Review Article

Histological Features, Risk Factors, and Classification of Breast Cancer: A Rapid Review

Abbas Abed Sharhan[1], Ahmed Neema AL-Mussawy[2], Rawaa S. A. AL-Azawi[2], Hamzah H. Kzar[3*]

[1]College of Biotechnology, Al-Qasim Green University, 51013, Babylon, Iraq
[2]Collage of Science, Al-Qasim Green University, 51013, Babylon, Iraq
[3]College of Veterinary Medicine, Al-Qasim Green University, 51013, Babylon, Iraq

*Corresponding Author: Hamzah H. Kzar
College of Veterinary Medicine, Al-Qasim Green University, 51013, Babylon, Iraq

Abstract: Breast cancer (BC) is developing from cells of breast tissue and is caused by the presence of malignant cells, which are characterized by uncontrolled cell division, leading to abnormal growth (in situ carcinoma), and their ability to invade normal tissue locally. BC's diagnosis and treatment strategies have recently improved, but the incidence rates continue to increase. Worldwide, BC is the most common cancer in women. The aim of this study is to combine histological, classification, and risk factors in a small review for easy searching by clinical researchers. Currently, there are many studies on BC in Iraq or in other regions of the world. Therefore, combining these studies in one work may give an advantage in the clinical trials of BC. In conclusion, BC is the first of the ten top cancers in Iraqi women up to 2018.

Keywords: Breast Cancer, Histological Features, Classification of BC, Breast Tumor.

1. INTRODUCTION

Breast cancer (BC) is the most frequent malignancy of women worldwide. The most repeatedly diagnosed cancer and cause of cancer death among women is BC [1]. "It is developing from cells of breast tissue, this carcinoma caused by the presence of malignant cells, which can be described as uncontrolled cells division, leading to abnormal growth (in situ carcinoma), and their ability to invade normal tissue locally [2]. The primary tumor begins in the breast, but once it becomes invasive, may progress to the regional lymph nodes and become metastasize [3]. Previously, BC progression was seen as a multi-step process involving progressive changes from normal to hyperplasia with and without atypia, carcinoma in situ, invasive carcinoma, and metastasis [4]. BC is a main cause of disability and mortality among women, predominately young women, in low- and middle-income areas. Despite the fact that overall mortality and incidence rates continue to be lower than that of most privileged areas, case fatality rates from breast cancer remain remarkably high [5]. These high case fatality rates are probably caused by an inadequate awareness of the benefits of treatment and early detection, moreover the lack of appropriate facilities for diagnosis and detection, also deficient accessibility to primary treatment. The diagnosis and treatment strategies of breast cancer are recently improved, but the incidence rates continue to increase [6]. Worldwide, BC is the most common cancer in women. The new cases of women with BC in 2018 were more than 250000 in the UAS, and breast cancer will be diagnosed in 12% of all women in the USA over their lifetimes [7]. Globally, about 2.1 million women were estimated with breast cancer in 2018 [8], as shown in figure (1.B). BC is the major public health problem and the leading cause of cancer-related deaths among Iraqi women [9]. In developed countries, the much higher incidence rates were counterparts in less developed and poor- resourced regions across the globe, the corresponding mortality rates are low, while Africa recorded 168,690 cases of diagnosed BC in 2018 with 74,072 deaths occurring, but in North America is reported to have recording 262,347 diagnosed cases of BC and 46,963 deaths [10-12]. In the other hand, in Iraq, BC ranks the first among the top ten malignant neoplasms affecting the community; comprising 19.5% of total (4996 cases) and 34.3% of female cancers (4922 cases). During 2016, 897 women died from that disease which is the registered as the first cause of cancer related mortality among Iraqi females (23.6%) and the second overall among males and females (12.1%) after bronchogenic cancer [13, 14]. The latest Iraqi cancer registry showed that the total number of BC cases was 4,529

(4,422 in females and 107 in males), of which 989 were newly diagnosed. It remained the most common cancer among the Iraqi population since three decades forming 12.90 per 100000 populations in general, and 25.66 per 100,000 Iraqi women [15]". The incidence Rate (Per 100,000Population) of Top Ten Cancer, Iraq, 2015 as shown in figure (1.A).
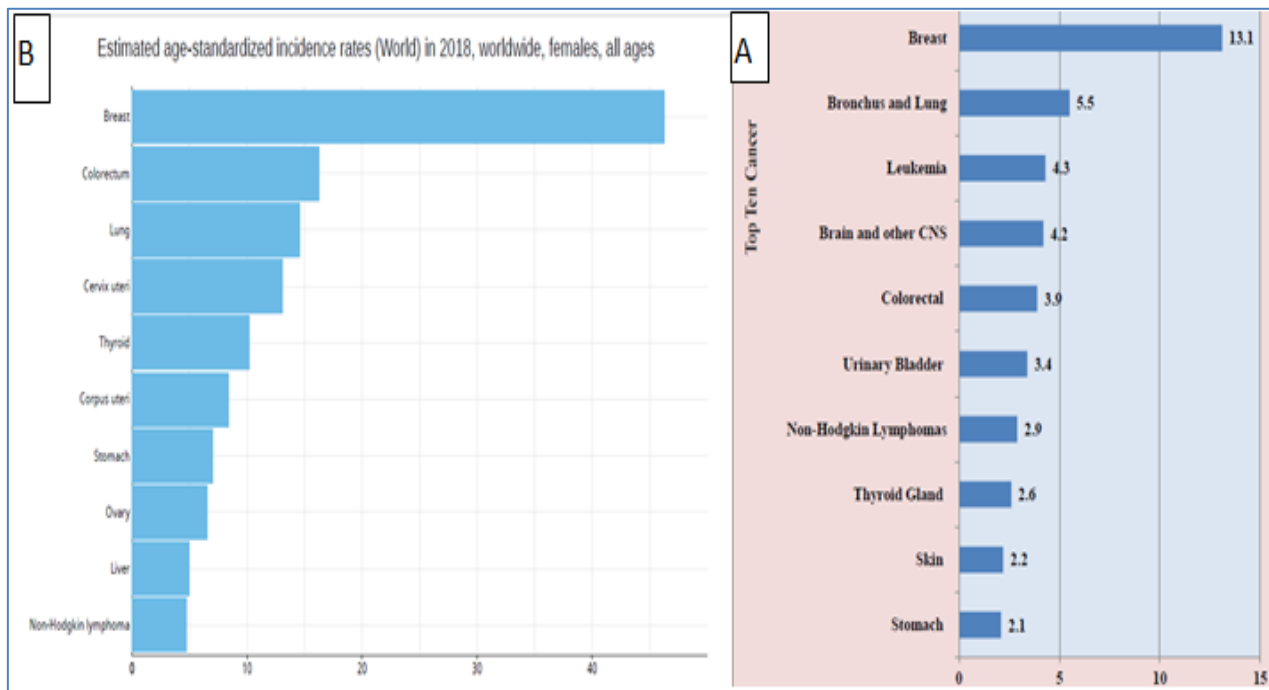

Figure 1: Incidence Rate (Per 100,000 Population) of Top Ten Cancer, Iraqi (A) and Globally (B), 2018 [13, 15].

2. Risk Factors of BC
2.1. Gender
"BC effects on both men and women but the incidence is much higher for women. Overall, women are at 100-fold higher risk of BC than men [16-20].**"**

2.2. Age
"Besides sex, the previous data suggested that the aging is one of the most important risk factors of the BC, because the incidence of BC is highly related to the increasing age. In 2016, approximately 99.3% and 71.2% of all BC associated deaths in America were reported in women over the age of 40 and 60 years, respectively [21]. Therefore, it is necessary to have a mammography screening ahead of time in women aged 40 or older [22]. In Iraq, the same study suggested the mean age of BC incidence was from 50 to 60 years [23]."

2.3. Family History
"Nearly a quarter of all BC cases are related to family history. Women, whose mother or sister has a breast cancer, are a higher risk factor to incidence with this disease [24]. A cohort study of over 113,000 women in UK demonstrated that women with one first-degree relative with breast cancer have a 1.75-fold higher risk of developing this disease than women without any affected relatives. Moreover, the risk becomes 2.5-fold or higher in women with two or more first-degree relatives with BC. The inherited susceptibility to BC is partially attributed to the mutations of BC related genes such as BRCA1 and BRCA2 [25]. Chronic disease of a family member dramatically affects the whole family. A family history score based on expected as well as observed breast cancers in a family can give greater risk discrimination on BC incidence than conventional parameters based solely on cases in affected relatives [26]."

2.4. Reproductive Factors
"Ellingjord-Dale *et al*., (2017) were reported that the reproductive factors were to some extent associated with all subtypes; the strongest trends were with luminal-like subtypes. There were also found a significant protective effect of high parity after controlling for age at first birth and the other menstrual factors [27]."

2.5. Hormonal replacement therapy (HRT)
"Both endogenous and exogenous estrogens are related to the danger of BC. The endogenous estrogen is normally delivered by the ovary in premenopausal ladies and ovariectomy can lessen the danger of BC [28]. Oral contraceptives have been broadly utilized since the 1960s and the details have been moved up to diminish results [29]. By the by, oral

contraceptives don't build the danger of BC in ladies who quit utilizing them for over 10 years [30]. HRT includes the organization of exogenous estrogen or different hormones for menopausal or postmenopausal ladies. Various investigations have indicated that the utilization of HRT can expand the BC hazard [31]. The danger of bosom malignant growth has been appeared to fundamentally diminish following two years of halting HRT [32]. The repeat rate is additionally high among bosom malignancy survivors who take HRT, and the HR for another bosom tumor is 3.6 [33]. Since the unfriendly impacts of HRT were distributed in 2003 dependent on the Women's Health Initiative randomized controlled preliminary, the frequency pace of BC in America has diminished by around 7% because of the decrease in the utilization of HRT [34]."

2.6. Lifestyle

"Current ways of life, for example, over the top liquor utilization and an excess of dietary fat admission can build the danger of BC. Liquor utilization can lift the degree of estrogen-related hormones in the blood and trigger the estrogen receptor pathways [35]. A meta-investigation dependent on 53 epidemiological examinations demonstrated that admission of 35-44 grams of liquor for every day can expand the danger of BC by 32%, with a 7.1% expansion in the relative danger (RR) for each extra 10 grams of liquor for each day [36]. The cutting-edge western eating routine contains a lot of fat and overabundance admission of fat, particularly soaked fat, which is related to mortality (RR=1.3) and helpless visualization in BC patients [37]. In spite of the fact that the connection between smoking and bosom disease hazard stays questionable, mutagens from tobacco smoke have been distinguished in the bosom liquid from non-lactating ladies. The danger of BC is additionally raised in ladies who both smoke and drink (RR=1.54) (41). Up to now, collecting proof shows that smoking, particularly at an early age, has a higher danger of BC event [38-41]". A Summary of BC hazard factors shows in figure (2).
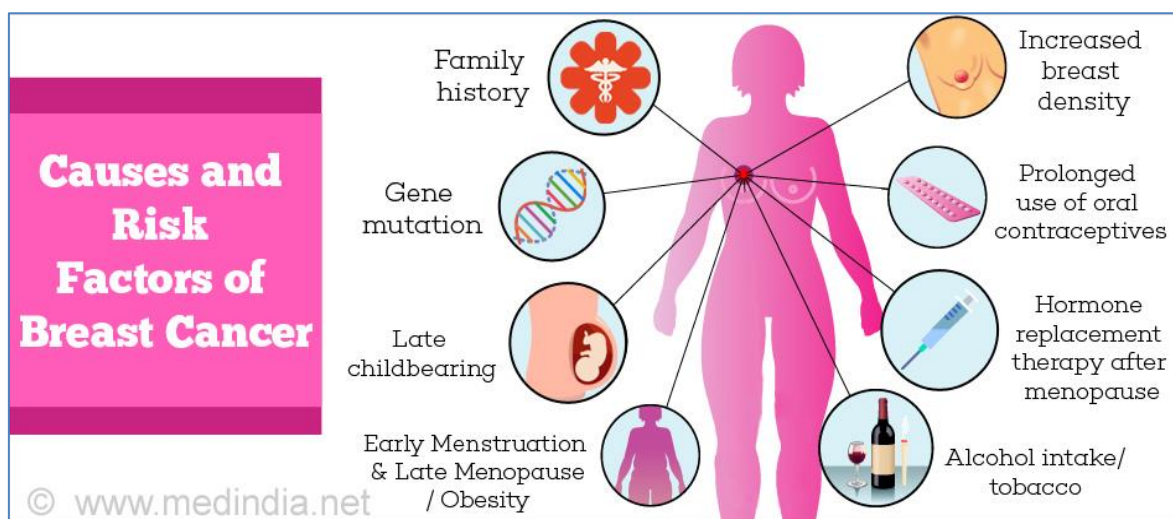

Figure 2: Risk factors of breast cancer [41].

3. Histological Features and Classification of BC

"In contrast to different malignant growths, characterizing the movement of BC has not been conceivable because of an absence of markers that characterize hyperplasia (average and atypical), carcinoma in situ, and obtrusive disease [42, 43]. Notwithstanding, BC can be comprehensively sorted into in situ carcinoma and intrusive (penetrating) carcinoma [44]. Bosom carcinoma in situ is further sub-delegated either ductal or lobular; development designs and cytological highlights structure the premise to recognize the two kinds. In situ Ductal carcinoma (IDC) is significantly more normal than it's in situ lobular carcinoma (ILC) partner and incorporates a heterogeneous gathering of tumors. IDC has customarily been further sub-characterized dependent on the building highlights of the tumor which has offered ascend to five very much perceived subtypes: Comedo, Cribiform, Micropapillary, Papillary, and Solid [45]", (figure 3).
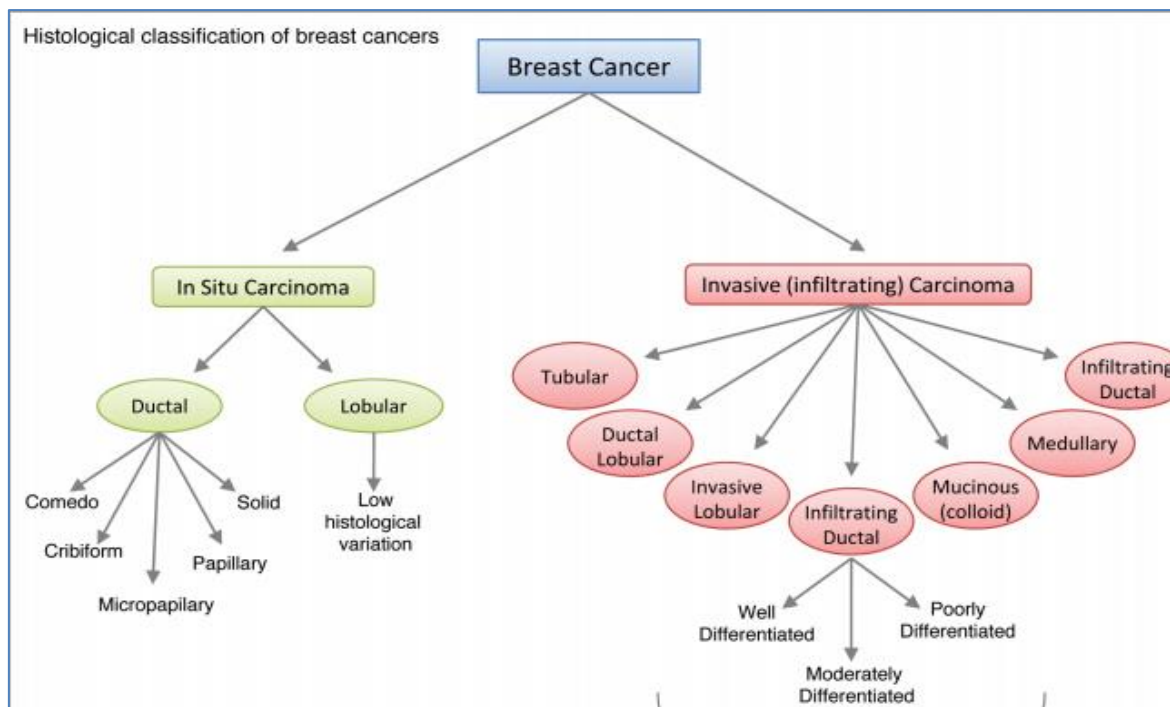
Figure 3: Histological Classification of BC [45]

4. Molecular Classification of BC

"Elidrissi M et al., (2017) were classified BC into distinct subgroups based on similarities in the gene expression profiles using the microarray technology [46]. At least five main molecular classes of breast cancer are currently recognized: Luminal A, Luminal B, HER-2, Basal, and Unclassified BC". The summery of above classification is shown in table (1):

Table 1: Molecular classification of breast cancer

No.	subtype	Clinic-pathological definition
1	Luminal A	Luminal A-like All of: ER and PR Positive, Her-2 (negative,Ki-67 low(<14
		Recurrence risk is low based on multi-gene expression assay
2	Luminal B	Luminal B-like (Her2 negative)ER positive, HER2 negative And at least one of:Ki-67 high($\geq$14), PR negative or low
		Recurrence risk is high based on multi-gene assay
		Luminal B-like (Her-2 positive) ER positive, Her-2 over expressed or amplified Any Ki-67, Any PR
3	HER2 Positive	Her-2 positive (non-luminal) Her-2 over expressed or amplified, ER and PR absent
4	Basal-like	Triple negative (ductal) ER and PR absent, Her-2 negative

5. CONCLUSION: BC is the first of the ten top cancers in Iraqi women up to 2018.

CONFLICT OF INTEREST: Nil

REFERENCES

1. Lauby-Secretan, B., Scoccianti, C., Loomis, D., Benbrahim-Tallaa, L., Bouvard, V., Bianchini, F., & Straif, K. (2015). Breast-cancer screening—viewpoint of the IARC Working Group. *New England journal of medicine*, *372*(24), 2353-2358.
2. Davies, E. (2012). Breast cancer. *Medicine, 40*, 5-9.
3. Zhou, J., Chen, Q., Zou, Y., Chen, H., Qi, L., & Chen, Y. (2019). Stem cells and cellular origins of breast cancer: updates in the rationale, controversies, and therapeutic implications. *Frontiers in oncology*, *9*, 820.
4. Siddharth, S., Goutam, K., Das, S., Nayak, A., Nayak, D., Sethy, C., ... & Kundu, C. N. (2017). Nectin-4 is a breast cancer stem cell marker that induces WNT/β-catenin signaling via Pi3k/Akt axis. *The international journal of biochemistry & cell biology*, *89*, 85-94.
5. Skibinski, A., & Kuperwasser, C. (2015). The origin of breast tumor heterogeneity. *Oncogene*, *34*(42), 5309-5316.
6. Najjar, H., & Easson, A. (2010). Age at diagnosis of breast cancer in Arab nations. *International journal of surgery*, *8*(6), 448-452.
7. National Institutes of Health; National Cancer Institute (2018). Surveillance, Epidemiology, and End Results Program. Cancer stat facts: female breast cancer.
8. Matsuda, T., & Okuyama, A. (2018). Cancer incidence rates in the world from the Cancer Incidence in Five Continents XI. *Japanese Journal of Clinical Oncology*, *48*(2), 202-203.
9. Al-Isawi, A. O. J. (2016). Breast cancer in western Iraq: clinicopathological single institution study. *Advances in breast cancer research*, *5*(2), 83-89.
10. Freddie, B. et al. (2018). Estimated cancer incidence, mortality and prevalence worldwide for 36 cancers in 185 countries CA: *A Cancer Journal for Clinicians. 0*, 1-31.
11. Brennan, M. (2017). Breast cancer in ethnic minority groups in developed nations: case studies of the United Kingdom and Australia. *Maturitas*, *99*, 16-19.
12. Bandera, E. V., Maskarinec, G., Romieu, I., & John, E. M. (2015). Racial and ethnic disparities in the impact of obesity on breast cancer risk and survival: a global perspective. *Advances in Nutrition*, *6*(6), 803-819.
13. Annual Statistical Report (2016). Planning Directorate, Ministry of Health/ Environment, Republic of Iraq.
14. Annual Report. Iraqi Cancer Registry (2016). Iraqi Cancer Board, Ministry of Health and Environment, Republic of Iraq.
15. Alwan, N. A., Tawfeeq, F., Maallah, A. S., Sattar, S. A., & Saleh, W. A. (2017). The stage of breast cancer at the time of diagnosis: correlation with the clinicopathological findings among Iraqi patients. *J Neoplasm*, *2*(3), 22.
16. PDQ Screening and Prevention Editorial Board. PDQ Cancer Information Summaries. National Cancer Institute (US); Bethesda (MD) (2018). Breast Cancer Screening (PDQ®): Health Professional Version.
17. Doren, A., Vecchiola, A., Aguirre, B., & Villaseca, P. (2018). Gynecological–endocrinological aspects in women carriers of BRCA1/2 gene mutations. *Climacteric*, *21*(6), 529-535.
18. Van Keymeulen, A., Lee, M. Y., Ousset, M., Brohée, S., Rorive, S., Giraddi, R. R., ... & Blanpain, C. (2015). Reactivation of multipotency by oncogenic PIK3CA induces breast tumour heterogeneity. *Nature*, *525*(7567), 119-123.
19. Wooster, R., & Weber, B. (2013). Breast and onvarian cancer. *N Engl J Med. 348*(23), 2339.
20. Cancer Genome, A. N. (2012). Comprehensive molecular portraits of human breast tumours. *Nature. 490*, 61–70.
21. Siegel, R., Miller, K., & Jemal, A. (2017). Cancer Statistics. *CA Cancer J Clin. 67*, 7–30.
22. DeSantis, C. E., Fedewa, S. A., Goding Sauer, A., Kramer, J. L., Smith, R. A., & Jemal, A. (2016). Breast cancer statistics, 2015: Convergence of incidence rates between black and white women. *CA: a cancer journal for clinicians*, *66*(1), 31-42.
23. Abedalrahman, S. K., Ali, B. M., Al-Khalidy, N. A. I., & Al-Hashimi, A. S. (2019). Risk factors of breast cancer among Iraqi women. *Journal of Contemporary Medical Sciences*, *5*(3).
24. Majid, R. A., Hassan, H. A., Muhealdeen, D. N., Mohammed, H. A., & Hughson, M. D. (2017). Breast cancer in Iraq is associated with a unimodally distributed predominance of luminal type B over luminal type A surrogates from young to old age. *BMC women's health*, *17*, 1-8.
25. Brewer, H. R., Jones, M. E., Schoemaker, M. J., Ashworth, A., & Swerdlow, A. J. (2017). Family history and risk of breast cancer: an analysis accounting for family structure. *Breast cancer research and treatment*, *165*, 193-200.
26. Brewer, H. R., Jones, M. E., Schoemaker, M. J., Ashworth, A., & Swerdlow, A. J. (2017). Family history and risk of breast cancer: an analysis accounting for family structure. *Breast cancer research and treatment*, *165*, 193-200.
27. Ellingjord-Dale, M., Vos, L., Tretli, S., Hofvind, S., dos-Santos-Silva, I., & Ursin, G. (2017). Parity, hormones and breast cancer subtypes-results from a large nested case-control study in a national screening program. *Breast cancer research*, *19*(1), 1-21.
28. Wu, Y., Hankinson, S. E., Smith-Warner, S. A., Wang, M., & Eliassen, A. H. (2019). Flavonoid Intake and Plasma Sex Steroid Hormones, Prolactin, and Sex Hormone-Binding Globulin in Premenopausal Women. *Nutrients*, *11*(11), 2669.

29. Soroush, A., Farshchian, N., Komasi, S., Izadi, N., Amirifard, N., & Shahmohammadi, A. (2016). The role of oral contraceptive pills on increased risk of breast cancer in Iranian populations: a meta-analysis. *Journal of cancer prevention*, *21*(4), 294.
30. Bethea, T. N., Rosenberg, L., Hong, C. C., Troester, M. A., Lunetta, K. L., Bandera, E. V., ... & Palmer, J. R. (2015). A case–control analysis of oral contraceptive use and breast cancer subtypes in the African American Breast Cancer Epidemiology and Risk Consortium. *Breast Cancer Research*, *17*, 1-13.
31. Antoine, C., Ameye, L., Paesmans, M., de Azambuja, E., & Rozenberg, S. (2016). Menopausal hormone therapy use in relation to breast cancer incidence in 11 European countries. *Maturitas*, *84*, 81-88.
32. Narod, S. A. (2011). Hormone replacement therapy and the risk of breast cancer. *Nature reviews Clinical oncology*, *8*(11), 669-676.
33. Fahlén, M., Fornander, T., Johansson, H., Johansson, U., Rutqvist, L. E., Wilking, N., & von Schoultz, E. (2013). Hormone replacement therapy after breast cancer: 10 year follow up of the Stockholm randomised trial. *European journal of cancer*, *49*(1), 52-59.
34. Ravdin, P. M., Cronin, K. A., Howlader, N., Berg, C. D., Chlebowski, R. T., Feuer, E. J., ... & Berry, D. A. (2007). The decrease in breast-cancer incidence in 2003 in the United States. *New England Journal of Medicine*, *356*(16), 1670-1674.
35. Bagnardi, V., Rota, M., Botteri, E., Tramacere, I., Islami, F., Fedirko, V., ... & La Vecchia, C. (2015). Alcohol consumption and site-specific cancer risk: a comprehensive dose–response meta-analysis. *British journal of cancer*, *112*(3), 580-593.
36. Jung, S., Wang, M., Anderson, K., Baglietto, L., Bergkvist, L., Bernstein, L., ... & Smith-Warner, S. A. (2016). Alcohol consumption and breast cancer risk by estrogen receptor status: in a pooled analysis of 20 studies. *International journal of epidemiology*, *45*(3), 916-928.
37. Makarem, N., Chandran, U., Bandera, E. V., & Parekh, N. (2013). Dietary fat in breast cancer survival. *Annual review of nutrition*, *33*, 319-348.
38. Knight, J. A., Fan, J., Malone, K. E., John, E. M., Lynch, C. F., Langballe, R., ... & WECARE Study Collaborative Group. (2017). Alcohol consumption and cigarette smoking in combination: A predictor of contralateral breast cancer risk in the WECARE study. *International journal of cancer*, *141*(5), 916-924.
39. Catsburg, C., Miller, A., Rohan, T. (2015). Active cigarette smoking and risk of breast cancer. *Int J Cancer. 136*, 2204–2209.
40. Gaudet, M. M., Carter, B. D., Brinton, L. A., Falk, R. T., Gram, I. T., Luo, J., ... & Gapstur, S. M. (2017). Pooled analysis of active cigarette smoking and invasive breast cancer risk in 14 cohort studies. *International journal of epidemiology*, *46*(3), 881-893.
41. McKenzie, F., Ellison-Loschmann, L., Jeffreys, M., Firestone, R., Pearce, N., & Romieu, I. (2013). Cigarette smoking and risk of breast cancer in a New Zealand multi-ethnic case-control study. *PLoS One*, *8*(4), e63132.
42. Kispert, S., & McHowat, J. (2017). Recent insights into cigarette smoking as a lifestyle risk factor for breast cancer. *Breast Cancer: Targets and Therapy*, 127-132.
43. Cotran, R., Kumar, V., Collins, T. (2016). Breast Cancer Facts and Figures 2015-2016. *American Cancer Society*.
44. Bruna, A., Rueda, O. M., Greenwood, W., Batra, A. S., Callari, M., Batra, R. N., ... & Caldas, C. (2016). A biobank of breast cancer explants with preserved intra-tumor heterogeneity to screen anticancer compounds. *Cell*, *167*(1), 260-274.
45. Gorringe, K. L., & Fox, S. B. (2017). Ductal carcinoma in situ biology, biomarkers, and diagnosis. *Frontiers in oncology*, *7*, 248.
46. Elidrissi, M., 7 Ouarzane, M. (2017). First report on molecular breast cancer subtypes and their clinico-pathological characteristics in Eastern Morocco: series of 2260 cases. *BMC Women's Health 17*, 3.