

Review Article

GENETIC PREDISPOSITION TO DUCTAL CARCINOMA IN SITU OF THE BREAST

ABSTRACT

The existence of atypical cells within the epithelium of a tube in the breast is known as ductal carcinoma in situ (DCIS). DCIS is divided into four categories, or so they believed. Papillary, Cribriform, Solid, and Comedo are the most aggressive types, with Comedo being ER-PR negative, or so they believed.

DCIS is widely regarded as the earliest form of breast cancer in a significant way. It is not invasive in nature, which is rather crucial. It does not spread outside of the duct and has a very minimal chance of becoming invasive, which is very important. DCIS is typically discovered during a mammography that is performed as component of examining of carcinoma of breast cancer or for evaluating a lump of the breast. It is, in essence, pretty significant.

In recent years our understanding of the genetic predisposition to carcinoma has greatly improved. 3 theoretic classes, categorised by the associated risks of carcinoma, are unit presently well-known. BRCA1 and BRCA2 are unit genes known by genome-wide and point biological research link analysis. Experimental modification tests associated with BRCA1 and / or BRCA2 unconcealed four genes, CHEK2, ATM, BRIP1, and PALB2; genetic mutations in these genes are unit rare and gift a moderate risk of carcinoma. The organization's study additionally known eight common variants related to a lower incidence of carcinoma. Despite these findings, most of the family risk of carcinoma has not been known. during this review, we tend to describe well-known genetic options, justify however they're known, and appearance at however more advances in technology and intelligence will facilitate determine the remaining genetic factors that contribute to carcinoma risk

CLINICAL FEATURES-

There are no usual signs and symptoms of DCIS. Nonetheless, it can once in a while cause signs like:

- A lump in the breast

- Discharge from the nipple

On mammography, Ductal Carcinoma In Situ is typically distinguished and shows up as little groups of calcifications that have unpredictable dimensions.

ETIOLOGY-

Although the specific aetiology is unknown, DCIS is caused by genetic abnormalities in Deoxyribonucleic acid of the cells of the duct.

Although the genetic defects lead the cells to appear aberrant, they lack the ability to break free from the breast duct.

There's no way of knowing what causes DCIS.

lifestyle, surroundings, the genes inherited from the parents are all causes having a role.

ACCIDENTAL RISKS-

Factors that can increase the risk of DCIS basically include prolonged exposure to estrogen.

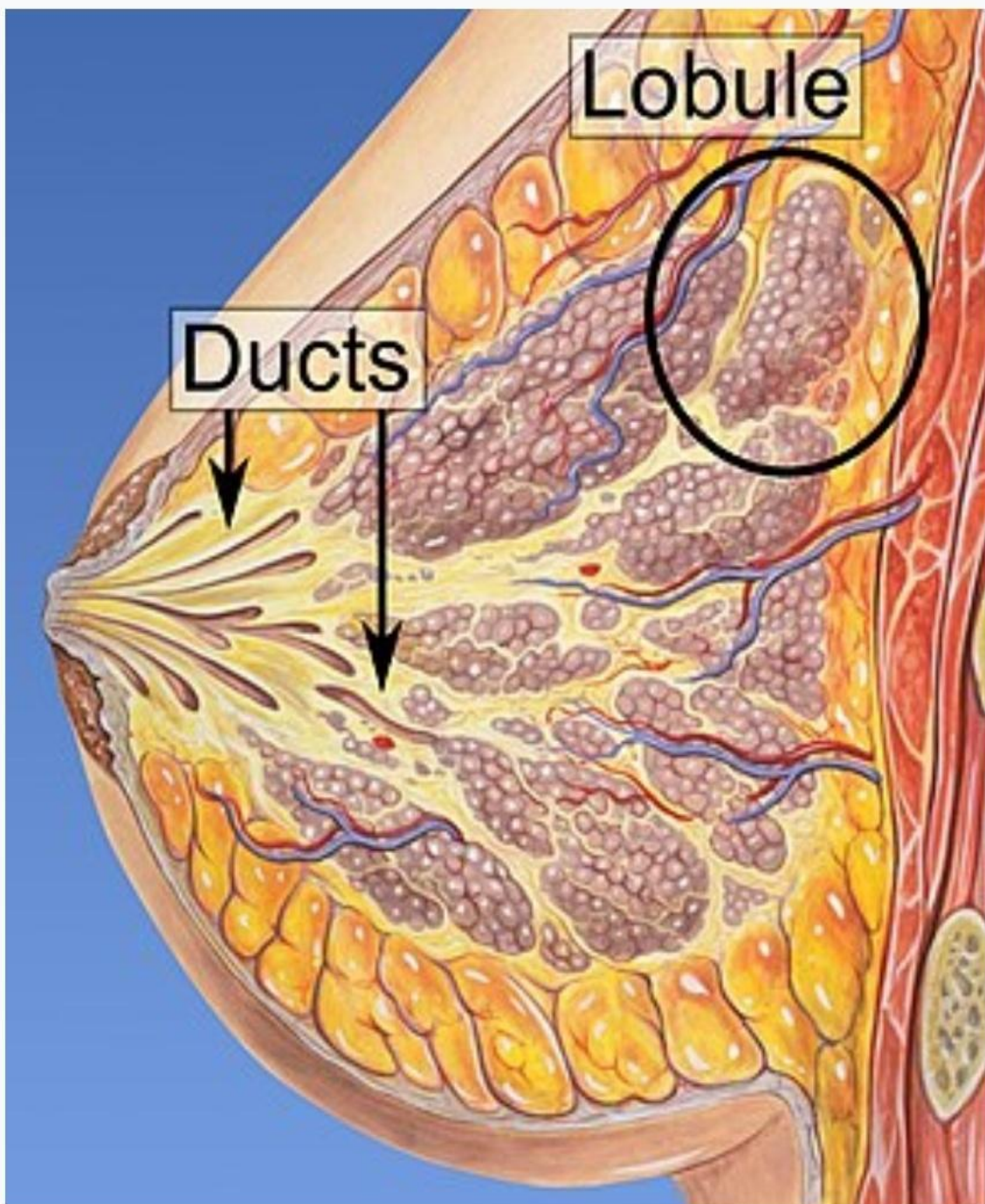
Guessing features can be:

- Age growth
- Personal history of serious breast disease, such as atypical hyperplasia
- Family history of breast cancer
- Having a first child after 30 years
- The age of onset of menstruation
- Menopause (cessation of menstruation)
- Genetic modifications that increase the risk of breast cancer, such as those for breast cancer BRCA1 and BRCA2

KEYWORDS-

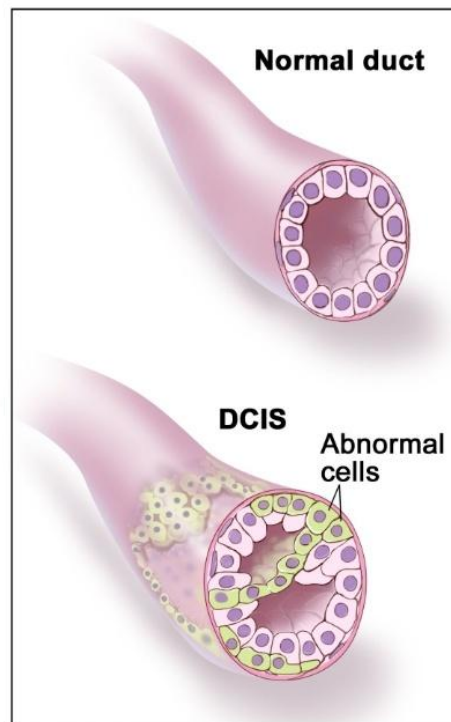
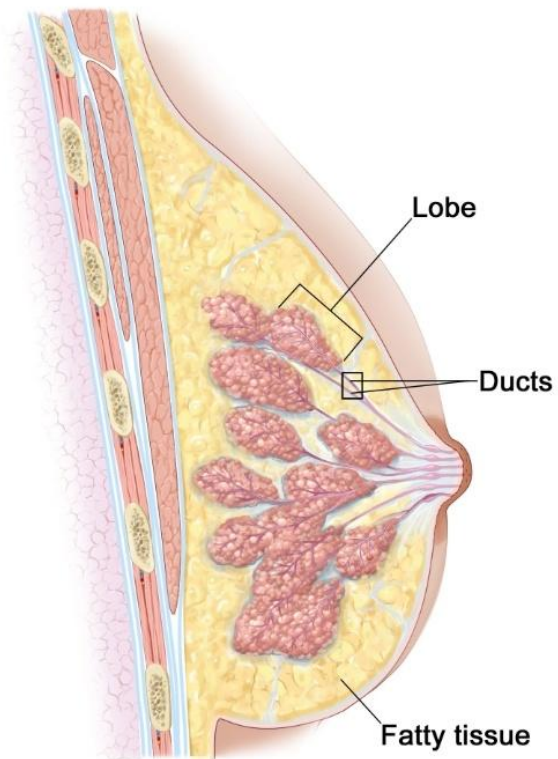
DCIS, ER, non-invasive, mammogram, mutation

UNDER PEER REVIEW



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Ductal Carcinoma In Situ (DCIS)



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INTRODUCTION

DCIS (ductal malignant neoplasm in situ) is a non-invasive cancer that occurs in the ducts. Associate degree is thought to be an unusual precursor of invasive ductal malignant neoplastic disease (IDC). It's yet unclear how many low-risk loci the two malignancies share, or whether the stiffness of the common loci link varies.

Since the introduction of diagnostic method testing, the number of DCIS cases reported in the United States has increased seven-fold, especially among biological time women, with DCIS accounting for around a hundredth of all screen-based implants. 45–78 percent of all breast infections are linked to DCIS. Because of shared genetic alterations, the offensive half is thought to have originated from DCIS in several of those patients. IDC and DCIS percentages differ by kind, with phenobarbital and human stratum protein receptor two (HER2)-positive IDC having greater DCIS levels (53 percent and 63%, respectively) than basal carcinoma the encroacher. (1)

Non-invasive carcinoma is understood as DCIS (ductal cancer in situ). Invasive ductal cancer is usually related to it (IDC). DCIS could be a non-mandatory IDC precursor. It's

unclear what proportion low-risk condition loci are shared across these 2 kinds of cancer, or whether or not there are any variations in locus sharing.

Breast cancer in place, conjointly referred to as Stage zero breast cancer or intraductal cancer, could be a style of cancer that develops within the breast while not inflicting any symptoms. The presence and multiplication of malignant cells (abnormal breast cells) at intervals the breast duct on top of the basal laminae while not spreading through the duct walls into the encompassing breast tissue (2)

The facultative Ductal cancer in place could be a precursor to invasive carcinoma. Consistent with reports, the amount of individuals diagnosed with DCIS has multiplied multiple. There's AN association of 45-70% carcinoma with DCIS. The fraction of IDC and DCIS that are synchronic varies primarily based from the barbiturate and Human epidermic protein receptor two subtypes (HER -2). (3,4)

An investigation of 150 instances of ensuing carcinoma of breast following Ductal carcinoma in situ noticed huge relationship in both the grading and estrogen resistance status between the file Ductal carcinoma in situ & the resulting carcinoma of breast (regardless of the site), proposing that females having Ductal carcinoma in situ are at hazard of developing ensuing breast cancers

of a similar phenotype. This finding supports the genetic predisposition data presented here, with estrogen resistance and grade-specific loci in Ductal carcinoma in situ having similar specificity in IDC.

Body – **Material and Methods**

Estrogen-positive breast tumours account for concerning eightieth of all primary breast cancers. Adjuvant endocrine medical aid is given to four,444 ER-positive patients once surgery, that improves prognosis significantly. Multigene expression prognostic tests could also be accustomed verify the hyperbolic risk of incidence once surgery and endocrine treatment, which could facilitate with judgments concerning whether or not or not or not medical care is crucial.

Having a family background of intrusive breast malignant growth is known should be involved along with a raised danger of the disease. Malignancy of breast televising norms, for example, those delivered by the American College Of Radiology, suggest that ladies with a family history of breast disease start televising prior. These and various principles, on the other hand, give no recommendations to family members of patients with breast carcinoma in situ, and it's murky accepting the direction for women with a family foundation of prominent bosom threatening development moreover applies to women with breast carcinoma in situ.

Method -

There are few methods for properly predicting Ductal carcinoma in situ activity. Although that grade has not been demonstrated to be a good indicator of resurrection despite its fast rate, many practitioners use it to decide whether or not to utilise radiotherapy after breast-conserving surgery. The grade of the in situ and coinciding obtrusive parts in ID have a cozy relationship, surmising that Ductal carcinoma in situ doesn't progress from minimum to maximum grade preceding appearing meddlesome.

Mammo-graphy detection has resulted in a rise in the number of women detected with breast-cancer in-situ. The objective of this review was to think about the danger of intrusive breast disease in relatives of patients with bosom carcinoma in situ to that of Relatives of patients with prominent malignancy of breast.

Individual information on breast malignancy in first-degree family members (moms, sisters, and girls) of 58209 ladies with breast disease and 101986 control subjects were gathered, checked, and dissected midway. Hazard proportions for breast malignant growth were determined utilizing

contingent strategic relapse, which was separated by age, menopausal status, the quantity of sisters, equality, and the age when the primary youngster was conceived. breast malignancy rate and death rates for specific family backgrounds were determined by applying age-explicit danger proportions to breast disease rates normal of more-created nations.(5,6)

Acer extricates DNA from border blood and will increase it on its claim (Fluidigm). The Custom Distinguished Grouping Board was used to produce prospects in 655 cases of pure Ductal carcinoma in situ in female at a lower place fifty and 1611 controls Data from thirty eight analysis encompassing five, DCIS cases, IDC cases, and controls genotyped victimisation the iCOGS chip were combined to uncover inheritable variants specific to DCIS. (7)

Scientists from King's faculty London estimated over two hundred, inheritable symptoms in DCIS cases in a veritably recent study published within the journal melanoma analysis. This can be the foremost comprehensive disquisition on heritable inheritable characteristics in DCIS up to now.

Dr. Elinor Sawyer and prof Montserrat GarcaClosas diode a platoon that compared desoxyribonucleic acid uprooted from blood samples of relatively five thousand girls with DCIS and twenty four thousand girls with ductal cancer (the most typical kind of bone

cancer) and discovered that the bulk of inheritable mutations and invasive ductal cancer were coupled, there have been no specific DCIS-related variations. (8)

Between Sept 1996 and Gregorian timetable month 2003, 129 BRCA-positive and 269non-BRCAnon-BRCA ladies were tested for BRCA mutations at the University of California, civic center. employing a Cox-type threat model for competitive pitfalls, breastfeeding events ar caterpillar-tracked from immaturity. Between brigades, the histological diapason of DCIS was also estimated. (9)

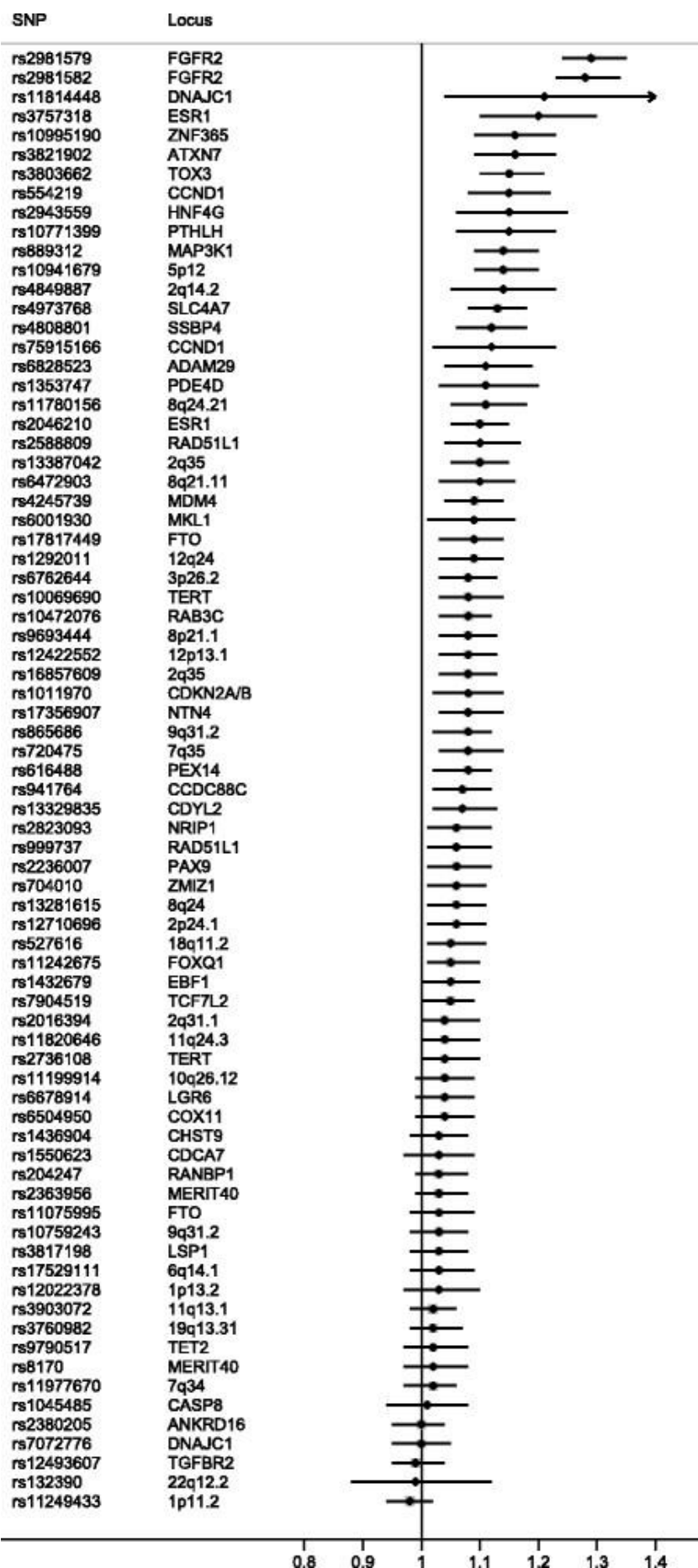
HER and ER phase testing

The DCton cytonuclear scale was detected in a brace of, cases within the ice disquisition, largely from native histopathology reports. The Hematoxylin and eosin classes were calculated and Ductal carcinoma in situ were screened by a histopathologist-SEP study harmonious with UK criteria and thus the faculty of yankee Pathologists in two hundred cases wherever Despite the standard knowledge being omitted from the search, a decline was detected

In the histopathological reports of 828 BCAC cases, knowledge on DCIS grade was discovered.

The ethics commission approved all of the studies, and the subjects gave their informed concurrence to share their information.

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Chromosome	SNP	Locus	RAF Controls	DCIS vs controls (meta-analysis)			IDC vs controls			Case-only DCIS vs IDC
				OR	(95 % CI)	<i>P</i>	OR	(95 % CI)	<i>P</i>	<i>P</i> -Het
10	rs2981579	FGFR2	0.40	1.29	(1.24, 1.35)	9.0×10^{-30}	1.24	(1.21, 1.28)	6.1×10^{-66}	0.14
10	rs2981582	FGFR2	0.38	1.28	(1.23, 1.34)	1.8×10^{-27}	1.23	(1.20, 1.26)	2.1×10^{-59}	0.21
16	rs3803662	TOX3	0.26	1.15	(1.10, 1.21)	1.7×10^{-8}	1.23	(1.20, 1.27)	1.5×10^{-50}	0.69
5	rs889312	MAP3K1	0.28	1.14	(1.09, 1.20)	6.9×10^{-8}	1.11	(1.08, 1.14)	2.2×10^{-14}	0.13
3	rs4973768	SLC4A7	0.47	1.13	(1.08, 1.18)	9.1×10^{-8}	1.09	(1.07, 1.12)	8.2×10^{-13}	0.58
5	rs10941679	5p12	0.25	1.14	(1.09, 1.20)	1.3×10^{-7}	1.14	(1.11, 1.18)	1.2×10^{-20}	0.90
3	rs3821902	ATXN7	0.13	1.16	(1.09, 1.23)	3.0×10^{-6}	1.06	(1.02, 1.09)	0.0030	0.33
19	rs4808801	SSBP4	0.65	1.12	(1.06, 1.18)	3.1×10^{-6}	1.09	(1.05, 1.11)	3.5×10^{-9}	0.16
10	rs10995190	ZNF365	0.85	1.16	(1.09, 1.23)	4.1×10^{-6}	1.15	(1.11, 1.19)	7.5×10^{-16}	0.61
2	rs13387042	2q35	0.51	1.10	(1.05, 1.15)	1.1×10^{-5}	1.14	(1.11, 1.16)	8.3×10^{-25}	0.34
6	rs3757318	ESR1	0.07	1.20	(1.10, 1.30)	1.4×10^{-5}	1.16	(1.10, 1.21)	1.2×10^{-9}	0.85
11	rs554219	CCND1	0.12	1.15	(1.08, 1.22)	2.8×10^{-5}	1.27	(1.22, 1.32)	6.4×10^{-38}	0.88
6	rs2046210	ESR1	0.34	1.10	(1.05, 1.15)	8.6×10^{-5}	1.09	(1.06, 1.12)	4.0×10^{-10}	0.32
12	rs10771399	PTHLH	0.88	1.15	(1.06, 1.23)	0.00021	1.18	(1.12, 1.22)	1.2×10^{-14}	0.53
8	rs11780156	8q24.21	0.16	1.11	(1.05, 1.18)	0.00027	1.10	(1.06, 1.14)	2.3×10^{-8}	0.88
16	rs17817449	FTO	0.60	1.09	(1.03, 1.14)	0.00052	1.06	(1.04, 1.10)	5.9×10^{-7}	0.32

SNP single nucleotide polymorphism, IDC invasive ductal carcinoma, OR odds ratio; *P*-Het *P* value for heterogeneity; RAF risk allele frequency

REVIEW ARTICLE

Breast malignancy is the most well-known reason for disease grimness and mortality, representing one-fourth of all new malignant growth cases around the world. Following

multiple studies that linked mammography screening to a reduction in breast cancer mortality, many high-income nations implemented national breast cancer screening programmes. Compelling Breast disease screening takes into account the identification and therapy of beginning phase malignancy, considering the counteraction of a further developed rendition of the condition. Be that as it may, populace wide screening programs have brought about a bigger extent of ladies being determined to have Breast malignancy in situ. and consequently a higher percentage of women reporting a family background of malignant breast growth. Therefore, an expanding nummber of ladies aare describing their family's background of breast malignant growth and breast disease in situ. Breast carcinoma situ, otherwise called stage 0 breast carcinoma or intraductal carcinoma, is portrayed by the presence and expansion of threatening cells that stay restricted inside the breast channel over the cellar film without spreading. Most of inclining hereditary changes associated with intrusive breast malignancy are additionally connected to in situ ailment, supporting the hypothesis that breast carcinoma in situ and obtrusive carcinoma are two juncture of a similar infection. (10)

Many hereditary causes of cancer have been discovered throughout the last few decades.

Some of these variables contribute to the development of monogenic cancers in people with monogenic predisposition syndromes.

The higher risk of cancer in many families is because to the aetiology of multiple cancer-prone hereditary genes that interact with natural circumstances.

Because of their family history, it is critical to detect these cancer risks, as genetic testing, advanced testing, preventative surgery, and chemoprophylaxis can be proved.

Breast cancer (BC) is the frequently analyzed malignant growth in ladies around the world, with multiple million new cases expected by 2020. Its rate and demise rates have increased over the most recent thirty years because of changes in hazard factor profiles, further developed disease enlistment, and malignancy identification. The quantity of hazard factors related with BC is huge, and it incorporates both modifiable and non-modifiable variables. Around 80% of patients with BC are over the age of 50 right now. Both age and sub-atomic subtype assume a part in endurance. Intrusive BCs are cancers with a wide scope of clinical show, conduct, and morphology. BC can be ordered into sub-atomic subtypes (Luminal, Luminal B, HER2-improved, and basal-like) in light of mRNA gene articulation levels. The atomic subtypes give experiences into novel treatment techniques and patient separations that affect BC patient the board. Notwithstanding physical highlights, the eighth version of TNM grouping presents

another arranging plan for BC that incorporates organic elements. Medical procedure, radiotherapy, chemotherapy, hormonal treatment, or natural treatment are a portion of the modalities used to treat breast malignant growth.

The hereditary concerns of cancer are examined in this article by evaluating two frequent kinds of cancer: breast cancer and breast cancer. (11)

Case analysis indicated no differences between the IDC and DCIS organisations after analysing various pieces of data.

The loci linked to IDC ER positivity were not linked to DCIS ER positivity after ER status analysis.

As with breast cancer, DCIS has been linked to the majority of loops. Case analysis indicated no differences between the IDC and DCIS organisations after analysing various pieces of data. The loci linked to IDC ER positivity were not linked to DCIS ER positivity after ER status analysis.

These organisations have distances that exist following the state's ER reform, and they can also be obtained via the IDC. In the higher Pivity level of $P 5.0 \times 10^{-8}$ there were no DCIS-specific loops observed. (12)

Data was gathered from 38 research, comprising 5,067 DCIS cases, 24,584 IDC cases, and 37,467 controls, To uncover genetic variations that predispose to DCIS, all of them were genotyped using the iCOGS chip (13) The majority 67 percent of 76 identified breast carcinoma predisposing site demonstrated a link to Ductal carcinoma in situ in the similar objective as invasive carcinoma of the breast. When several tests were taken into account, a single case study did not confirm the distinction between IDC and DCIS. On examination of Estrogen Receptor status, Estrogen Receptor positive invasive ductal carcinoma related loci had been associated to Oestrogen receptor possitive Ductaal caarcinoma in-situ was verified. (13)

DCIS grade study revealed that two separate SNPs near CCND1 on 11q13.3 were unique for low to medium grade DCIS (rs75915166, rs554219).

After adjusting for the ER status, these connections with this level remained, and the IDC confirmed them. At the genomewide significance threshold of $P = 5.0 \times 10^{-8}$, no novel loci were found to describe DCIS. Finally, this research provides the most thorough confirmation of the genetic susceptibility distribution for IDC and DCIS to date. (14)

To determine whether specific IDC or DCIS loci exist, a large number of DCIS studies are required.

There is no indication of natural continuation of untreated DCIS because most DCIS is treated surgically. However, in a limited study of very low-income patients who had been misdiagnosed as having malignant asthma and had not undergone surgical intervention, a DCIS scale that had been misdiagnosed as having malignant asthma and had not undergone surgical surgery, Six out of thirteen patient evolved same-sided cancer of invasive type, with ample age to progress to non-invading cancer after 9 year. A drawn out follow-up of two DCIS therapies in which the DCIS was treated by only breastfeeding a medical procedure without radiation has displayed at 30% of ladies repeat in ten years.(15)

There are no reliable strategies for forecasting how this disease will behave. Despite the fact that no levels have been demonstrated to be a decent indicator of revival, a large number utilize this grouping to choose whether to manage radio stations or not. It is apparent that there is a coherence between the level of attack in situ and parts in IDC, implying that DCIS doesn't move from low to high prior to becoming invading. The majority of non-genetic breast cancer risk variables are comparable to DCIS and IDC, implying that DCIS is a precursor to invasive disease.(16)

Epidemiological studies have also found indications of a familial propensity to DCIS. DCIS patients are 2.4 times (95 percent CI 0.8, 7.2) more likely than control patients to have a mother or sibling with carcinoma of breast. (17) Furthermore, a research of nearly 40,000 women found that DCIS has a higher family relative risk than invasive carcinoma of breast.

The odds ratio came out to be 2.4 when surveyed among women of 30 to 49 years of age having a family history of carcinoma of breast. (95% CI 1.1, 4.9) The risks were modestly reduced for women aged 50 and up, but considerably more so for Ductal carcinoma in situ (Odds Ratio = two-point two, ninety-five percent CI: 1.0, 4.2) than intrusive disease (OR = one point five, ninety-five percent CI: one. Two-point two). The link with family history was comparable for Ductal carcinoma in situ and Invasive Ductal Carcinoma in the Million Women Study, although this was not verified. BRAC1/2 transformations are recognized in a comparative extent of DCIS and obstructive breast disease cases, clarifying a minor piece of this hereditary danger. Most first breast carcinoma's association learnings have not been established to find out relationships with ductal-carcinoma-in-situ for common low risk carcinoma of breast predilection allele. As a result, it's uncertain if all of the low-risk susceptibility loci that have

been discovered are linked to Ductal_carcinoma-in-situ what's more obvious is that several lower-risk sites are linked to distinct clinical subtypes of carcinoma of breast, reinforcing the hypothesis that different sub-atomic pathways cause assorted sorts of breast cancer growths.

It will be important to examine certain morphologic subtypes, such as DCIS and cytologic grade, as well as the disease's oestrogen receptor (ER) status, to find all the more okay defenselessness sites. 2,352 in-situ+cases from the (CAC) of Mamaroneck and 3,078 pure DCIS patients from the ICICLE research (which looked into the genetics of DCIS) (BCAC).

The scientists planned to check whether there were any DIS-explicit generally safe alleles, just as if either of the known low-risk mammary vulnerability alleles had various associations with Ductal-carcinoma-in-situ and invasive-ductal-carcinoma.

Because of mammography screening, the quantity of ladies determined to have breast malignancy in situ has expanded. The analysts needed to inspect if family members of patients with obstructive breast malignant growth had a more serious danger of intrusive breast disease than family members of patients with obstructive breast malignancy. (18,19)

8 among each 9 ladies who foster carcinoma of breast don't have a mother, sister, or little girl who is tormented Despite the way that ladies with first-degree family members with a background marked by carcinoma of breast are at an expanded danger of fostering the infection, most of the people who do will be over the age of 50 when their malignancy is analyzed. In countries where breast cancer is common, the lifetime excess incidence of breast cancer is 5.5% for women with one affected first-degree relative and 13.3% for women with two

in spite of the fact that we didn't distinguish any original loci that arrived at genome wide importance, we recognized three potential novel Ductal carcinoma in situ predisposition loci two of which were Ductal carcinoma in situ explicit (rs12631593, rs73179023), and thusly need further examination in different accomplices of Ductal carcinoma in situ. as at minimum 45% of patients with invasive ductal carcinoma have related Ductal carcinoma in situ present at determination reliable with direct forerunner conduct it might appear to be organically impossible that a Single Nucleotide Protein inclines to Ductal carcinoma in situ yet isn't associated with invasive ductal carcinoma. However it is conceivable that there is aa subset of patients with Ductal carcinoma in situ with exceptionally low likelihood of progression. in the event that the finding of Ductal carcinoma in situ explicit inclination loci were affirmed in

different investigations identifying such a subset of patients with generally safe Ductal carcinoma in situ would be clinically important (20-26)

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CONCLUSION

Taking everything into account, this is the biggest review researching the hereditary predilection to DCIS and show that of breast malignancy intrusion are likewise positioned by DCIS. This underlines that for irresistible sickness, various SNPs target oestrogen receptor positive and oestrogen receptor DCIS. Furthermore, it demonstrates the role of distance in both DCIS and IDC. Research evaluating genetic susceptibility to DCIS indicates that most loci of susceptibility to invasion breast cancer also predispose to DCIS. It underlines that various SNPs are inclining to ER positive versus ER negative Ductal Carcinoma In Situ, just as the significance of degree in the two Ductal Carcinoma In Situ and Invasive Ductal Carcinoma. Awareness of the family cancer case is focused on clinical research and management. In a multidisciplinary study, family cancer research revealed students' genes, their functions

that determine mechanisms of tumor formation and pressure in developing treatment strategies. In the clinical arena, families in which cancer is most prevalent can be identified; Genetic testing, screening and surgery for prevention can save lives. Caution also applies to cancer detection at the same time in people who have been shown to be at moderate risk because of their family history. It is explained that as genes for infectious cancer proliferate, performing genetic testing, interpreting its results and appropriately distributing observations will be a challenge for individual physicians and a challenge for health care providers. Cancer screening agreements already vary in the UK. With increasing public awareness and the development of multiple genetic variants, invasive precautions, and perhaps even genetically targeted chemoprophylaxis, the need for cancer screening is likely to increase rapidly. Cancer growth should be a priority on the public health agenda.

ABBREVIATIONS-

1. Bavarian Breast Cancer Case & Control (BBBC) is an acronym for Bavarian Breast Cancer Case & Control. DCIS (ductal carcinoma in situ) is a type of cancer that develops in the ducts of the ICICLE: A study to look into the genetics of the ductal subtype of in situ cancer Invasive ductal carcinoma (IDC) is a type of cancer that affects the ducts of ER stands for Estrogen Receptor. PR stands for progesterone receptor. SNP (single nucleotide polymorphism) is an abbreviation for single nucleotide polymorphism.

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