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Modern interpretation of risk factors in breast cancer of women

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ABSTRACT

Breast cancer is a major public health problem, being the most common cancer diagnosed in women and accounting for more than 1 in 10 new diagnoses of cancer each year. It is the most common neoplasm of women under the age of 40 and the second leading cause of cancer death in this age group, with more frequent detection of pathogenic mutations in breast cancer susceptibility genes. Women with $BRCA_1$ and $BRCA_2$ mutations are about 70% more likely to develop breast cancer. The incidence is rising in most countries and it is expected to have a growing trend in the next 20 years, despite the current efforts to prevent the disease. In order to improve the survival rate, it is necessary to make a diagnosis as early as possible and to initiate the appropriate therapeutic management as soon as possible. Therefore, in order to detect breast formations, mammography screening is very important, breast density being an important factor in predicting the risk of breast cancer. Thus, the presence of high breast density represents a 4-6 times higher risk of developing breast cancer compared to women with low breast density. Aging and menopause are also risk factors for breast cancer. Hormone replacement therapy for postmenopausal women has the benefit of relieving symptoms such as hot flashes, depression or sleep disturbances, but it increases the risk of developing breast cancer.

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Introduction

Breast cancer is the most common type of cancer worldwide. At the end of 2020, breast cancer had an incidence of 47.8%, with a mortality rate of 13.6%. Prostate cancer was on the second position, with an incidence of 30.7% and a mortality rate of 7.7%. The following places were occupied by lung, colorectal and cervical cancer [1].

Breast cancer has become the most common cancer globally since 2021, accounting for 12% of all new annual cancer cases worldwide, according to the World Health Organization. It is the most commonly diagnosed cancer in women in the United States, in addition to skin cancers, and about one in 8 women (about 13%) will develop invasive breast cancer throughout their lifetime, compared to a man's lifetime risk of breast cancer, which is about 1 in 833 [2].

By 2022, it is estimated that about 30% of the newly diagnosed cancers in women will be breast cancer. In women under the age of 45, breast cancer is more common among women of color than in white women, and consequently the death rate is higher for this group. For Asian, Hispanic, and Native American women, the risk of developing and implicitly the risk of dying from breast cancer is lower [3].

Most patients discover their disease during a routine screening, or by accidental discovery of a lump, a change in the shape or size of the breast or a nipple discharge. Also, the history of cosmetic augmentation surgery may be a source of concern about breast implant illness [3,4]. These, along with mastalgia, are relatively common, causing significant anxiety in the patient and leading to the appointment to a specialist. This will include an initial assessment and a detailed medical history along with physical examination. Mammography is usually preferred to support the diagnosis of breast cancer, but ultrasonography appears to be more sensitive in women under 30 years of age [5].

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About 5-10% of breast cancers may be related to known and inherited genetic mutations, and breast cancer in the history of first-degree relatives may double the risk of developing the disease. However, fewer than 15% of women who develop breast cancer have a family member diagnosed with it, with the male hereditary collateral component present in 50% of the cases [6].

Mutations in the $BRCA_1$ and $BRCA_2$ genes should be diagnosed in cases where a hereditary predisposition is suspected. On average, women with a $BRCA_1$ mutation have a lifetime risk of up to 72% of developing breast cancer, and those with a $BRCA_2$ mutation have a 69% risk, and tend to develop more often with breast cancer. Some women have a higher risk of breast cancer due to a higher rate of BRCA mutations, as colorectal cancer does [7].

About 85% of breast cancers occur in women who do not have a family history of breast cancer. In these cases, they develop due to genetic mutations that occur as a result of aging and life in general, rather than inherited mutations [7,8].

The article is an analysis of several studies on the assessment of risk factors for breast cancer. The most common factors and their influence on patient groups were discussed: young or menopausal women, the presence of genetic mutations, patients undergoing hormone replacement therapy, women with a healthy or unfavorable lifestyle who associate or do not consume alcohol and tobacco. The studies were accessed through several scientific platforms, such as PubMed, Scopus, etc.

Discussion

Breast cancer is a heterogeneous disease, whose complexity is genetically rooted and reflected in its phenotypic characteristics [6,8].

Luminal cancers (A and B) are characterized by the expression of estrogen receptors (ER) and/or progesterone receptors (PgR), while tumors enriched with human epidermal growth factor 2 (HER_2) show the overexpression of HER_2 and/ or inherent gene amplification. In triple-negative breast cancer (TN), none of the above targets are identifiable or adequately represented for therapeutic use [7-9].

The risk of developing breast cancer in postmenopausal women is associated with changes in circulating sex hormone levels and the administration of hormone replacement therapy (MHT). Such therapy is used to relieve common menopausal symptoms such as hot flashes, sleep disturbances, depression, and muscle or joint pain [10,11].

The initiation of hormone therapy for menopause may be a safe option for women under the age of 60 who have entered menopause less than 10 years before, who have no history of breast cancer and who are not associated with diseases such as stroke, thromboembolic disorders, active liver disease or coronary heart disease [12,13].

Elevated levels of endogenous estrogen are associated with an increased risk of breast cancer (especially the hormone-positive form of disease) for both pre- or postmenopausal women. However, the association of estrogen levels with the risk of breast cancer among premenopausal women can be difficult to measure due to changes in the menstrual cycle [14,15].

A multicenter study on 767 premenopausal women with breast cancer and 1,699 control patients measured estradiol, estrone, androstenedione, dehydroepiandrosterone and testosterone and associated positive for breast cancer [13].

At the same time, hormone therapy combined with estrogen/ progesterone in postmenopausal women with the uterus present increases the risk of subsequent positive ER breast cancer. In women with a history of hysterectomy, replacement with a single estrogen has not been associated with an increased risk of breast cancer [11,14].

A study by Ellingjord et al. analyzed hormonal risk factors, including reproductive factors (age at first birth, number of pregnancies, breastfeeding), as well as other hormonal factors (the use of oral contraceptives, intrauterine devices and menopausal hormone replacement therapy). The latter included only the use of estrogen or the use of combination therapy with estrogen and progestin . The analysis showed that the body mass index, the age at first birth, the age at menopause, the duration of use of oral contraceptives or intrauterine devices, and the use of hormone therapy at menopause were positively associated with the risk of breast cancer. The age of onset of menarche and the number of pregnancies were associated with a low risk [16].

Compared to women who have never been pregnant, those with more than 3 pregnancies have a risk of about 40% or less of developing luminal breast cancer. For HER_2-positive and triple-negative tumors, there were no statistically significant associations. The heterogenicity test comparing triple negative cancer with luminal type A cancer was statistically significant. Older age at first birth has been associated with an increased risk of breast cancer in general. Mothers older than 30 years at first birth had a slightly increased risk of developing A-like luminal tumors and HER2-negative B-like luminal breast cancer. The heterogenicity test comparing each subtype with A-like luminal breast cancer was not statistically significant for age at first birth [16].

Abubakar et al. conducted an analysis of two study populations from Poland and the United Kingdom. The analysis included 2,498 women with similar luminal-like tumors, ER + and/ or PR + for which complete data on scores based on image analysis for ER, PR, HER2 and Ki67 could be accessed. Patients were screened at the Eastern Cancer Registry and Information Center. The study included women under the age of 55 diagnosed with invasive breast cancer from 1991-1996. The data on the relevant clinical-pathological features, including ER, PR,

HER_2, histological grade, tumor size, lymph node involvement, endocrine therapy and systemic therapy were obtained from the clinical records. Among the patients included in this analysis, there were 316 deaths due to breast cancer. The results showed in both populations of the study that most tumors (82%) were of medium or low histological grade and only 18% of high grade, and approximately 97% of the detected tumors were classified as stage I and II disease. Small (<2 cm) and intermediate (2–5 cm) tumors were predominant in both studies (98% and 97% for the Polish population, respectively). About 70% of the tumors were invasive ductal carcinomas. Only 9% of the patients had HER2 + and this did not differ on the study population [17].

A recent meta-analysis found a positive association between high blood pressure and the risk of breast cancer [18,19]. This was recently confirmed by a cohort study that reported a positive association between arterial hypertension and breast cancer mortality, supporting it as an independent risk factor for breast cancer [20].

Smoking has potential breast carcinogens, and it has been recently shown to be an increased risk factor for ER-positive breast cancer [21].

Breast cancer is the most commonly diagnosed cancer in women worldwide, and mammographic breast density (MD) assessment is one of the strongest factors for assessing the risk of developing this disease. Women with high breast density have a 4-6 times higher risk of developing breast cancer compared to women with low breast density [22-25]. However, studies analyzing the relationship between MD and endogenous plasma hormones have shown insufficient results [26-30]. MD may be an inherited trait or influenced by breast cancer risk factors [31,32].

A study by Howell et al. reviewed several available mammographic density data in relation with breast cancer risk [33]. An overview of 42 studies of white breast density (dense breast tissue appears white on mammography, while adipose tissue is radiolucent and it appears black) visually assessed on mammography indicated that the relative risk of breast cancer for women with a density of 70% or more was 4.64 times higher compared to women with less than 5% density.

In this report, the magnitude of the risk was higher using percentage density than for other visual density estimation methods, such as Wolffe patterns or the Breast Imaging Reporting and Data Classification (BI-RADS), which divides density into four categories, visually evaluated and widely used in the US [34].

Randomized clinical trials have shown that both MHT with estrogen alone and estrogen plus progestogen increase MD in postmenopausal women [35-38]. The Women's Health Initiative (WHI) study found that postmenopausal women who received combined estrogen plus progesterone significantly increased the incidence of breast cancer over a 5-year period compared to the placebo group. In addition, they showed that the frequency of mammograms with suspicious findings in the estrogen plus progesterone group was higher than in the placebo group [39].

The presence of estrogen receptors in the structure of benign breast formations offers the opportunity to use tamoxifen (a selective modulator of estrogen receptors) to treat this pathology. Some authors suggest that low doses of the drug may be effective in treating benign proliferative lesions with a low incidence of side effects and a potential benefit in preventing the development of premalignant lesions [40].

The change in MD over time is not influenced by the typical risk factors for breast cancer. The factors most strongly associated with MD change are age, body mass index, pregnancy and physical activity [41-46].

A high BMI has been positively associated with postmenopausal breast cancer [47,48]. Several studies have reported an inverse relationship between being overweight and the risk of developing breast cancer at premenopause [49]. An increased body mass index is often associated with lifestyle. Thus, the most consistent dietary risk factor for breast cancer is alcohol, and alcohol consumption has been associated with higher estradiol levels and increased mammographic density in women with breast cancer and control [50,51].

In a large prospective study that included mainly postmenopausal women with a healthy lifestyle, the risk of breast cancer was low, especially for ER-positive breast tumors [52,53]. The Nurse's Health Study cohort found a decrease in the risk of menopausal breast cancer, especially ER-positive, among women who did not use MHT and adopted a healthy, alcohol-free lifestyle and without any weight gain [54].

The UK Biobank study found that a healthy lifestyle including diet, regular physical activity, smoking cessation and alcohol consumption mitigates the impact of genetic factors on breast cancer [55].

An important aspect that is difficult to assess is mental health, as it is known that depression affects the immune status and immune deficiencies can facilitate the appearance and progression of tumors. Many studies suggest an influence of psychological factors on survival, but this link could be influenced by other factors (stage, prognosis, aggressiveness of treatment, adherence to treatment) [56-59].

An analysis of $BRCA_1$ and/or $BRCA_2$ mutations associated a later onset of breast cancer in women who had a healthy lifestyle [60,61]. An unfavorable lifestyle can accelerate aging, and aging increases the risk of breast cancer.

According to the Surveillance, Epidemiology, and End Results (SEER) database, the likelihood of a woman

developing breast cancer in the United States between 2013 and 2015 by age range was [61]:

- 0 - 49 years - 2.1% (1 in 49 women)
- 50 - 59 years - 2.4% (1 in 42 women)
- 60 - 69 years - 3.5% (1 in 28 women)
- 70 years and over - 7.0% (1 in 14 women)
- lifetime - 12.9% (1 in 8 women)

Numerous studies have evaluated the incidence of breast cancer in women by age and ethnicity. A study conducted in the United States showed a higher frequency of breast cancer among white women [61]. Many of the racial differences are associated with the presence of risk factors and lifestyle. A cohort study of 156,000 postmenopausal women showed that the age-related incidence of breast cancer for white women was higher than for other groups. The presence of risk factors for breast cancer explained the differences for all groups except African Americans [62].

Mutations in the $BRCA_1$/ $BRCA_2$ genes affect only a small number of women, while variation in the location or susceptibility of low-impact common single-nucleotide polymorphisms (SNPs) may be responsible for the increased incidence. Common places with low penetration have recently been identified. Their polygenic inheritance is associated with an increased risk of breast cancer [63,64]. SNPs are common changes in the DNA code that are thought to be non-functional variants that occur frequently outside of functional genes. However, the number of validated SNPs associated with the risk of breast cancer has now exceeded 70 and it is believed that there may be as many as hundreds that influence the risk of breast cancer [65,66].

Research has shown that DNA methylation is influenced by aging. Telomere length has been proposed as a biomarker of biological age and as a risk factor for cancer. Some studies have shown conflicting results between the association of telomere length and the risk of breast cancer. A healthy lifestyle can reduce the rate of telomere shortening and delay the onset of age-related diseases, including breast cancer [67-70].

Conclusions

This paper highlights the complexity of risk factors and their mechanisms of action in relation to the incidence of breast cancer. The risk factors for breast cancer are many, the most incriminated being genetic predisposition, the administration of hormone replacement therapy, age and lifestyle.

High levels of endogenous estrogen increase the risk of breast cancer (especially hormone-positive breast cancer) in both postmenopausal and in premenopause women. Hormone therapy for menopause can be a safe option for women under the age of 60, with no history of breast cancer and who have been menopausal for up to 10 years.

Combination hormone therapy at menopause for women with intact uterus increases the risk of ER-positive breast cancer. The level of endogenous hormones has been associated with an increase in the mammographic density of the breasts. Periodic mammographic screening is an alternative to the early detection of potentially malignant breast lesions.

High body mass index has also been positively associated with postmenopausal breast cancer. Alcohol intake is associated with increased mammographic density, and smoking with increased risk of ER-positive breast cancer.

The most common cause of breast cancer among young women is the presence of $BRCA_1$ or $BRCA_2$ mutations. Patients with these mutations are about 70% more likely to develop breast cancer. Of the total number of cases diagnosed with breast cancer annually, only 5-10% of the tumors are associated with the presence of genetic mutations.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

References

1. Kwee RM, Kwee TC. Mapping the cancer imaging research landscape: which cancers are more and which cancers are less frequently investigated? *Clin Imaging*. 2022;85:89-93. doi: 10.1016/j.clinimag.2022.03.004
2. Giordano SH. Breast Cancer in Men. *N Engl J Med*. 2018; 378(24):2311-2320. doi: 10.1056/NEJMra1707939
3. Miricescu D, Diaconu CC, Stefani C, Stanescu AMA, Totan A, et al. The Serine/Threonine Protein Kinase (Akt)/ Protein Kinase B (PkB) Signaling Pathway in Breast Cancer. *J Mind Med Sci*. 2020;7(1):34-39. doi: 10.22543/7674.71.P3439
4. Salzman B, Collins E, Hersh L. Common Breast Problems. *Am Fam Physician*. 2019;99(8):505-514.
5. Danciu R, Marina CN, Ardeleanu V, Marin R, Scăunașu RV, Răducu L. Breast implant illness: a step forward in understanding this complex entity and the impact of social media. *J Mind Med Sci*. 2019;6(2):351-355. doi: 10.22543/7674.62.P351355
6. Lynch HT, Watson P, Conway TA, Lynch JF. Clinical/ genetic features in hereditary breast cancer. *Breast Cancer Res Treat*. 1990 Feb;15(2):63-71. doi: 10.1007/BF01810778

7. Mirman Z, Sharma K, Carroll TS, de Lange T. Expression of BRCA1, BRCA2, RAD51, and other DSB repair factors is regulated by CRL4WDR70. *DNA Repair (Amst)*. 2022 Mar 15;113:103320. doi: 10.1016/j.dnarep.2022.103320
8. Perou CM, Sørlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, Pollack JR, Ross DT, Johnsen H, Akslen LA, Fluge O, Pergamenschikov A, Williams C, Zhu SX, Lønning PE, Børresen-Dale AL, Brown PO, Botstein D. Molecular portraits of human breast tumours. *Nature*. 2000 Aug 17;406(6797):747-52. doi: 10.1038/35021093
9. Barchiesi G, Mazzotta M, Krasniqi E, et al. Neoadjuvant Endocrine Therapy in Breast Cancer: Current Knowledge and Future Perspectives. *Int J Mol Sci*. 2020 May 16;21(10):3528. doi: 10.3390/ijms21103528
10. Katuwal S, Tapanainen J, Pukkala E. Multivariate analysis of independent roles of socioeconomic status, occupational physical activity, reproductive factors, and postmenopausal hormonal therapy in risk of breast cancer. *Breast Cancer Res Treat*. 2022 Apr 2. doi: 10.1007/s10549-022-06571-x
11. Ibrahim Kale. The predictive role of monocyte-lymphocyte ratio and platelet-lymphocyte ratio in postmenopausal osteoporosis. *J Clin Invest Surg*. 2021; 6(2):141-147. doi: 10.25083/2559.5555/6.2.9
12. Tan DA, Dayu ARB. Menopausal hormone therapy: why we should no longer be afraid of the breast cancer risk. *Climacteric*. 2022 Feb 11:1-7. doi: 10.1080/13697137.2022.2035711
13. Endogenous Hormones and Breast Cancer Collaborative Group, Key TJ, Appleby PN, Reeves GK, Travis RC, Alberg AJ, Barricarte A, Berrino F, Krogh V, Sieri S, Brinton LA, Dorgan JF, Dossus L, Dowsett M, Eliassen AH, Fortner RT, Hankinson SE, Helzlsouer KJ, Hoff man-Bolton J, Comstock GW, Kaaks R, Kahle LL, Muti P, Overvad K, Peeters PH, Riboli E, Rinaldi S, Rollison DE, Stanczyk FZ, Trichopoulos D, Tworoger SS, Vineis P. Sex hormones and risk of breast cancer in premenopausal women: a collaborative reanalysis of individual participant data from seven prospective studies. *Lancet Oncol*. 2013; 14(10):1009-19. doi: 10.1016/S1470-2045(13)70301-2
14. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Aromatase inhibitors versus tamoxifen in premenopausal women with oestrogen receptor-positive early-stage breast cancer treated with ovarian suppression: a patient-level meta-analysis of 7030 women from four randomised trials. *Lancet Oncol*. 2022; 23(3):382-392. doi: 10.1016/S1470-2045(21)00758-0
15. Lazar AL, Vulturar R, Fodor A, et al. The molecular mechanisms linking metabolic syndrome to endometrial and breast cancers. *J Mind Med Sci*. 2021; 8(2):167-178. doi: 10.22543/7674.82.P167178
16. Ellingjord-Dale M, Vos L, Tretli S, Hofvind S, Dos-Santos-Silva I, Ursin G. Parity, hormones and breast cancer subtypes - results from a large nested case-control study in a national screening program. *Breast Cancer Res*. 2017 Jan 23;19(1):10. doi: 10.1186/s13058-016-0798-x
17. Abubakar M, Figueroa J, Ali HR, Blows F, Lissowska J, Caldas C, Easton DF, Sherman ME, Garcia-Closas M, Dowsett M, Pharoah PD. Combined quantitative measures of ER, PR, HER2, and KI67 provide more prognostic information than categorical combinations in luminal breast cancer. *Mod Pathol*. 2019 Sep;32(9): 1244-1256. doi: 10.1038/s41379-019-0270-4
18. Seretis A, Cividini S, Markozannes G, Tseretopoulou X, Lopez DS, Ntzani EE, Tsilidis KK. Association between blood pressure and risk of cancer development: a systematic review and meta-analysis of observational studies. *Sci Rep*. 2019 Jun 12;9(1):8565. doi: 10.1038/s41598-019-45014-4
19. Han H, Guo W, Shi W, Yu Y, Zhang Y, Ye X, He J. Hypertension and breast cancer risk: a systematic review and meta-analysis. *Sci Rep*. 2017 Mar 20;7: 44877. doi: 10.1038/srep44877
20. Dibaba DT, Ogunsina K, Braithwaite D, Akinyemiju T. Metabolic syndrome and risk of breast cancer mortality by menopause, obesity, and subtype. *Breast Cancer Res Treat*. 2019 Feb;174(1):209-218. doi: 10.1007/s10549-018-5056-8
21. Johnson KC, Miller AB, Collishaw NE, Palmer JR, Hammond SK, Salmon AG, Cantor KP, Miller MD, Boyd NF, Millar J, Turcotte F. Active smoking and secondhand smoke increase breast cancer risk: the report of the Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk (2009). *Tob Control*. 2011 Jan; 20(1):e2. doi: 10.1136/tc.2010.035931
22. Boyd NF, Byng JW, Jong RA, Fishell EK, Little LE, Miller AB, Lockwood GA, Tritchler DL, Yaffe MJ. Quantitative classification of mammographic densities and breast cancer risk: results from the Canadian National Breast Screening Study. *J Natl Cancer Inst*. 1995 May 3;87(9):670-5. doi: 10.1093/jnci/87.9.670
23. Li T, Houssami N, Noguchi N, Zeng A, Marinovich ML. Differential detection by breast density for digital breast tomosynthesis versus digital mammography population screening: a systematic review and meta-analysis. *Br J Cancer*. 2022 Mar 28. doi: 10.1038/s41416-022-01790-x
24. Stoian AP, Hainarosie R, Pietrosanu C, Rusescu A, Andronache LF, et al. Modern concepts in non-surgical esthetics; a review. *J Mind Med Sci*. 2019;6(2):190-195. doi: 10.22543/7674.62.P190195
25. McCormack VA, dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. *Cancer Epidemiol Biomarkers Prev*.

2006 Jun;15(6):1159-69. doi: 10.1158/1055-9965.EPI-06-0034

26. Boyd NF, Stone J, Martin LJ, Jong R, Fishell E, Yaffe M, Hammond G, Minkin S. The association of breast mitogens with mammographic densities. *Br J Cancer*. 2002 Oct 7;87(8):876-82. doi: 10.1038/sj.bjc.6600537
27. Greendale GA, Huang MH, Ursin G, Ingles S, Stanczyk F, Crandall C, Laughlin GA, Barrett-Connor E, Karlamangla A. Serum prolactin levels are positively associated with mammographic density in postmenopausal women. *Breast Cancer Res Treat*. 2007 Nov;105(3):337-46. doi: 10.1007/s10549-006-9454-y
28. Tamimi RM, Byrne C, Colditz GA, Hankinson SE. Endogenous hormone levels, mammographic density, and subsequent risk of breast cancer in postmenopausal women. *J Natl Cancer Inst*. 2007 Aug 1;99(15):1178-87. doi: 10.1093/jnci/djm062
29. Bertrand KA, Eliassen AH, Hankinson SE, Rosner BA, Tamimi RM. Circulating Hormones and Mammographic Density in Premenopausal Women. *Horm Cancer*. 2018 Apr;9(2):117-127. doi: 10.1007/s12672-017-0321-6
30. Johansson H, Gandini S, Bonanni B, Mariette F, Guerrieri-Gonzaga A, Serrano D, Cassano E, Ramazzotto F, Baglietto L, Sandri MT, Decensi A. Relationships between circulating hormone levels, mammographic percent density and breast cancer risk factors in postmenopausal women. *Breast Cancer Res Treat*. 2008 Mar;108(1):57-67. doi: 10.1007/s10549-007-9577-9
31. Ursin G, Lillie EO, Lee E, Cockburn M, Schork NJ, Cozen W, Parisky YR, Hamilton AS, Astrahan MA, Mack T. The relative importance of genetics and environment on mammographic density. *Cancer Epidemiol Biomarkers Prev*. 2009 Jan;18(1):102-12. doi: 10.1158/1055-9965.EPI-07-2857
32. Azam S, Sjölander A, Eriksson M, Gabrielson M, Czene K, Hall P. Determinants of Mammographic Density Change. *JNCI Cancer Spectr*. 2019 Feb 4;3(1): pkz004. doi: 10.1093/jncics/pkz004
33. Howell A, Anderson AS, Clarke RB, Duffy SW, Evans DG, Garcia-Closas M, Gescher AJ, Key TJ, Saxton JM, Harvie MN. Risk determination and prevention of breast cancer. *Breast Cancer Res*. 2014 Sep 28;16(5): 446. doi: 10.1186/s13058-014-0446-2
34. Choi E, Suh M, Jung SY, et al. Estimating Age-Specific Mean Sojourn Time of Breast Cancer and Sensitivity of Mammographic Screening by Breast Density among Korean Women. *Cancer Res Treat*. 2022 Apr 4. doi: 10.4143/crt.2021.962
35. McTiernan A, Martin CF, Peck JD, Aragaki AK, Chlebowski RT, Pisano ED, Wang CY, Brunner RL, Johnson KC, Manson JE, Lewis CE, Kotchen JM, Hulka BS; Women's Health Initiative Mammogram Density Study Investigators. Estrogen-plus-progestin use and mammographic density in postmenopausal women: Women's Health Initiative randomized trial. *J Natl Cancer Inst*. 2005 Sep 21;97(18):1366-76. doi: 10.1093/jnci/dji279
36. Greendale GA, Reboussin BA, Sie A, Singh HR, Olson LK, Gatewood O, Bassett LW, Wasilauskas C, Bush T, Barrett-Connor E. Effects of estrogen and estrogen-progestin on mammographic parenchymal density. Postmenopausal Estrogen/Progestin Interventions (PEPI) Investigators. *Ann Intern Med*. 1999 Feb 16;130(4 Pt 1):262-9. doi: 10.7326/0003-4819-130-4_part_1-199902160-00003
37. McTiernan A, Chlebowski RT, Martin C, Peck JD, Aragaki A, Pisano ED, Wang CY, Johnson KC, Manson JE, Wallace RB, Vitolins MZ, Heiss G. Conjugated equine estrogen influence on mammographic density in postmenopausal women in a substudy of the women's health initiative randomized trial. *J Clin Oncol*. 2009 Dec 20;27(36):6135-43. doi: 10.1200/JCO.2008.21.7166
38. Crandall CJ, Guan M, Laughlin GA, Ursin GA, Stanczyk FZ, Ingles SA, Barrett-Connor E, Greendale GA. Increases in serum estrone sulfate level are associated with increased mammographic density during menopausal hormone therapy. *Cancer Epidemiol Biomarkers Prev*. 2008 Jul;17(7):1674-81. doi: 10.1158/1055-9965.EPI-07-2779
39. Chlebowski RT, Hendrix SL, Langer RD, Stefanick ML, Gass M, Lane D, Rodabough RJ, Gilligan MA, Cyr MG, Thomson CA, Khandekar J, Petrovitch H, McTiernan A; WHI Investigators. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. *JAMA*. 2003;289(24):3243-53. doi: 10.1001/jama.289.24.3243
40. Bălălău C, Voiculescu S, Motofei I, Scăunașu RV, Negrei C. Low dose tamoxifen as treatment of benign breast proliferative lesions. *Farmacia*. 2015;63(3): 371-5.
41. Maskarinec G, Pagano I, Lurie G, Kolonel LN. A longitudinal investigation of mammographic density: the multiethnic cohort. *Cancer Epidemiol Biomarkers Prev*. 2006 Apr;15(4):732-9. doi: 10.1158/1055-9965.EPI-05-0798
42. Kale İ, Helvacıoğlu Ç, Muğurtay TE. Evaluation of complete blood count parameters in the first trimester: an early indicator of miscarriage? *J Clin Invest Surg*. 2021; 6(1):48-52. doi: 10.25083/2559.5555/6.1.9
43. Jordan WJ. Mental Health & Drugs; A Map the Mind. *J Mind Med Sci*. 2020;7(2):133-140. doi: 10.22543/7674.72.P133140
44. Kelemen LE, Pankratz VS, Sellers TA, Brandt KR, Wang A, Janney C, Fredericksen ZS, Cerhan JR, Vachon CM. Age-specific trends in mammographic

density: the Minnesota Breast Cancer Family Study. *Am J Epidemiol*. 2008 May 1;167(9):1027-36. doi: 10.1093/aje/kwn063

45. Bălălău OD, Olaru OG, Dumitru AV, et al. Maternal infections with an increased risk of transmission to the foetus; a literature review. *J Clin Invest Surg*. 2020; 5(2):66-72. doi: 10.25083/2559.5555/5.2/66.72
46. Olaru OG, Stanescu AD, Raduta C, et al. Caesarean section versus vaginal birth in the perception of woman who gave birth by both methods. *J Mind Med Sci*. 2021;8(1):127-132. doi: 10.22543/7674.81.P127132
47. Han X, Stevens J, Truesdale KP, Bradshaw PT, Kucharska-Newton A, Prizment AE, Platz EA, Joshu CE. Body mass index at early adulthood, subsequent weight change and cancer incidence and mortality. *Int J Cancer*. 2014;135(12):2900-9. doi: 10.1002/ijc.28930
48. Key TJ, Appleby PN, Reeves GK, et al; Endogenous Hormones Breast Cancer Collaborative Group. Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. *J Natl Cancer Inst*. 2003 Aug 20;95(16):1218-26. doi: 10.1093/jnci/djg022
49. Chan DSM, Abar L, Cariolou M, et al. 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*. 2019 Nov; 30(11):1183-1200. doi: 10.1007/s10552-019-01223-w
50. Shield KD, Soerjomataram I, Rehm J. Alcohol Use and Breast Cancer: A Critical Review. *Alcohol Clin Exp Res*. 2016 Jun;40(6):1166-81. doi: 10.1111/acer.13071
51. Frydenberg H, Flote VG, Larsson IM, Barrett ES, Furberg AS, et al. Alcohol consumption, endogenous estrogen and mammographic density among premenopausal women. *Breast Cancer Res*. 2015 Aug 7;17(1):103. doi: 10.1186/s13058-015-0620-1
52. Harris HR, Bergkvist L, Wolk A. Adherence to the World Cancer Research Fund/American Institute for Cancer Research recommendations and breast cancer risk. *Int J Cancer*. 2016 Jun 1;138(11):2657-64. doi: 10.1002/ijc.30015
53. Keskin A, Karslioglu B. Did Covid-19 pandemic narrow the spectrum of surgical indications? *J Clin Invest Surg*. 2021;6(1):58-63. doi: 10.25083/2559.5555/6.1.11
54. Tamimi RM, Spiegelman D, Smith-Warner SA, Wang M, Pazaris M, Willett WC, Eliassen AH, Hunter DJ. Population Attributable Risk of Modifiable and Nonmodifiable Breast Cancer Risk Factors in Postmenopausal Breast Cancer. *Am J Epidemiol*. 2016 Dec 15;184(12):884-893. doi: 10.1093/aje/kww145
55. Arthur RS, Wang T, Xue X, Kamensky V, Rohan TE. Genetic Factors, Adherence to Healthy Lifestyle Behavior, and Risk of Invasive Breast Cancer Among Women in the UK Biobank. *J Natl Cancer Inst*. 2020 Sep 1;112(9):893-901. doi: 10.1093/jnci/djz241
56. Scaunasu RV, Voiculescu S, Popescu B, et al. Depression and breast cancer; postoperative short-term implications. *J Mind Med Sci*. 2018;5(1):82-84. doi: 10.22543/7674.51.P8284
57. Bălălău OD, Bacalbașa N, Olaru OG, Pleș L, Stănescu DA. Vaginal birth after cesarean section – literature review and modern guidelines. *J Clin Invest Surg*. 2020;5(1):13-17. doi: 10.25083/2559.5555/5.1/13.17
58. van Oers H, Schlebusch L. Indicators of psychological distress and body image disorders in female patients with breast cancer. *J Mind Med Sci*. 2020;7(2):179-187. doi: 10.22543/7674.72.P179187
59. Pătru CL, Marinaș MC, Tudorache Ș, et al. The performance of hyperadherence markers in anterior placenta praevia overlying the Caesarean scar. *Rom J Morphol Embryol*. 2019;60(3):861-867.
60. King MC, Marks JH, Mandell JB; New York Breast Cancer Study Group. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. *Science*. 2003;302(5645):643-6. doi: 10.1126/science.1088759
61. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. *CA Cancer J Clin*. 2021 Jan;71(1):7-33. doi: 10.3322/caac.21654
62. Chlebowski RT, Chen Z, Anderson GL, Rohan T, Aragaki A, Lane D, Dolan NC, Paskett ED, McTiernan A, Hubbell FA, Adams-Campbell LL, Prentice R. Ethnicity and breast cancer: factors influencing differences in incidence and outcome. *J Natl Cancer Inst*. 2005;97(6):439-48. doi: 10.1093/jnci/dji064
63. Kedmi A, Kadouri L, Sagy I, Hamburger T, Levin G, Zimhony-Nissim N, Peretz T. Genetic anticipation of breast cancer among BRCA1/BRCA2 mutation carriers: A retrospective study. *Int J Gynaecol Obstet*. 2022 Mar 12. doi: 10.1002/ijgo.14179
64. Çalım-Gürbüz B, Güvendir İ, Ünal B, Erdoğan-Durmuş Ş, Topal CS, Ağaoğlu NB, Doğanay HL, Kızılboğa T, Zemheri IE. Immunohistochemical Evaluation of BAP1 Expression in Breast Cancer with Known BRCA1 and BRCA2 Mutations and Comparison with Histopathological Features. Int J Surg Pathol. 2022 Mar 9:10668969221085969. doi: 10.1177/10668969221085969
65. Pharoah PD, Antoniou AC, Easton DF, Ponder BA. Polygenes, risk prediction, and targeted prevention of breast cancer. *N Engl J Med*. 2008 Jun 26;358(26): 2796-803. doi: 10.1056/NEJMsa0708739
66. Michailidou K, Hall P, Gonzalez-Neira A, Ghoussaini M, Dennis J, Milne RL, et al. Large-scale genotyping identifies 41 new loci associated with breast cancer risk. *Nat Genet*. 2013 Apr;45(4):353-61, 361e1-2. doi: 10.1038/ng.2563
67. Yu M, Hazelton WD, Luebeck GE, Grady WM. Epigenetic Aging: More Than Just a Clock When It Comes to Cancer. *Cancer Res*. 2020 Feb 1;80(3):367-374. doi: 10.1158/0008-5472.CAN-19-0924

68. Herrmann M, Pusceddu I, März W, Herrmann W. Telomere biology and age-related diseases. *Clin Chem Lab Med*. 2018;56(8):1210-1222. doi: 10.1515/cclm-2017-0870
69. Wang Z, Zhang Z, Guo Y, Shui H, Liu G, Jin T, Wang H. Shorter Telomere Length Is Associated with Increased Breast Cancer Risk in a Chinese Han Population: A Case-Control Analysis. *J Breast Cancer*. 2018;21(4):391-398. doi: 10.4048/jbc.2018.21.e52
70. Campa D, Barrdahl M, Santoro A, Severi G, Baglietto L, Omichessan H, Tumino R, Bueno-de-Mesquita HBA, Peeters PH, Weiderpass E, Chirlaque MD, Rodríguez-Barranco M, Agudo A, Gunter M, Dossus L, et al. Mitochondrial DNA copy number variation, leukocyte telomere length, and breast cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Breast Cancer Res*. 2018;20(1):29. doi: 10.1186/s13058-018-0955-5