



Role of 2D:4D Ratio in the Histopathologically Diagnosed Breast Cancer Females

Authors

Dr Sajjad Jafar¹, Dr Vishram Singh², Dr Nisha Kaul³, Dr Bindu Singh⁴

¹Assistant Professor, Dept of Anatomy, BRD Medical College, Gorakhpur

²Professor and Ex HOD Dept. of Anatomy, Santosh Medical College, Ghaziabad

³Professor and HOD Dept. of Anatomy, Santosh Medical College, Ghaziabad

⁴Associate Professor, Dept. of Anatomy, B.R.D Medical College, Gorakhpur

Abstract

Introduction: Carcinoma of breast is most frequent cancer in India followed by cervical cancer among females as reported in registries from Mumbai, Delhi, Kolkata and Bangalore. Breast cancer is the most common malignancy among women in the world. According to the NCRP (National Cancer Registry Program), around 25% of the total cancer cases are reported to be that of breast cancer. Several anthropological studies have found sex differences in 2D:4D ratio, with man having lower average 2D:4D ratio than women.

Aim and Objective: The aims of this study is to investigate 2D:4D ratio in the diagnosis of breast cancer females and control groups.

Material and Methods: The study was conducted on 145 histopathological diagnosed breast cancer women and their finger length ratio, compared with 145 normal healthy women with no family history of breast cancer. Digit length was measured by the Vernier caliper with a resolution of 0.01 mm.

Results: The finger length 2D:4D ratio were analyzed between breast cancer and control group of individuals that showed statistically difference. In present study 2D:4D ratio (P value < 1) is significantly higher in case group as compared to the control group. (table-3). High 2D:4D ratio of significantly associated with breast cancer.

Conclusion: The finger length (2D:4D) ratio may help in identifying women with risk of breast cancer. It can serve as an inexpensive, noninvasive anatomical and effective tool to determine the individuals with breast cancer in their future.

Keywords: Digits ratio 2D:4D, Breast cancer, prenatal sexual Hormone.

Introduction

Breast cancer is the most common malignancy among women in the world. Breast Cancer constitutes a major public health issue globally with over 1 million new cases diagnosed annually, resulting in over 400,000 annual deaths and about 4.4 million women living with the disease. It is the

commonest site specific malignancy affecting women and the most common cause of cancer mortality in women worldwide^(1,2).

According to the NCRP (National Cancer Registry Program), around 25% of the total cancer cases are reported to be that of breast cancer⁽³⁾. In 2009, estimated 40610 men & women were dying

of breast cancer in the United States ⁽⁴⁾. There is evidence that genes involved in the differentiation of fetal 2D:4D may also be involved in mammary gland development and breast cancer in females.

The ratio of the lengths of the index (2D) and ring (4D) fingers, expressed as the ratio 2D:4D, has been proposed as a marker of prenatal androgen action or sensitivity to androgens in 1998 by John Manning and colleagues. The formation of the digit in humans utero, is thought to occur by 13 weeks and the bone to bone ratio is consistent from this point into an individual's adulthood ⁽⁵⁾. However, testosterone production in the male fetus starts at 8-9 weeks of gestation and peak between 14-19 weeks. If indeed, the 2D:4D index does not change with gestational age ⁽⁶⁾. The investigation of digit ratios as possible markers of androgen action in early life began with the long-recognized observation. In comparison to women, adult males tend to have longer ring finger relative to index finger ⁽⁷⁾.

Several anthropological studies have found sex differences in 2D:4D ratio, with men having lower average 2D:4D ratio than women. During the development of second and fourth digits, at least 19 skeletogenic genes are activated or deactivated by prenatal testosterone and oestrogen ⁽⁸⁾.

Among these there are three genes Wnts, Fgfs and FGFR1 that influence Tbx genes, which initiates mammary gland formation. ⁽⁹⁾ The development of mammary glands in utero is linked to predisposition of breast cancer in adult thus 2D:4D ratio could be act as a possible proxy marker for disease susceptibility.

According to Raman et al in 2000 showed that the loss of HOX_{A5} expression can reduce the expression of tumor suppressor gene p53 in breast tumors. Thus Mutation of p53 gene leading to breast cancer. Homeobox (HOX) family genes, which are essential for the differentiation of fingers are related to breast carcinogenesis, HOXA₁ represents a human mammary epithelial oncogene and HOX_{A5} limits the p53 expression in breast tumors.

These are the causes of mutation

- Radiation
- X-rays
- Ultraviolet rays
- α -rays, β -rays
- Temperature
- Formaldehyde
- Chemical exposure
- Spontaneous
- Benzopyrene (in cigarette smoke)

Patterning genes for the limb axes have been determined, it is the HOX genes that regulate the types and shapes of the bones of the limb. There is evidence that the development of genitalia, finger length and toes are influenced by the genes of Homeobox family (HOX) the gene groups A and D. HOX genes regulate the types and shapes of the bones of the limb Thus hox gene expression, which results from the combinatorial expression, of SHH, FGFS, and WNT7a, occurs in phases in three plates in the limb that correspond to formation of the proximal, middle, and distal parts. Extensive work has been carried out from hand measurements to estimate stature and to determine sex from hand dimensions ^(10,11).

Recent researchers have found that men with lower 2D:4D ratio are nicer to women than men with higher 2D:4D ratios. Several evidence indicate that prenatal testosterone exposure, or underlying sensitivity to testosterone, is inversely related to the difference between right and left 2D:4D. Recent evidence from a mouse model suggest that 2D:4D depends critically on the utero exposure to androgens relative to estrogen exposure, with higher right 2D:4D.

Material & Methods

- 145 Histopathologically diagnosed breast cancer Females subjects
- 145 healthy females
- Digital Vernier caliper



Digital Vernier Caliper

Methodology

In this study 145 histopathologically diagnosed breast cancer females, 25 to 70 years of age group were taken from the Department of oncology and Radiotherapy B.R.D. government Medical College , Gorakhpur, U.P, India .145 control of the same age group females was selected those who had no sign and symptoms of breast cancer and no family history ,with no permanent scars on their fingers and without any systemic diseases

Procedure for obtaining length of index and ring finger:

The hand of the participants were placed on a flat surface with the palm facing upward and finger should be extended maximally and close to each other. Digit length was measured in centimeters by the Vernier caliper with a resolution of 0.01 mm.

The length of index and ring finger of both hands were measured from the middle of the bottom crease of finger to tip of distal phalange. The 2D:4D ratio is calculated by dividing the length of the index finger by the length of the ring finger of both hands. The difference between the right and left 2D:4D is known as DR-L.



Measurement of finger length by Vernier caliper

Observation & Results

- The finger length 2D:4D ratio were analyzed between breast cancer and control group of individuals that showed statistically difference.
- Mean value of 2D:4D ratio of both hands where high in case group as compared to control group.
- In present study (2D:4D) Ratio is highly statistically significant in case group as compared to the control group where p value of 2D:4D ratio is less than <1(table-3). Higher 2D:4D ratio is significantly associated with breast cancer.
- 2D:4D ratio in left hand is higher than the right hand in breast cancer females.

Table No-1 Mean value of 2D:4D ratio in case group.

Digit ratio	N0.	Mean	SD
R2D:4D	290	0.9998	0.0352
L2D:4D	290	1.00204	0.03367
TOTAL	580		

Table No-2 Mean value of 2D:4D ratio in control group

Digit ratio	N0.	Mean	SD
R2D:4D	290	0.9792	0.03753
L2D:4D	290	0.97705	0.0311
TOTAL	580		

Table No-3 Comparison of 2D: 4D ratio in case and control group

Digits ratio	Case group		Control group		t-test	p-value
	Mean	SD	Mean	SD		
R2D:4D	0.9998	0.0352	0.9792	0.03753	4.8209	< 0.0001
L2D:4D	1.00204	0.03367	0.97705	0.0311	6.5652	< 0.0001

Discussion

Manning *et al* found an association between left 2D:4D ratio and age at onset of breast cancer such that women with high 2D:4D presented with cancer earlier. Trichopoulos *et al* Suggested that high concentrations of endogenous oestrogen in utero may increase the risk for subsequent breast cancer and that high sensitivity to prenatal estrogen exposure was correlated with high

2D:4D ratio (Manning JT, Scutt D, Wilson J, Lewis-Jons DI). Therefore, high 2D:4D has a positive correlation with risk of breast cancer. The present study showed that 2D:4D ratio is high in breast cancer women comparison to control group. Further we found an direct association between left 2D:4D and breast cancer women. My study goes with manning *et al* 2003: Hurdet et al, 2011 that Δ_{r-1} is a stronger correlation of exposure and sensitivity prenatal testosterone than right 2D:4D. Breedlove, 2010; Honekopp and Watson, 2010 reported that both right 2D:4D and Δ_{r-1} are inversely associated with prenatal exposure and sensitivity to testosterone, where there is only relative weak evidence of any association with left 2D:4D.

Conclusion

The present study concludes that the finger length ratio is an easy, cost effective and a non-invasive procedure and would serve as a tool, for early screening of breast cancer females with predisposing factor in the age group of 25 to 70 years. This study can be helpful in early diagnosis and treatment; preventive measure can be taken early to avoid the risk and complications of breast cancer, which could occur in advancing age.

Sex differences in digits' ratios develop early in child hood and are unaffected by pubertal growth. The present study provides additional evidence that the relationship between high 2D:4D ratio as a putative biomarker associated with breast cancer, showing that high 2D:4D is associated with higher intrauterine exposure to estrogen which increase the risk of breast cancer in women. 2D:4D ratio could therefore correlate with both testosterone and estrogen related risk factors for breast cancer.

Clinical significance

- By 2D:4D ratio breast cancer patients are identified and karyotyping could be done if the muted genes are found.
- It could be treated by gene therapy in future.

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