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BREAST CANCER IN INDIA: INCIDENCE, RISK FACTORS AND PREVENTION STRATEGIES

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ABSTRACT Breast cancer is now the most common type of cancer in females of urban India [1]. The incidence of breast cancer in India is 25.8 per 100,000 women and mortality is 12.7 per 100,000 women [1]. In comparison, the incidence in USA is 124.9 per 100,000 and mortality is 21.2 per 100,000[2].The USA has a fivefold higher incidence than India but nearly 90 percent have a 5 year survival, while in India the 5 year survival is barely 50 percent. Breast cancer incidence is increasing in India, while also presenting in patients at a younger age [1]. The major risk factors for breast cancer are- diet, lifestyle, weight, reproductive cycle, hormone use and lactation [3]. A program aimed at prevention, coupled with increased awareness and early detection strategies can have a substantial impact on reducing the mortality from this deadly disease. This has to be combined effort of government, Non-government agencies, society and people at large to allow every Indian woman to have the least risk of developing the disease and the best chance of surviving if they happen to develop it. This paper reviews the current data on risk factors and strategies to minimize the risk.

KEYWORDS : Breast Cancer, Risk Factor, Prevention

INTRODUCTION
Over a million women worldwide are diagnosed with breast cancer every year [3]. In the developed countries, the mortality rate of women with breast cancer is low, while in developing countries like India, a majority of those with breast cancer will die from it. The incidence of breast cancer is increasing in India [1]. Breast cancer specifically, is potentially a preventable disease and additionally with early detection, it can frequently be cured. India is a country with large population and limited resources. The goal should be to concentrate on prevention and early detection methods rather than spending the limited resources on treatment of advanced disease.

INCIDENCE OF BREAST CANCER IN INDIA
Incidence of breast cancer in India is 25.8 per 100,000[1]. The Incidence varies across the country, with Delhi– 29.6 per 100,000 , Bangalore – 26.5 per 100,000 Mumbai – 25.7 per 100,000, Chennai 23.1 per 100,000, Ahmedabad rural-10.3 per 100,000, Barshi rural- 8.8 per 100,000 and Sikkim state-8.5 per 100,000[4].Comparing the incidence and mortality in India with   USA according to National Cancer Institute statistics based on 2010-2014 – for USA , 124.9 per 100,000 cases were newly detected with breast cancer and 21.2 per 100,000 died from it [2] .Thus for every 5 or 6 women newly diagnosed with breast cancer , one is dying of it. But for India, 25.8 per 100,000 women were newly detected with breast cancer and 12.7 per 100,000[1] women died of it. This means for every 2 women newly diagnosed with breast cancer, one is dying of it. This is graphically detected in Figure 1.
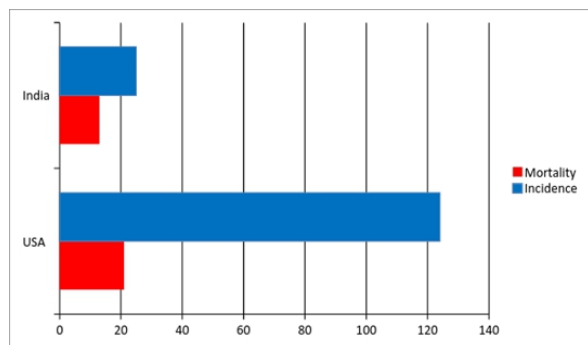

Figure 1 Incidence and Mortality of India Vs USA

RISK FACTORS FOR ETIOLOGY OF BREAST CANCER
A large body of evidence has been accumulated from epidemiological studies in the western countries in an attempt to elucidate the causes of breast cancer [3]. No specific studies have been conducted in India. It is reasonable to assume that similar causative factors may be responsible for Breast Cancer in India. Studies on migrant population from low risk to high risk areas consistently show that the risk of breast cancer rises rapidly in the migrants within a couple of generations to equal the risk of native population of the adopted new country [5].

This data strongly suggest that lifestyle or socioeconomic factors rather than genetic factors play an important role in the development of breast cancer [5]. Developing strategies to prevent the risk require proper understanding of potential risk factors. These factors are discussed in further detail as follows. HORMONAL FACTORS

AGE AT MENARCHE
Early commencement of menstrual cycles before the age of 12 is associated with a higher risk for developing breast cancer [6]. The increased risk is noticeable in both pre- and postmenopausal breast cancer. This phenomenon may be related to longer lifetime exposure to estrogenic activity [3].

AGE AT MENOPAUSE
Bilateral oophorectomy before the age of 45 lessens the risk of breast cancer by 50% as compared to women who have natural menopause at age 55 years or later [7,8]. It has been estimated that the risk of breast cancer increases by about 3% per year for menopause past the age of 45[3]. This delay in menopause leads to an extended exposure to endogenous hormones and continued proliferation of the ductal epithelium. {3,7,8}

MENSTRUAL CYCLES
Some studies suggest a shorter duration of menstrual cycle from age 20-39 is associated with higher risk [6]. This may be due to greater duration of time spent in the luteal phase, where both estrogen and progesterone levels are elevated. On the other hand, longer duration between menstrual cycles and irregular cycles are associated with lower risk [9].

PREGNANCY FACTORS
Generally, parous women have a lower risk of breast cancer than nulliparous women [6,10] Various studies report a decrease risk of developing breast cancers with a first full-term pregnancy before the age of 20 [,6,11]. This may be due to the maturation of glandular epithelium of the mammary cells, which occurs in the first pregnancy [12].

SPACING OF PREGNANCIES
Each added childbirth after the first generally decreases the long-term risk of developing breast cancer. This beneficial effect is more distinct with more closely spaced births [13].

BREAST FEEDING
In early 1926 it was observed that females who never lactated were more susceptible to develop breast cancer [14]. Nevertheless, the predictable level of risk reduction has varied substantially from different reports. [3] The most favorable results indicates a 50%

reduction in the risk for females who breastfed each child for two or more years [15].

EXOGENOUS HORMONE INFLUENCE
Exposure to exogenous hormones as oral contraceptives and hormone replacement therapy result in an increase in the risk of breast cancer. {[16]}Multiple studies have shown that the use of oral contraceptive pills does not increase the risk for breast cancer [17]. But, the use of oral contraceptive pills before the first full-term pregnancy or before the age of 20 may lead to modest increase in risk [3, 18]. According to The Women's Health Initiative, a large randomized study of greater than 16,000 females in the U.S., revealed that combined effect of both estrogen and progestin replacement in postmenopausal women increased the risk of breast cancer by 26 percent [19]

INHERITED GENETIC MUTATION
5 to 10 percent of the breast cancers in the Western world are related to genetic mutations [20]. The two most common ones are autosomal dominant mutations of BRCA1 and BRCA2. The risk of these patients presenting with breast cancer is estimated to be 26% to 85%. [21]. Studies on genetic analysis for BRCA and other genes in India have been very limited. Few reports based on small number of patients report an incidence ranging from 10 to 28 percent [22] A family history of breast cancer raises the risk in a particular individual [3]. The relative risk of developing cancer is

(a) 1.5 times higher if a first-degree relative developed postmenopausal breast cancer , and
(b) 2.0 times higher if a first-degree relative developed premenopausal breast cancer. If two or more first-degree relatives had breast cancer, the risk is almost increased to 6-fold. Additionally, a first-degree family member having had bilateral breast cancers also raises the risk by 6 fold [23]

NON-HORMONAL FACTORS NUTRITION AND PHYSICAL ACTIVITY
Nutritional factors have been evaluated very extensively to account for the increasing incidence of breast cancer. It has been difficult to prove an exact correlation between diet and breast cancer [3]. The association may be more complex and probably related to weight. Weight gain after age 18 is associated with a higher risk for developing postmenopausal breast cancer [3, 24]. Following the diagnosis of breast cancer, either weight loss or weight maintenance decreases the risk of relapse [25]. Table 1 summarizes the risk factors' and proportionate risk

Table1. RISK FACTORS FOR BREAST CANCER

RISK FACTORS	PROPORTIONATE RISK
HORMONAL	
Age at menarche [6] (Less than 12 years vs. more than 15 years)	1.3
Age at menopause [8] (Less than 45 years vs. more than 55 years)	2.0
Age at first live birth [6] (Less than 18 years vs. more than 30 years or no live births)	1.9
Combined hormone replacement therapy in postmenopausal [19] (at least 5 years of use or current use vs. no use)	1.6
NON HORMONAL	
Age [26] (Less than 65 vs. more than 65)	5.8
Physical activity [25,26] (Regular activity vs. inactivity)	1.25-1.4
Obesity (postmenopausal) [24, 25] (BMI more than 25kg per m2 vs, less than 25kg per m2)	1.3-2.1

Biology of Breast Cancer
The current hypothesis for the development of breast cancer proposes that a normal cell undergoes hyperplasia, which changes into atypical hyperplasia, further progressing to in situ cancer, and finally to invasive cancer [27]. The cancer becomes radiographically noticeable at 1 mm and clinically palpable at 1 cm. It takes many years for the transformation from a normal cell to the earliest clinically noticeable cancer [27]. This long duration gives us many chances to stop the progression of cancer and prevent the development of invasive disease.

RISK ASSESSMENT
Estimating the risk for a given patient requires assessment of all known causative factors. Two models are generally used clinically to estimate an individual's risk, The Gail model and The Claus model, both developed in US [28, 29]. In India Gail model is preferred [30]. The Gail model is based on data from U.S. cancer Registries. It combines age, race, age at menarche, age at first live birth, first degree relatives with breast cancer, previous breast biopsies, and atypical hyperplasia on any previous breast biopsy, but it does not give significant importance to family history [28]. The model includes a range of risk factors to assess a patient's risk as compared to the average American. A

5-year cumulative risk of at least 1.67 times greater than a baseline is defined as high risk. The model has not been validated in non U.S. populations. For the females with family history of breast cancer, Claus Model is more useful [29].

Strategies for Risk Reduction
The pathophysiology and the gradual evolution of breast cancer make it suitable for intervention at various stages. General risk reduction strategies could reduce the risk by 40 percent [3]. These simple measures applicable to all women include balanced diet, physical activity, weight management, breastfeeding and avoiding postmenopausal hormone replacement. Additional risk reduction strategies for high risk females include chemoprevention and surgical interventions. Family history of cancer should be routinely enquired by physicians from their patients. Those with family history should be referred for genetic counseling for risk stratification and possible genetic testing for BRCA1 and BRCA2. These high risk women should be encouraged to modify their lifestyle, perform self-breast examinations and seek regular clinical follow-up and should be managed at high risk clinics. Regular screening with imaging studies like mammography could detect cancers early, leading to better long-term outcomes.

PHYSICAL ACTIVITY
There is considerable evidence that the risk of breast cancer can be decreased by increasing physical activity [3]. There are several studies including prospective studies which uniformly reveal a decrease of risk in incidence of breast cancer with physical activity, [31]. Recent review of 73 observational studies indicated that the breast cancer risk can be reduced by approximately 25% in women with moderate to vigorous physical activity compared with inactive women [32]

NUTRITION FACTORS
Nutrition factors play a very important role in risk reduction. Results of prospective studies do not support a significant role of dietary fat or any other single ingredient being the cause of breast cancer. Weight gain in the middle age years is associated with higher risk. Available evidence suggests that minimizing weight gain in adulthood is associated with a decrease in the risk. [3,25]. Weight gain in the premenopausal period and being overweight or obese after menopause increase breast cancer risk which is supported by strong observational data [33,34].

CHEMOPREVENTION
Selective estrogen receptor modulators (SERMs) consist of Tamoxifen and Raloxifene that have demonstrated efficacy in large randomized trials for breast cancer prevention [35, 36]. They were used in women 35 years of age or older, with a predicted Gail model risk of greater than 1.67. [35, 36] The combination of four studies revealed a 38% reduction in the risk of developing breast cancer [37]. Tamoxifen for 5 years is recommended for women at high risk, by Gail model over the age of 35 [35]. Raloxifene, a second generation SERM, is as effective as Tamoxifen in reducing risk, as shown in a randomized trial of almost 20,000 women.[38] But, because of lower side effects Raloxifene is preferred over tamoxifen [38].

PROPHYLACTIC SURGERIES
Bilateral total mastectomy –
It has been demonstrated that women with BRCA1 and BRCA2 mutation can achieve a high degree of protection by having a bilateral total mastectomy according to two small prospective studies but with a relatively short follow up [39, and 40]. Retrospective follow up of 13 to 14 years in females with BRCA1 and BRCA2 mutation who underwent bilateral mastectomy revealed a 90% risk reduction [41-42].

Bilateral salpingo-oophorectomy-
Bilateral salpingo-oophorectomy at or before the age of 40 in females

with BRCA1 and BRCA2 mutations reduce the risk of breast cancer by approximately 40% [43] .These females are also at an increased risk of ovarian cancer, although it is much lower risk than breast cancer. A salpingo- oophorectomy would accomplish the purpose of reducing the risk of both ovarian and breast cancer [3]. Table 2 summarizes general strategies for Breast cancer risk reduction

Table 2. BREAST CANCER RISK REDUCTION INTERVENTIONS

RISK REDUCTION MEASURES	PROPORTIONATE RISK REDUCTION
Breast feeding	4 percent reduction for every 12 Months of breastfeeding
Physical Activity	20-30 percent
Nutrition	20-30 percent
Postmenopausal weight management	20-30 percent
Avoiding exogenous hormone supplement	26 percent
Reproductive patterns (First live birth under 18 vs. over 30 or nulliparity)	40 percent

EARLY DETECTION STRATEGIES

BREAST SELF EXAMINATION

Scientific data has not consistently shown that breast self-examination decreases breast cancer mortality [3]. BSE correlates with an earlier clinical stage which has better prognosis and as such could be a valuable tool in developing countries like India with limited medical resources and lacking more sophisticated screening methods [44} simple but effective tools to teach women the technique of self-examination need to be developed for educating rural women.

MAMMOGRAPHY

Annual or biennial screening in females aged 50 to 69 years reduces the cancer mortality by 50 percent according to some randomized studies [45]. But in females younger than 50 years randomized trial data has not shown a significant reduction in mortality. This could be due to small number of women screened and other limitations of study design [45].

CONCLUSION

India is witnessing an increasing burden of breast cancer. The gradual clinical evolution of breast cancer from normal cells over a long period of time makes it suitable for preventive interventions at various stages. In a country like India with large population and limited resources, the goal should be aimed at better utilization of resources in prevention rather than treating advanced cancer which is not only more expensive but less successful. Simple strategies of dietary changes, regular exercise, weight management combined with regular screening, can significantly reduce the risk and mortality from this deadly disease. Society should make vigorous efforts to educate women to understand the risk factors, realize the importance of early detection and seeking prompt treatment. This will require a combined effort by physicians, government, non-government agencies, society and people at large.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable. COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Malvia, S., Bagadi, S. A., Dubey, U. S. and Saxena, S. (2017), Epidemiology of breast cancer in Indian women. Asia-Pac J Clin Oncol. doi:10.1111/ajco.12661
2. https://seer.cancer.gov/statfacts/html/breast.html
3. S. Rehman Noor, N. Noor, M.M Haq,16(10): 1-11, 2016, Article no.BJMMR.27345 ISSN: 2231-0614, NLM ID: 101570965
4. Time Trends in Breast Cancer Among Indian women population- An Analysis of Population Based Cancer Registry Data. Chaturvedi, M., Vaitheeswaran, K., Satishkumar, K. et al. Indian J Surg Oncol (2015) 6: 427.
5. Ziegler RG, Hoover RN, Pike MC, Hildesheim A, Nomura AM, West DW, et al. Migration patterns and breast cancer risk in Asian-American women. J Natl Cancer Inst.1993;85(22):1819-27.
6. Kelsey JL, Gammon MD, John EM. Reproductive factors and breast cancer. Epidemiol Review. 1993;15(1):36-47.
7. Velie EM, Nechuta SJ, Osuch J. Lifetime reproductive and anthropometric risk factors for breast cancer in postmenopausal women. Breast Dis.2006;26:1–19.
8. Trichopoulos D, MacMahon B, Cole P. Menopause and breast cancer risk. J Natl Cancer Inst 1972;48(3):605-13.
9. Garland M, Hunter DJ, Colditz GA, Manson JE, Stampfer MJ, Spiegelman D, et al. Menstrual cycle characteristics and history of ovulatory infertility in relation to breast cancer risk in a large cohort of US women. Am J of Epidemiol. 1998;147(7):636-43.
10. Haq N, Haq MM, Haque A. Breast cancer incidence and risk reduction with special references to Muslim Countries. JIMA: 38486-IMANA. 2009;41. DOI: http://dx.doi.org/10.5915/41-1-4424
11. International Agency for Research on Cancer (IARC) and World Health Organization (WHO). GLOBOCAN 2012: Estimated cancer incidence, mortality and prevalence worldwide in 2012; 2016. Available:http://globocan.iarc.fr/Pages/fact _ sheets _cancer.aspx
12. Russo J, Tay LK, Russo IH. Differentiation of the mammary gland and susceptibility to carcinogenesis. Breast Cancer Res Treat. 1982;2(1):5-73.
13. Rosner B, Colditz GA, Willett WC. The nurses' health study. Am J Epidemiol 1994;139(8):819-35
14. Lane-Claypon J. A further report on cancer of the breast, with special reference to its associated antecedent condition. London: Ministry of Health; 1926.
15. Romieu I, Hernandez-Avila M, Lazcano E, Lopez L, Romero-Jaime R. Breast cancer and lactation history in Mexican women. Am J Epidemiol. 1996;143(6):543-52.
16. Heck KE, Pamuk ER. Explaining the relation between education and postmenopausal breast cancer. Am J Epidemiol. 1997;145:366-372.
17. Marchbanks PA, McDonald JA, Wilson HG, Folger SG, Mandel MG, Daling JR, et al. Oral contraceptives and the risk of breast cancer. N Engl J Med. 2002; 346:2025-2032. DOI: 10.1056/NEJMoa013202
18. Breast cancer and hormonal contraceptives: Collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. Collaborative Group on hormonal factors in breast cancer. Lancet. 1996;347(9017):1713-27.
19. Rossouw JE, Anderson GL, Prentice RL,LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the women's health initiative randomized controlled trial. JAMA. 2002;288(3):321-333. DOI: 10.1001/jama.288.3.321.
20. Kenneth Offit; BRCA Mutation Frequency and Penetrance: New Data, Old Debate. J Natl Cancer Inst 2006; 98 (23): 1675-1677. doi: 10.1093/jnci/djj500.
21. Hofstatter EW. Molecular biology of breast cancer. In: DeVita, VT Jr, Lawrence TS, Rosenberg SA, DePinho RA, Weinberg RA, editors. DeVita, Hellman and Rosenberg's cancer: Principles and practice of oncology. 9th ed. Philadelphia: Lippincott Williams & Wilkins. 2011;1393- 400.
22. Somasundaram K. BRCA1 and BRCA1 Genes and Inherited Breast and/or Ovarian Cancer: Benefits of Genetic Testing. Indian journal of surgical oncology. 2010;1(3):245-249. doi:10.1007/s13193-011-0049-7.
23. Hoskins KF, Stopfer JE, Calzone KA, et al. Assessment and counseling for women with a family history of breast cancer. A guide for clinicians. JAMA 1995;273(7):577-85.
24. McTiernan A. Behavioral risk factors in breast cancer: Can risk be modified? Oncologist. 2003;8(4):326-34.
25. Holmes MD, Chen WY, Feskanich D, Kroenke CH, Colditz GA. Physical activity and survival after breast cancer diagnosis. JAMA. 2005;293(20):2479-86.
26. Irwin ML. Randomized controlled trials of physical activity and breast cancer prevention. Exerc Sport Sci Rev. 2006;34(4):182-93.
27. Allred DC, Mohsin SK. Biological features of premalignant disease in the human breast. J Mammary Gland Biol Neoplasia. 2000;5(4):351-64.
28. Gail MH, Brinton LA, Byar DP, Corle DK, Green SB, Schairer C, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst. 1989;81(24):1879-86
29. . Claus EB, Risch N, Thompson WD. The calculation of breast cancer risk for women with a first degree family history of ovarian cancer. Breast Cancer Res Treat. 1993;28(2):115-20.
30. Augustine P, Jose R, Amrtithlal A, Nujum ZT, Peter A, Haran JC. Usefulness of Gail Model Breast Cancer Risk Assessment Tool in Estimating the Risk for Development of Breast Cancer in Women of Kerala, India. Academic Medical Journal of India. 2015 Dec 28;3(4):117-122.
31. Thune I, Brenn T, Lund E, Gaard M, et al. Physical activity and the risk of breast cancer. N Engl J Med. 1997;336:1269-1275. DOI: 10.1056/NEJM199705013361801
32. Lynch BM, Neilson HK, Friedenreich CM. Physical activity and breast cancer prevention. Recent Results Cancer Res. 2011;186:13-42. DOI: 10.1007/978-3-642-04231-7_2
33. Colditz GA, Bohlke K. Priorities for the primary prevention of breast cancer. CA Cancer J Clin. 2014;64:186–194. DOI: 10.3322/caac.21225
34. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: A systematic review and meta-analysis of prospective observational studies. Lancet. 2008; 371(9612):569-78.
35. Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, et al. Tamoxifen for prevention of breast cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst. 1998; 90(18):1371-88.
36. Cummings SR, Eckert S, Krueger KA, Grady D, Powles TJ, Cauley JA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: Results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation. JAMA. 1999;281(23):2189-97.
37. Cuzick J, Powles T, Veronesi U, Forbes J, Edwards R, Ashley S, et al. Overview of the main outcomes in breast-cancer prevention trials. Lancet. 2003; 361(9354):296-300.
38. Land SR, Wickerham DL, Costantino JP, et al. Patient-reported symptoms and quality of life during treatment with tamoxifen or raloxifene for breast cancer prevention: The NSABP study of tamoxifen and raloxifene (STAR) P-2 trial. JAMA. 2006; 295(23):2742-
51. (Epub 2006 Jun 5)
39. Meijers-Heijboer H, van Geel B, van Putten WL, Henzen-Logmans SC, Seynaeve C,Menke- Pluymers, et al. Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med. 2001;345(3):159-64.
40. Rebbeck TR, Friebel T, Lynch HT, Neuhausen SL, Van T Veer L, Garber JE, et al. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: The PROSE study group. J Clin Oncol. 2004;22(6):1055-62. (Epub 2004 Feb 23)
41. Hartmann LC, Schaid DJ, Woods JE, Crotty TP, Myers JL, Arnold PG, et al. Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. N Engl J Med. 1999;340(2):77-84.
42. Hartmann LC, Sellers TA, Schaid DJ, Frank TS, Soderberg CL, Sitta DL, et al. Efficacy of bilateral prophylactic mastectomy in BRCA1 and BRCA2 gene mutation carriers. J Natl Cancer Inst. 2001;93(21):1633-7.
43. Kauff ND, Satagopan JM, Robson ME, Scheuer L, Hensley M, Hudis CA, et al. Risk reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med. 2002;346:1609-1615. DOI: 10.1056/NEJMoa020119
44. Weiss NS. Breast cancer mortality in relation to clinical breast examination and breast self examination. Breast J. 2003;9(Suppl 2):S86-9.
45. Kopans DB. Screening mammography for women younger than 50 years. JAMA. 1999;282(13):1225-6. http://dx.doi.org/10.5915/41-1-4424