Fluctuating asymmetry of dermatoglyphics and the lifetime estrogen exposure in breast cancer risk – an epigenetic perspective

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Abstract

Background: Through an epigenetic mechanism, a woman's total lifetime oestrogen exposure accumulates changes in her DNA methylation pattern. These changes can influence the developing fetus and the resulting epigenetic aberrations is said to be reflected in the dermatoglyphic patterns. Fluctuating asymmetry (FA) is the difference of dermatoglyphic patterns between the right and left hand. **Aim:** To explore the association of FA of dermatoglyphics with the reproductive factors in an epigenetic perspective to identify breast cancer risk. **Methods:** The participants are grouped into three based on the selection criteria as a breast cancer, high risk and control group. The data are collected through digital photographic images. The variables include FA of the finger ridge count (FRC) of Thumb, Ring Finger, and the A-B Ridge Count. The variables of reproductive factors includes increased menstrual age, Nulliparity and first full-term pregnancy >30yrs, and Positive Family History. **Result:** Among the reproductive factors involved in the study, The FA thumb is strongly associated with increased menstrual age, FA ring finger is strongly associated with nulliparity and FA subtotal ridge count is observed to be strongly associated with increased menstrual age at significance level of $p<0.0001$. Age at first full term pregnancy is not significantly associated with any of the dermatoglyphic variables Positive family history is significantly associated with all the dermatoglyphic variable with $p<0.0001$.**Conclusion:** FA of dermatoglyphics aids to identify the in-utero epigenetic aberrations of a females linked to breast cancer risk.

Key Words – Dermatoglyphics, Fluctuating asymmetry, estrogen exposure, finger ridge count, reproductive factors.

Introduction

The global burden of breast cancer worldwide using GLOBOCAN, 2018 estimates the incidence of breast cancer at a rate of 11.6% among new cancer cases diagnosed in females and is the leading cause of death among female cancers. [(1)] and ranked number one among Indian females. [(2)] These changes can influence the developing fetus through epigenetic alternations and the resulting genomic instability is said to be reflected in the dermatoglyphic patterns. Fluctuating asymmetry (FA) is the difference of dermatoglyphic patterns between the homogenous digits of right and left hand. Since the incidence of breast cancer is increased in cases with a positive family history, as well as in population with early menarche and late menopause, it may be an epigenetic factor that plays an important role. Finger print determination is genetic, and has been reported to be affected by the environment factors in the first trimester of pregnancy. [(3)]

Sex hormones play a vital role in breast carcinogenesis. Estrogen increases the risk at different phases of life with progesterone acting synergistically. High doses of exposure to placental hormones, namely estrogen and progesterone during pregnancy period suggested to play a crucial role in decreasing the subsequent breast cancer susceptibility. [(4, 5)] The established risk factor for breast cancer, including genetics accounts for about 30%. Experimental evidences

suggest that environmental chemicals act as xenoestrogens and affects the estrogen production and metabolism. These xenoestrogens produces oxidative stress influencing epigenetic alteration and causes carcinogenesis. Induction of breast carcinogenesis occurs through interaction between genetic and environmental carcinogens. Screening tools to test the estrogenicity helps to identify the population at risk for breast cancer. [6, 7] The acquired modifiable and non-modifiable risk factors generate oxidative stress that produces polymorphism and epigenetic alteration of the specific genes which may be carried to the next generation. Epigenetic alterations are the changes caused by the endogenous and exogenous environmental factors that turn the gene active or inactive affecting the gene expression. [8, 9, 10] The aim of the present study is to explore the association of fluctuating asymmetry of dermatoglyphics with the hereditary and reproductive factors in breast cancer risk in an epigenetic perspective.

Material and Methods

We collected the demographic status of the participants as part of their subjective assessment. Finger ridge patterns are collected in the form of digital photographic images of the fingers and palm of the right and left hand and the variables are analyzed using the computer. The patterns are assessed by a trained rater who is blind to the study and group status. The outcome variables used to assess the fluctuating asymmetry includes a FA finger ridge count of thumb ≥3, FA of the finger ridge count of ring finger ≥3 and FA of A-B ridge count of palm ≥5. The variables of reproductive factors representing lifetime estrogen exposure and genetic factor are increased menstrual age, Nulliparity, FFTP>30yrs, and Positive Family History.

Data analysis and Results

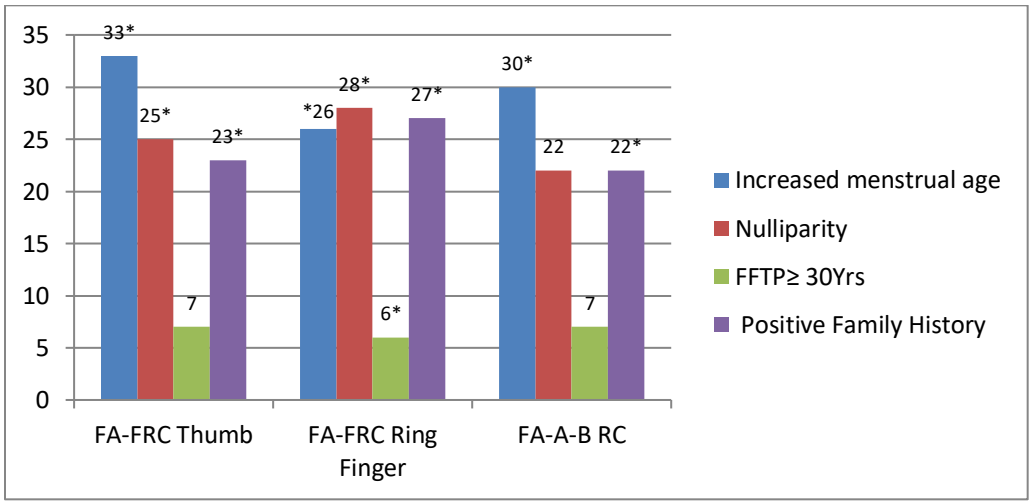
The odds ratio was used to examine the frequency of relationship between Fluctuating asymmetry of dermatoglyphics and genetic and reproductive variables, with the level of significance determined by the P-value.

The dermatoglyphic variable FA FRC thumb ≥3 is observed in 33% of females with increased menstrual age, among which 18% fall under breast cancer group, 13% high risk females and 2% normal females with significance level of $p<0.0001$. Similarly the 25% females with nulliparity are linked to the FA FRC of thumb ≥3 among which 16% fall under breast cancer group, 7% higher risk females and 2% normal population with a significance level of $p<0.0001$. The findings suggests 7 % of first full term pregnancy >30 years of age is linked to FA FRC of thumb ≥3 among which 4 and 3 percent, respectively fall under breast cancer and high risk females which is not significantly associated. 25% of the study population with positive family history in their first round relative are observed to have FA FRC of thumb ≥3 among which 13 and 9 percent, respectively fall under breast cancer and high risk group with a significance level of $p<0.0001$. (Figure 1, Table -1)

The dermatoglyphic variable FA FRC of ring finger ≥3 is observed in 26% of females with increased menstrual age, among which 13% fall under breast cancer group, 11% higher risk females and 2% normal females with a significance level of p<0.0004. Similarly the 28% females with nulliparity are linked to the FA FRC of ring finger ≥3 among which 13% fall under breast cancer group, 15% higher risk females and 2% normal population significance level of p<0.0001. The findings suggests 6 % of first full term pregnancy >30 years of age is linked to FA FRC of ring finger ≥3 among which 3 and 2 percent respectively fall under breast cancer and high risk females and not associated significantly.27% of study population with positive family history in their first round relative are observed to have FA FRC of ring finger ≥3 among which 16 and 11 percent respectively fall under breast cancer and high risk group significance level of p<0.0001. (Figure 1, Table -1)

The dermatoglyphic variable FA A-B ridge count ≥ 5 is observed in 30% of females with increased menstrual age, among which 12% fall under breast cancer group, 18% higher risk females and not observed in normal females with a significance level of p<0.0001. Similarly the 22% females with nulliparity are linked to the FA A-B ridge count ≥5 among which 12% fall under breast cancer group, 10% high risk females and not observed in normal population. The findings suggests 7 % of first full term pregnancy >30 years of age is linked to FA FRC A-B ridge count ≥5 among which 3% fall under breast cancer group, 2% fall under high risk females and 2% in normal group. The nulliparity and age at first full term pregnancy is not associated significantly with the given dermatoglyphic variable. 22% of study population with positive family history in their first round relative are observed to have FA FRC A-B ridge count ≥5 among which 13 and 9 percent respectively fall under breast cancer and high risk group with significance level of p<0.0001.(Figure 1, Table -1)

Figure – 1 Association of Fluctuating Asymmetry of dermatoglyphics with reproductive and hereditary factors



*****Statistically significant

Table -1 Association of Fluctuating Asymmetry of dermatoglyphics with reproductive and hereditary factors (Risk factors)

Risk Factors		Dermatoglyphic Variables		
		FA–FRC-THUMB	FA-FRC –RING FINGER	FA –A-B RC
Increased menstrual age	OR(95 % CI)	0.07 (0.03-0.16)	0.28 (0.14-0.57)	0.06 (0.02-0.17)
	P Value	**0.0001**	**0.0004**	**0.0001**
Nulliparity	OR(95 % CI)	0.12 (0.51-0.30)	0.24 (0.12-0.47)	0.82 (0.43-1.57)
	P Value	**0.0001**	**0.0001**	0.55
FFTP >30Years	OR(95 % CI)	0.56 (0.21- 1.48)	0.91 (0.34-2.38)	0.80 (0.30-2.11)
	P Value	0.24	0.84	0.66
Positive Family History	OR(95 % CI)	0.16 (0.07-0.35)	0.05 (0.01-0.13)	0.25 (0.12-0.54)
	P Value	**0.0001**	**0.0001**	**0.0003**

Discussion

The findings of the study suggest FA FRC thumb ≥3 to have significant association with reproductive factors, namely increased menstrual age, nulliparity and in population with positive family history and not significantly associated with first full term pregnancy status. The FA thumb is strongly associated with increased menstrual age when compared with other reproductive factors. The findings of the FA ring finger suggest a significant association with reproductive factors, namely increased menstrual age, nulliparity and in population with positive family history and not significantly associated with first full term pregnancy status. The FA ring finger is strongly associated with nulliparity when compared with other reproductive factors. The findings of the FA FRC A-B subtotal ridge count ≥5 suggest a significant association with reproductive factor, namely increased menstrual age and in population with positive family history and not significantly associated with nulliparity and first full term pregnancy status. The FA subtotal ridge count is observed to be strongly associated with increased menstrual age when compared with other reproductive factors. The study proved a significant association of FA FRC thumb and FA A-B subtotal ridge count with increased menstrual age and FA FRC ring finger with nulliparity.

The purpose of the study is to explore the association of the fluctuating asymmetry of dermatoglyphic variables with the hereditary and reproductive factors. The reproductive factors

and the positive family history are risk factors that are suggested to have a genetic base. The distinctly non- modifiable risk factors, namely increased menstrual age and positive family history presented significant association with all the Fluctuating asymmetry of dermatoglyphic variation in breast cancer risk. Association of increased menstrual age and FA of dermatoglyphic variable is suggestive of epigenetic influence in the prenatal period. The distinct modifiable risk factors associated with lifetime estrogen exposure, namely nulliparity and First Full Term Pregnancy >30yrs doesn't observe to have significant linkage. Nulliparity and First Full Term Pregnancy >30yrs are the incidences in life time may be due to either inherited or acquired. Epigenetic mechanism may play a vital role here. The nulliparous population with prenatal epigenetic aberrations are more likely to have dermatoglyphic representation. The significant association of FA of dermatoglyphic variables with modifiable and non- modifiable risk factors reflect the linkage of FA dermatoglyphics and the prenatal epigenetic mechanism.

A review performed on a maternal diethylstilbestrol level in the prenatal period and the breast cancer risk of daughters focus on the determination of breast cancer on the germ line inheritance and the hormonal environment induced epigenetic alterations. Also states the increased risk driven by the epigenetic alterations in genes are reversible. Studies reported significant linkage of lifetime estrogen exposure and epi-genome wide association in breast cancer risk. [11, 12] The findings of the study suggest possible epigenetic disturbances in the prenatal period that suggests to reflect in dermatoglyphics.

Hardly any studies in the literatures reviewed reported the fluctuating asymmetry of dermatoglyphics in breast cancer and its association with reproductive factors in epigenetic perspectives. A meta-analysis performed in the year 2015, on dermatoglyphics revealed the early epigenetic outcomes and its implications on the genomic zygosity in type -2 diabetes. The analysis concludes the epigenetic insults occur primarily in the first three months of gestation and to a lesser extent in the period between four to five months of gestation, least likely associated with the gestation period beyond five months. The evidences are suggestive of reflection of epigenetic aberrations occurring in prenatal period in the dermatoglyphics. The author also recommends for future research in exploring the prenatal origin of the disease. [15].

Evidences provides an overview of the role of nutrition and environmental exposure in epigenetic alterations. Findings suggest various estrogen sources correlate with the development of breast cancer in the future. Author suggested the influence of macro and micronutrient balance to play a vital role in the genomic regulation. Identifying the science behind the fetal epigenetics can aid in the developing new therapeutic strategies and take preventive measures. The lifestyle of a woman during pregnancy period can highly influence the growing fetus through epigenetic aberration. Evidences are suggestive of an association of fetal epigenetics in breast cancer risk. [16].

Quantitative and qualitative analysis of a study performed in Bosnian population presented significant association for ATD angle and not for Subtotal ridge counts, namely A-B, B-C, and

C-D, did not show a significant association for both right and left hand. These findings are not in agreement with the results of the current study. [13] The findings of the results suggests the dermatoglyphics can be used as effective biomarker for identifying breast cancer risk. A Study performed to analyze association of the fluctuating asymmetry of dermatoglyphics with DNA repair gene polymorphism in identifying the breast cancer risk suggests the variables, namely FA Finger ridge count of thumb, ring and A-B ridge count to have significant association compared to other quantitative variables in identifying breast cancer risk which is in agreement with the present study. [3,10]

Evidences suggest the influence of reproductive factors in modifying the global DNA methylation and breast cancer risk. The findings suggests two fold more risk of methylation in breast cancer risk among females with age greater than 23 years at first full term pregnancy. There is no evidence for parity status and lactation. The age of menarche and the age at first full term pregnancy can act as modifiers for DNA methylation and breast cancer risk. Evidences suggest the association of reproductive factor and breast cancer risk in postmenopausal women. [14]. The results are suggestive of influence of reproductive factors, namely menstrual age in altering the methylation status of DNA that can be represented in dermatoglyphics.

A review reported the role of prenatal epigenetic diets in protection against environmental pollution, where the author focus on the causes and consequences of the prenatal environment pollution towards epigenetic alternations and the protective role of diets to overcome the epigenetic aberrations. The study results support our hypothesis by reporting the epigenetic reprogramming and the role of DNA methylation in gene expression during the prenatal period which is said to exhibit in the dermatoglyphic patterns. [17, 18,19]

Since breast cancer is the most common cause of mortality among cancer deaths, approaching the preventive measures through epigenetic perspective helps to effectively control the incidence of breast cancer. Future studies with a huge sample size in different races should be performed to strongly support the results of the current study and to explore the epigenetic science behind the dermatoglyphics. The Fluctuating asymmetry of dermatoglyphics suggests to act as a potential marker to identify the genetic and epigenetic aberrations occurred during the prenatal period. The fluctuating asymmetry of dermatoglyphics can be used as a community screening procedure to identify the high risk population. Apart from taking preventive measure to protect the quality of life of women at high risk, epigenetic counselling can be delivered to the population to prevent the transfer of breast cancer and protect the next generation.

Conclusion

In spite of numerous preventive measures in practice at the community level, still there is raised in the incidence of breast cancer morbidity and mortality. Focusing the prevention strategy through epigenetic perspective aids in preventing the current population at risk and also the future generations. Fluctuating asymmetry of dermatoglyphics in this aspect acts as an effective

tool to identify the in-utero epigenetic aberrations of a female linked to breast cancer risk. Through the factors that reverses the epigenetic aberrations, the high risk females and their generations can be protected from breast cancer.

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