrete margin normal tissue and medullary tissue [24] with no special type with medullary features, it is a rare and distinct subgroup of breast carcinomas which accounts for <5% of all breast cancers [35].

1.4.2.4 Mucinous Breast Carcinoma: another rare subtype which accounts for about 2% of all breast carcinomas [36] which contains an invasive ductal epithelial component with (pure) or without (mixed) mucin [24].

1.4.2.5 Tubular Breast Carcinoma: usually has a higher chance of survival [24] and lymph node status is not associated with significant breast cancer-specific survival [37].

1.4.2.6 Inflammatory Breast Cancer (IBC): even though very uncommon, it is one of the most aggressive forms of breast cancer due to rapid spread [38] where cancer cells block the lymph vessels or channels in the skin.

1.4.3 Paget's disease of the Breast: rare and usually prevalent in postmenopausal women with resemblance with the skin disorders such as eczema and psoriasis [39].

1.4.4 Phyllodes Tumor of the Breast: a type of rare fibroepithelial neoplasm, which accounts for 0.3-1% of all breast cancers [40] and can be either benign or malignant, develops in the connective tissues [24].

1.4.5 Triple-negative breast cancer (TNBC): is a highly destructive subtype of breast cancer which is prevalent in younger premenopausal women [41] due to deficiency of oestrogen and progesterone, absence or overexpression of HER-2, and accounts for 10–15% of cases in white females [24].

2 Obesity, MetS and Breast Cancer

According to American Cancer Society 2017 survey, breast cancer is the principal form of cancer in women worldwide [42]. Obesity defined by BMI of ≥ 30 kg/m² is an independent risk factor for MetS and T2D which have direct link with the breast cancer. Studies have shown that increasing body size helps increasing the premenopausal TNBC by 67% and Luminal B by 73% [3], [23], [43]. Several meta-analysis showed that T2D and obesity are also associated with increasing risk of developing postmenopausal breast cancer [44], [45].

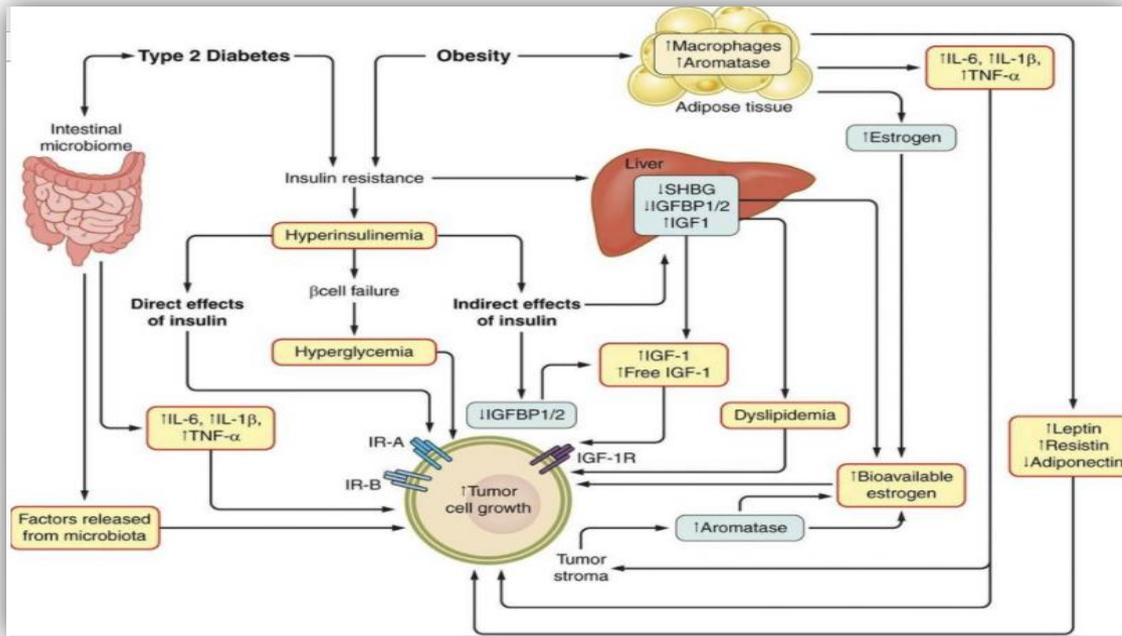


Figure 1: Potential mechanisms linking obesity/diabetes and cancer[3]

Studies have shown that cancer cells depend upon aerobic glycolysis rather than mitochondrial oxidative phosphorylation [3] to produce Adenosine Tri Phosphate (ATP) when comparing with the regular tissue, which leads to increase of glucose uptake by the cancer cells. However, hyperglycemia alone may not be responsible for increasing the cancer growth without hyperinsulinemia [46], [47]. In addition, dyslipidemia which is also linked with obesity and T2D plays a major role in increasing cholesterol, triglycerides and decreasing HDL cholesterol which eventually increase the risk of breast cancer [48]. Adipose tissue is a biologically active part of the endocrine system which synthesizes adipokines, inflammatory cytokines, and small amounts of estrogen which increases the risk of breast cancer by overproducing estrogen in postmenopausal women [49]. Cross-sectional studies shown that reproductive and hormonal characteristics are linked to luminal subtype, whereas obesity increase the risk of TNBC in postmenopausal women by overexpressing HER-2 [23]. Obesity reprograms adipose tissue in a manner that leads to insulin resistance with or without diabetes that alters the phosphoinositide 3-kinase (PI3K) and Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathways which eventually create a microenvironment for tumor growth.

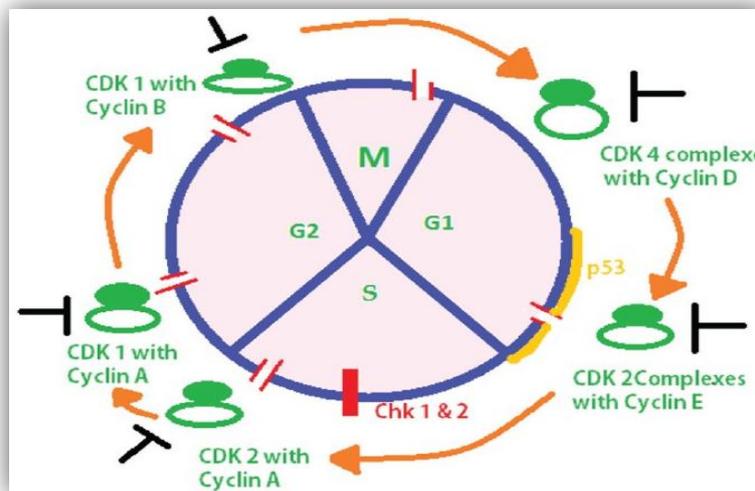


Figure 2: “Cancer cell cycle regulation mechanism. Cyclin EAD and B are mytogens and stimulate the cell to proliferate and when complexes with cyclin-dependent kinase (CDKs).

Activation or arrest of cell cycle depends on CDK complex. G1 phase can respond to extra cellular signals like hormones and metal ions. p53 play a main role in DNA damage repair. P27 arrest the cell cycle at G1 and cell will enter into resting phase, that is, G0 phase”, source: Journal of Cancer Research and Therapeutics, [22].

Gut microbiome are known to be associated with overall metabolism and obesity. A member of the angiopoietin-like family of proteins called fasting-induced adipose factor (FIAF) is expressed in the intestine, liver and adipose tissue, which is an inhibitor of the circulating lipoprotein lipase that gets knocked out in an obese microenvironment so that adipose storage is activated for the gut microbiome[50].

3 Conclusion

As obesity, metabolic syndrome and diabetes are increasing worldwide everyday with the rate of mortality by breast cancer- accounting 23% of all cancer deaths, it is crucial to understand the mechanism of the connection among them. Obesity can be defined by measuring BMI. However, since BMI cannot be appropriate when considering the ethnicity and race, other factors including fat mass index (FMI), waist/hip ratio and waist circumference need to be taken into consideration.

4 Reference

- [1] E. Kassi, P. Pervanidou, G. Kaltsas, and G. Chrousos, “Metabolic syndrome: definitions and controversies,” *BMC Med.*, vol. 9, p. 48, May 2011, doi: 10.1186/1741-7015-9-48.
- [2] K. Esposito *et al.*, “Metabolic syndrome and postmenopausal breast cancer: systematic review and meta-analysis,” *Menopause N. Y. N.*, vol. 20, no. 12, pp. 1301–1309, Dec. 2013, doi: 10.1097/GME.0b013e31828ce95d.
- [3] C. Kang, D. LeRoith, and E. J. Gallagher, “Diabetes, Obesity, and Breast Cancer,” *Endocrinology*, vol. 159, no. 11, pp. 3801–3812, Sep. 2018, doi: 10.1210/en.2018-00574.
- [4] E. C. Dietze, T. A. Chavez, and V. L. Seewaldt, “Obesity and Triple-Negative Breast Cancer,” *Am. J. Pathol.*, vol. 188, no. 2, pp. 280–290, Feb. 2018, doi: 10.1016/j.ajpath.2017.09.018.
- [5] G. C. Kabat *et al.*, “Metabolic Obesity Phenotypes and Risk of Breast Cancer in Postmenopausal Women,” *Cancer Epidemiol. Biomark. Prev. Publ. Am. Assoc. Cancer Res. Cosponsored Am. Soc. Prev. Oncol.*, vol. 26, no. 12, pp. 1730–1735, Dec. 2017, doi: 10.1158/1055-9965.EPI-17-0495.
- [6] A. A. F. Gravena *et al.*, “The Obesity and the Risk of Breast Cancer among Pre and Postmenopausal Women,” *Asian Pac. J. Cancer Prev. APJCP*, vol. 19, no. 9, pp. 2429–2436, 2018, doi: 10.22034/APJCP.2018.19.9.2429.
- [7] M. Picon-Ruiz, C. Morata-Tarifa, J. J. Valle-Goffin, E. R. Friedman, and J. M. Slingerland, “Obesity and adverse breast cancer risk and outcome: Mechanistic insights and strategies for intervention,” *Ca*, vol. 67, no. 5, pp. 378–397, 2017, doi: 10.3322/caac.21405.
- [8] F. Fallone, R. Deudon, C. Muller, and C. Vaysse, “Cancer du sein, obésité et tissu adipeux - Un trio à haut risque,” *médecine/sciences*, vol. 34, no. 12, Art. no. 12, Dec. 2018, doi: 10.1051/medsci/2018298.
- [9] A. G. Renehan, M. Zwahlen, and M. Egger, “Adiposity and cancer risk: new mechanistic insights from epidemiology,” *Nat. Rev. Cancer*, vol. 15, no. 8, Art. no. 8, Aug. 2015, doi: 10.1038/nrc3967.
- [10] M. L. Kwan *et al.*, “Obesity and Mortality After Breast Cancer by Race/Ethnicity: The California Breast Cancer Survivorship Consortium,” *Am. J. Epidemiol.*, vol. 179, no. 1, pp. 95–111, Jan. 2014, doi: 10.1093/aje/kwt233.

- [11] M. S. Mohammed, S. Sendra, J. Lloret, and I. Bosch, "Systems and WBANs for Controlling Obesity," *J. Healthc. Eng.*, vol. 2018, Feb. 2018, doi: 10.1155/2018/1564748.
- [12] K. M. Flegal, D. Kruszon-Moran, M. D. Carroll, C. D. Fryar, and C. L. Ogden, "Trends in Obesity Among Adults in the United States, 2005 to 2014," *JAMA*, vol. 315, no. 21, pp. 2284–2291, Jun. 2016, doi: 10.1001/jama.2016.6458.
- [13] "Waist circumference and waist-hip ratio: report of a WHO expert consultation." <https://www.who.int/publications-detail-redirect/9789241501491> (accessed May 30, 2021).
- [14] T. L. Kelly, K. E. Wilson, and S. B. Heymsfield, "Dual Energy X-Ray Absorptiometry Body Composition Reference Values from NHANES," *PLoS ONE*, vol. 4, no. 9, Sep. 2009, doi: 10.1371/journal.pone.0007038.
- [15] K. Bhaskaran, I. Douglas, H. Forbes, I. dos-Santos-Silva, D. A. Leon, and L. Smeeth, "Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5·24 million UK adults," *Lancet*, vol. 384, no. 9945, pp. 755–765, Aug. 2014, doi: 10.1016/S0140-6736(14)60892-8.
- [16] S. B. Heymsfield, D. Gallagher, L. Mayer, J. Beetsch, and A. Pietrobelli, "Scaling of human body composition to stature: new insights into body mass index," *Am. J. Clin. Nutr.*, vol. 86, no. 1, pp. 82–91, Jul. 2007.
- [17] P. L. Huang, "A comprehensive definition for metabolic syndrome," *Dis. Model. Mech.*, vol. 2, no. 5–6, pp. 231–237, 2009, doi: 10.1242/dmm.001180.
- [18] C. M. Dieli-Conwright *et al.*, "Effects of Aerobic and Resistance Exercise on Metabolic Syndrome, Sarcopenic Obesity, and Circulating Biomarkers in Overweight or Obese Survivors of Breast Cancer: A Randomized Controlled Trial," *J. Clin. Oncol.*, vol. 36, no. 9, pp. 875–883, Mar. 2018, doi: 10.1200/JCO.2017.75.7526.
- [19] M. G. Saklayen, "The Global Epidemic of the Metabolic Syndrome," *Curr. Hypertens. Rep.*, vol. 20, no. 2, 2018, doi: 10.1007/s11906-018-0812-z.
- [20] P. Pasanisi, F. Berrino, M. De Petris, E. Venturelli, A. Mastroianni, and S. Panico, "Metabolic syndrome as a prognostic factor for breast cancer recurrences," *Int. J. Cancer*, vol. 119, no. 1, pp. 236–238, Jul. 2006, doi: 10.1002/ijc.21812.
- [21] G. S. Calip, K. E. Malone, J. R. Gralow, A. Stergachis, R. A. Hubbard, and D. M. Boudreau, "Metabolic syndrome and outcomes following early-stage breast cancer," *Breast Cancer Res. Treat.*, vol. 148, no. 2, pp. 363–377, Nov. 2014, doi: 10.1007/s10549-014-3157-6.
- [22] Donepudi, "Breast cancer statistics and markers." <https://www.cancerjournal.net/article.asp?issn=0973-1482;year=2014;volume=10;issue=3;page=506;epage=511;aulast=Donepudi> (accessed May 30, 2021).
- [23] F. P. Turkoz *et al.*, "Association between common risk factors and molecular subtypes in breast cancer patients," *Breast Edinb. Scotl.*, vol. 22, no. 3, pp. 344–350, Jun. 2013, doi: 10.1016/j.breast.2012.08.005.
- [24] M. Akram, M. Iqbal, M. Daniyal, and A. U. Khan, "Awareness and current knowledge of breast cancer," *Biol. Res.*, vol. 50, Oct. 2017, doi: 10.1186/s40659-017-0140-9.
- [25] Y. Jia *et al.*, "Exosome: emerging biomarker in breast cancer," *Oncotarget*, vol. 8, no. 25, pp. 41717–41733, Jun. 2017, doi: 10.18632/oncotarget.16684.

- [26] M. M. Alegre, M. H. Knowles, R. A. Robison, and K. L. O'Neill, "Mechanics behind breast cancer prevention - focus on obesity, exercise and dietary fat," *Asian Pac. J. Cancer Prev. APJCP*, vol. 14, no. 4, pp. 2207–2212, 2013, doi: 10.7314/apjcp.2013.14.4.2207.
- [27] G. Alco *et al.*, "Vitamin D levels in patients with breast cancer: importance of dressing style," *Asian Pac. J. Cancer Prev. APJCP*, vol. 15, no. 3, pp. 1357–1362, 2014, doi: 10.7314/apjcp.2014.15.3.1357.
- [28] A. Roulot *et al.*, "Tumoral heterogeneity of breast cancer," *Ann. Biol. Clin. (Paris)*, vol. 74, no. 6, pp. 653–660, Dec. 2016, doi: 10.1684/abc.2016.1192.
- [29] H. Y. Wen and E. Brogi, "Lobular Carcinoma In Situ," *Surg. Pathol. Clin.*, vol. 11, no. 1, pp. 123–145, Mar. 2018, doi: 10.1016/j.path.2017.09.009.
- [30] P. Clauser, M. A. Marino, P. A. T. Baltzer, M. Bazzocchi, and C. Zuiani, "Management of atypical lobular hyperplasia, atypical ductal hyperplasia, and lobular carcinoma in situ," *Expert Rev. Anticancer Ther.*, vol. 16, no. 3, pp. 335–346, 2016, doi: 10.1586/14737140.2016.1143362.
- [31] J. M. Daniel and A. B. Reynolds, "The tyrosine kinase substrate p120cas binds directly to E-cadherin but not to the adenomatous polyposis coli protein or alpha-catenin.," *Mol. Cell. Biol.*, vol. 15, no. 9, pp. 4819–4824, Sep. 1995.
- [32] M. van Seijen *et al.*, "Ductal carcinoma in situ: to treat or not to treat, that is the question," *Br. J. Cancer*, vol. 121, no. 4, pp. 285–292, Aug. 2019, doi: 10.1038/s41416-019-0478-6.
- [33] S. Badve and Y. Gökmen-Polar, "Ductal carcinoma in situ of breast: update 2019," *Pathology (Phila.)*, vol. 51, no. 6, pp. 563–569, Oct. 2019, doi: 10.1016/j.pathol.2019.07.005.
- [34] Z. Chen *et al.*, "Invasive lobular carcinoma of the breast: A special histological type compared with invasive ductal carcinoma," *PloS One*, vol. 12, no. 9, p. e0182397, 2017, doi: 10.1371/journal.pone.0182397.
- [35] F. Limaiem and M. Mlika, "Medullary Breast Carcinoma," in *StatPearls*, Treasure Island (FL): StatPearls Publishing, 2021. Accessed: May 30, 2021. [Online]. Available: <http://www.ncbi.nlm.nih.gov/books/NBK542292/>
- [36] F. Limaiem and F. Ahmad, "Mucinous Breast Carcinoma," in *StatPearls*, Treasure Island (FL): StatPearls Publishing, 2021. Accessed: May 30, 2021. [Online]. Available: <http://www.ncbi.nlm.nih.gov/books/NBK538334/>
- [37] S.-L. Chen, W.-W. Zhang, J. Wang, J.-Y. Sun, S.-G. Wu, and Z.-Y. He, "The Role of Axillary Lymph Node Dissection in Tubular Carcinoma of the Breast: A Population Database Study," *Med. Sci. Monit. Int. Med. J. Exp. Clin. Res.*, vol. 25, pp. 880–887, Jan. 2019, doi: 10.12659/MSM.913077.
- [38] F. Mamouch, N. Berrada, Z. Aoullay, B. El Khanoussi, and H. Errihani, "Inflammatory Breast Cancer: A Literature Review," *World J. Oncol.*, vol. 9, no. 5–6, pp. 129–135, Nov. 2018, doi: 10.14740/wjon1161.
- [39] L. L. Lopes Filho, I. M. R. S. Lopes, L. R. S. Lopes, M. M. S. S. Enokihara, A. O. Michalany, and N. Matsunaga, "Mammary and extramammary Paget's disease," *An. Bras. Dermatol.*, vol. 90, no. 2, pp. 225–231, Apr. 2015, doi: 10.1590/abd1806-4841.20153189.
- [40] F. Limaiem and S. Kashyap, "Phyllodes Tumor Of The Breast," in *StatPearls*, Treasure Island (FL): StatPearls Publishing, 2021. Accessed: May 30, 2021. [Online]. Available: <http://www.ncbi.nlm.nih.gov/books/NBK541138/>

- [41] A. R. T. Bergin and S. Loi, "Triple-negative breast cancer: recent treatment advances," *F1000Research*, vol. 8, Aug. 2019, doi: 10.12688/f1000research.18888.1.
- [42] C. E. DeSantis, J. Ma, A. Goding Sauer, L. A. Newman, and A. Jemal, "Breast cancer statistics, 2017, racial disparity in mortality by state," *CA. Cancer J. Clin.*, vol. 67, no. 6, pp. 439–448, Nov. 2017, doi: 10.3322/caac.21412.
- [43] M. M. Gaudet *et al.*, "Risk factors by molecular subtypes of breast cancer across a population-based study of women 56 years or younger," *Breast Cancer Res. Treat.*, vol. 130, no. 2, pp. 587–597, Nov. 2011, doi: 10.1007/s10549-011-1616-x.
- [44] S. C. Larsson, C. S. Mantzoros, and A. Wolk, "Diabetes mellitus and risk of breast cancer: a meta-analysis," *Int. J. Cancer*, vol. 121, no. 4, pp. 856–862, Aug. 2007, doi: 10.1002/ijc.22717.
- [45] M. L. Neuhouser *et al.*, "Overweight, Obesity, and Postmenopausal Invasive Breast Cancer Risk: A Secondary Analysis of the Women's Health Initiative Randomized Clinical Trials," *JAMA Oncol.*, vol. 1, no. 5, pp. 611–621, Aug. 2015, doi: 10.1001/jamaoncol.2015.1546.
- [46] P. Muti *et al.*, "Fasting glucose is a risk factor for breast cancer: a prospective study," *Cancer Epidemiol. Biomark. Prev. Publ. Am. Assoc. Cancer Res. Cosponsored Am. Soc. Prev. Oncol.*, vol. 11, no. 11, pp. 1361–1368, Nov. 2002.
- [47] J. C. Heuson, N. Legros, and R. Heimann, "Influence of insulin administration on growth of the 7,12-dimethylbenz(a)anthracene-induced mammary carcinoma in intact, oophorectomized, and hypophysectomized rats," *Cancer Res.*, vol. 32, no. 2, pp. 233–238, Feb. 1972.
- [48] J. C. Melvin, L. Holmberg, S. Rohrmann, M. Loda, and M. Van Hemelrijck, "Serum lipid profiles and cancer risk in the context of obesity: four meta-analyses," *J. Cancer Epidemiol.*, vol. 2013, p. 823849, 2013, doi: 10.1155/2013/823849.
- [49] P. J. Goodwin and V. Stambolic, "Impact of the obesity epidemic on cancer," *Annu. Rev. Med.*, vol. 66, pp. 281–296, 2015, doi: 10.1146/annurev-med-051613-012328.
- [50] F. Bäckhed *et al.*, "The gut microbiota as an environmental factor that regulates fat storage," *Proc. Natl. Acad. Sci. U. S. A.*, vol. 101, no. 44, pp. 15718–15723, Nov. 2004, doi: 10.1073/pnas.0407076101.