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A Study on the Relationship between 2D:4D Ratio and Breast Cancer among Bengalee Hindu Women

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ABSTRACT: Breast cancer is the most common of all cancers in women in both developed and developing countries. Worldwide incidence has increased by more than 20 percent since 2008; and in India this rate of increase is 27 percent (in 2012), overtaking that of cervical cancer. It is evidenced that the sex hormones and, therefore, the genes involved in the development mammary glands are also responsible for differential development of the 2nd and the 4th digit of the hands, in early fetal life. Hence, a relationship between the ratio, 2D:4D and breast cancer has been speculated. In the case of any positive relationship, the 2D:4D ratio in early life can be taken as a proxy-indicator for the risk of breast cancer in later life.

Many studies around the world, including one in India, established an association between 2D:4D and Breast cancer. The present study had been conducted on a sample of Breast cancer patients, with a control of nearly equal number, among Bengali Hindu population of West Bengal, India. The analysis does not indicate any relationship between 2D:4D and breast cancer.

Key words: Breast cancer, 2D:4D, $\Delta_{r-l.}$ (Difference between right and left 2D:4D)

INTRODUCTION

Breast cancer is the most common cancer in women both in the developed and developing countries. In worldwide estimate, over 5, 08,000 women died in 2011 due to breast cancer (*WHO, 2013*). In 2012, 1.7 million (11.9 % of all cancers) women were diagnosed with breast cancer. Incidence of breast cancer has increased by more than 20 per cent since 2008, and mortality has increased by 14 per cent. Breast cancer is also the most common cause of cancer-death among women (5, 22, 000 deaths in 2012) and it now represents one in four (25.2 %) of all cancers in women. In India during 2008 and 2012, the frequencies of different types of cancer among women reveals an incidence of 27 per cent, followed by cervical cancer with an incidence of about 23 per cent (Figure 1).

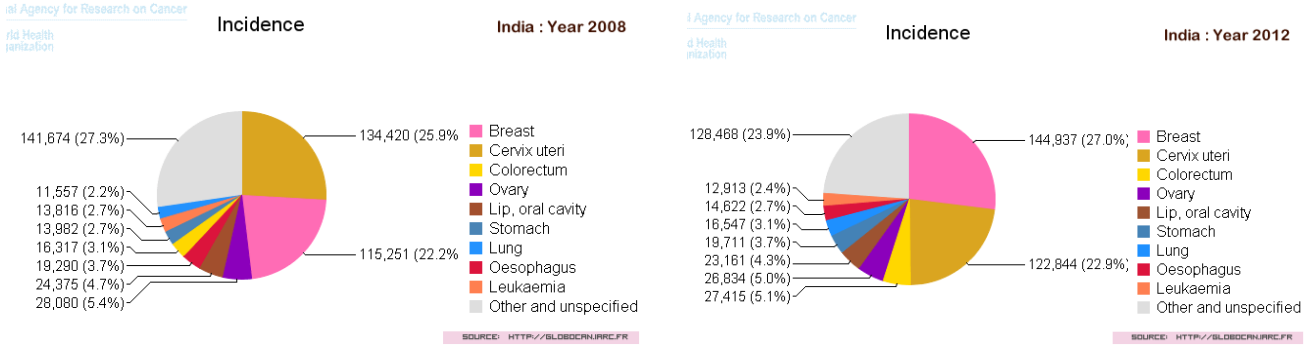

Figure 1: **Incidence of different types of cancer in women in India: 2008 and 2012**
[Globocan: 2008 and 2012]

There are many factors both endogenous and exogenous that may cause breast cancer in women. The exogenous factors include radiation to chest, obesity, duration of lactation and breast feeding, oral contraceptive use, hormone replacement therapy, alcohol consumption, lack of physical exercise, smoking, eating disorder and exposure to chemicals in cosmetics. On the other hand the endogenous factors responsible for breast cancer include age, genetic predisposition to cancer (mutations in breast cancer genes *BRCA1* and *BRCA2*), family history, early age at menarche, late age at menopause and high levels of endogenous estrogens and androgens, and sensitivity of these two hormones during prenatal development.

There have been attempts to find out any proxy measure that can indicate the probability of developing breast cancer. In India to identify such relationship, the initial work done on Dermatoglyphic characteristics (Bhardwaj *et al*., 1978); Serum protein polymorphism (Kaur *et al*., 1984); and the mean immunoglobulin levels (Kaur *et al*., 1986). Although some association could be found with respect to Dermatoglyphic characteristics and Serum protein polymorphism, no significant relationship could be established with the mean immunoglobulin levels and breast cancer.

Recently, a few attempts have been made to establish an association between 2D:4D and breast cancer (Muller *et al*., 2012). The relationship between 2D:4D and cancer was first hypothesized for breast cancer (Trichpoulos, 1990; Manning *et al*., 2003), but the first study to confirm a correlation was

published in 2012. Before this, in oncology, it was suggested that 2D:4D may be predictive of susceptibility to different types of cancers like prostate cancer, mouth tumors, gastric cancer, colorectal cancer, cervical cancer etc.

In human hands, the relative lengths of the second and fourth fingers differ between males and females. In males, the second digit (2D, or index finger) is usually shorter than the fourth digit (4D, or ring finger), whereas in females the index finger is generally equal to or longer than the ring finger. The ratio of 2D length to 4D length, known as the 2D:4D ratio, is therefore 2D:4D < 1 for most men and 2D:4D > 1 for most women. 2D:4D ratio is a proxy marker for the prenatal influence of sexual hormones. Studies hypothesized that a low 2D:4D ratio reflects embryonic exposure to high levels of testosterone, whereas a high 2D:4D ratio reflects a prenatal environment low in testosterone. Conversely it is positively correlated to prenatal estrogen (Breedlove, 2010).

There has been increasing use of the 2D:4D ratio as an index of prenatal hormone exposure, and extensive studies in humans have found correlations between digit ratios and a variety of physiological and psychological conditions and used as a biomarker for several diseases.

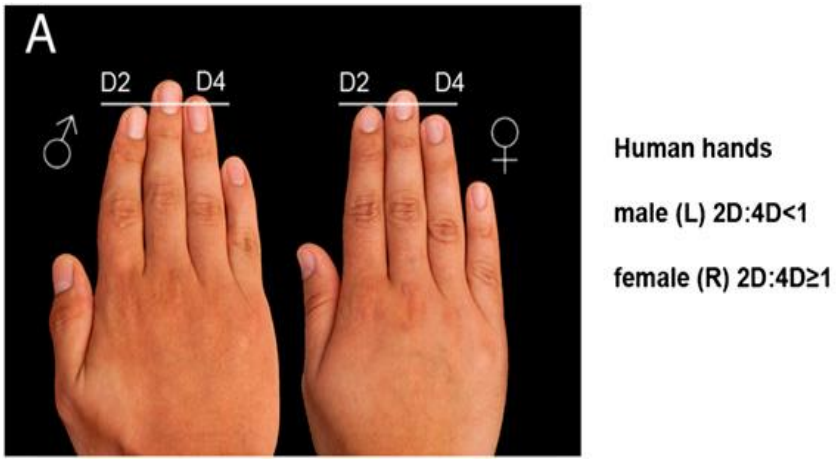

Figure 2**: 2D:4D Ratios of male and female**

Previous studies showed that susceptibility to breast cancer might be predetermined *in utero*. Hormonal exposure in early life might have a particularly important effect on the later risk of breast cancer. In recent years, evidence from mouse models suggested that the sex hormones and genes are involved in the differentiation of fetal 2D:4D which may also be involved in mammary gland initiation. During the development of 2D:4D, there are at least 19 skeletogenic genes that are activated or deactivated by prenatal testosterone (PT) and prenatal estrogen (PE) (Zheng and Cohn, 2011). Among them there are three genes namely Wnts, Fgfs, and FGFR1, that influence the Tbx genes, which initiate mammary gland formation (Eblaghie*et al*., 2004). Homeobox (HOX) family genes, which are essential for the differentiation of fingers, are related to breast carcinogenesis. HOXA5 limits the p53 expression in breast tumors and HOXA1 represents a human mammary epithelial oncogene. Furthermore, the SOX9 gene, which also acts during development of 2D:4D might be

important for breast tumour initiation and metastasis (Chakravarty *et al*., 2011). So, if fetal development of mammary glands is linked to predisposition to adult breast cancer then 2D:4D might be an indicator of this disease predisposition.

This makes 2D:4D an excellent candidate biomarker for examining putative associations between prenatal testosterone exposure and sensitivity to testosterone and so, risk of breast cancer. In such contextual background the present work has been extended to the Bengalee Hindu women of West Bengal, India, to investigate if there is an association between 2D:4D ratio and breast cancer in this small sample from West Bengal.

MATERIALS AND METHODS:

Material: A case-control study was performed between April and June of 2015 with a total of 102 women (aged between 30-76 years) including 52clinically and histopathologically diagnosed breast cancer patients and, sex and age matched 50 normal controls. All participants were drawn from Bengalee Hindu women of West Bengal, India. The breast cancer patients were recruited form Netaji Subhas Chandra Bose Cancer Research Institute, Kolkata, and the normal controls were apparently selected from those who do not have any family history of breast cancer. All participants provided written informed consent and the data were collected by using a pre-structured schedule. Participants were asked about age, age at onset of breast cancer, age at menarche, age at menopause, use of oral contraceptive, and family history of breast cancer.

Methodology: (i) Determination of 2D:4D ratio: The 2D:4D ratio was determined by measuring the index and ring fingers of both hands using Martin's sliding caliper nearest to 1.0 mm, starting from the proximal baseline on the palmar side of the metacarpophalangeal joint to the finger tip (Kemper and Schwerdtfeger, 2009). The length of the index finger was divided by the length of the ring finger to obtain 2D: 4D and $\Delta_{r-l}$was calculated as the difference between right and left ratios.

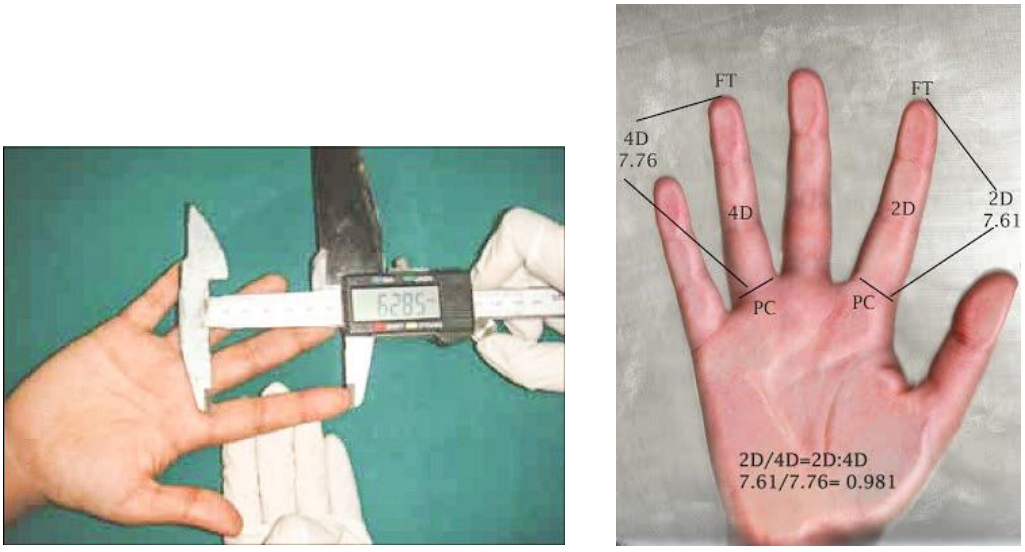

Figure 3: Method of taking measurements 2D and 4D & their ratio

(ii) Statistical analyses: Descriptive and inferential statistical analyses have been done and the data were analyzed by SPSS software (Version: 16.0). The cut off value was set as p=0.05.

RESULTS

The age of cancer patients (n = 52) ranged from 30 – 76 years with a mean of 49.87 ± 10.11 years and age at diagnosis of this group ranged from 30 – 75 years with a mean of 47.73 ± 10.11) years (Table 1). This group attained menarche at the age ranged between 10 – 16 years with a mean of 13.15 ± 1.51 years. Out of the breast cancer patients 69.23 % (n = 36), attained menopause, with a mean age at menopause of 46.11 (± 5.48) years having a range between 33 – 61 years. Table-1 also represents the distribution of age and age at different biological events of the control group. The mean present age of control group (n = 50) is 41.48 ± 10.26 years with a range between 25 – 70 years and the mean age at menarche is 13.06 ± 1.48 years with a range of 9 – 16 years. Twenty percent of the control females (n = 10) experienced menopause and show a mean of 47.5 ± 4.06 years with the range between 41 – 55 years.

No significant difference has been found in age at menarche and age at menopause between Breast Cancer patients and Control groups (Table-2).

No significant difference of any 2D:4D ratio has been found between patients and control group (Table-4). Though the finding is statistically not significant, the graphical representation reveals a slightly higher value of the right 2D:4D in breast cancer patients than that in control group (Figure-4).

Both left hand and right hand 2D:4D are negatively, and the Right minus Left (Δ_{r-l}) value is positively correlated with the age at diagnosis in breast cancer patients, but the association does not show any significance (Table-5).

No significant relationship has been found between any 2D:4D ratio and age at different biological events in both groups (Table-6).

DISCUSSION

It is evidenced that the sex hormones and genes are involved in the differentiation of fetal 2D:4D which may also be involved in mammary gland initiation. The 2D:4D measures give specific information about exposure and sensitivity of prenatal testosterone and estrogen. These hormonal exposures in early fetal life have an effect on the later risk of breast cancer. Therefore, the 2D:4D measure could be the proxy marker for breast cancer.

With this view, a study by Muller *et al.* (2012) found a positive correlation between left2D:4D and breast cancer risk, negative correlation for Δ_{r-l} and no association between right 2D:4D and breast cancer risk. Another study by Hong *et al.* (2014) found that the 2D:4D measures of breast cancer patients were significantly higher than that of controls. Later, a Brazilian population based study by Mendes et al (2016) suggests that the patients with breast cancer presented significantly higher right

and left 2D:4D and higher DR-L than controls. In India, a study by Jafar et al (2018) found that 2D:4D ratio is significantly higher in breast cancer patients of Uttar Pradesh compared to control group. But in the present study, no statistical association has been found between any 2D:4D measures and breast cancer risk. So, findings of the present study indicate that the patients might not have higher prenatal estrogen exposure (i.e., lower PT) during their fetal period compared to the controls.

An earlier study by Manning et al (2001) found a negative association between left 2D: 4D and age at onset of breast cancer. But an interesting inverse result was found from the study by Muller *et al.* (2012) where, both right 2D:4D and Δ_{r-l} were negatively associated with age at onset. The China-based study (Hong *et al.*, 2014) showed a significant negative correlation between both left and right 2D:4D and the presented age with breast cancer. The Brazilian population based study (Mendes et al, 2016) found a significantly negative correlation between left 2D:4D and age at diagnosis. But the present study among patients shows no association between any 2D:4D measure and age at diagnosis.

A higher value of right 2D: 4D and Δ_{r-l} were both associated with slightly earlier age at menopause (Muller *et al.*, 2012). But the present study shows no significant correlation between any 2D:4D measure and age at menopause; however, the present study is consistent with the Muller's in showing no association between 2D:4D measure and age at menarche. In the present study no significant difference in age at menarche and age at menopause between the breast cancer patients and control group has been evidenced. The reason for this non-patterned variation in findings may be sought in geographical, ethnic, or in sample size.

Table – 1: Distribution of age and age at different biological events of the breast cancer patients and control group

Variables (in years)	Breast Cancer patients			Control group		
	N	Range	Mean ± SD	N	Range	Mean ± SD
Present age	52	30 - 76	49.87 ± 10.11	50	25 - 70	41.48 ± 10.26
Age at diagnosis	52	30 - 75	47.73 ± 10.11	-		
Age at Menarche	52	10 - 16	13.15 ± 1.51	50	9 - 16	13.06 ± 1.48
Age at menopause	36 (69.23 %)	33 -61	46.11 ± 5.48	10 (20.0%)	41 - 55	47.5 ± 4.06

Table – 2: Comparison of age and age at different biological events between breast cancer patients and control group

Variables (in years)	Breast Cancer patients	Control Group	
	Mean ± SD	Mean ± SD	t
Age at Menarche	13.15 ± 1.51	13.06 ± 1.48	0.317
Age at menopause	46.11 ± 5.48	47.5 ± 4.06	0.745

Table – 3: Distribution of 2D:4D of both hands of breast cancer patients and control group

2D:4D	Breast Cancer patients N=52		Control group N=50	
	Range	Mean ± SD	Range	Mean ± SD
Left hand	0.86765 – 1.05	0.9781473 ± 0.036	0.90278 – 1.07813	0.9788998 ± 0.044
Right hand	0.9 – 1.10769	0.9900200 ± 0.04	0.90909 – 1.05	0.9772486 ± 0.035
Right minus left (Δ_{r-l})	(-) 0.06303 – 0.14694	0.0135212 ± 0.045	(-)0.10761 – 0.10387	-0.0016512 ± 0.044

Table – 4: Comparison of 2D:4D of both hands between breast cancer patients and control group

2D:4D	Breast Cancer patients N=52	Control group N=50	
	Mean ± SD	Mean ± SD	t
Left hand	0.9781473 ± 0.036	0.9788998 ± 0.044	0.095
Right hand	0.9900200 ± 0.04	0.9772486 ± 0.035	1.687
Right minus left (Δ_{r-l})	0.0135212 ± 0.045	-0.0016512 ± 0.044	1.716

Table – 5: Relationship between 2D:4D of both hands and age at diagnosis of breast cancer patients

Breast Cancer patients N = 52		
	Correlation	r
Left hand	2D:4D vs. Age at diagnosis	-0.060
Right hand	2D:4D vs. Age at diagnosis	-0.078
Right minus left (Δ_{r-l})	2D:4D vs. Age at diagnosis	0.012

Table – 6: Relationship between 2D:4D of both hands and age at different biological events in breast cancer patients and control group

Variables		Breast cancer patients	Control group
Left hand		r	r
	2D:4D vs. Age at menarche	-0.095	0.192
	2D:4D vs. age at menopause	0.243	-0.626
Right hand	2D:4D vs. Age at menarche	-0.073	-0.023
	2D:4D vs. age at menopause	0.227	-0.164
Right minus left hand (Δ_{r-l})	2D:4D vs. Age at menarche	0.031	-0.208
	2D:4D vs. age at menopause	0.079	0.484

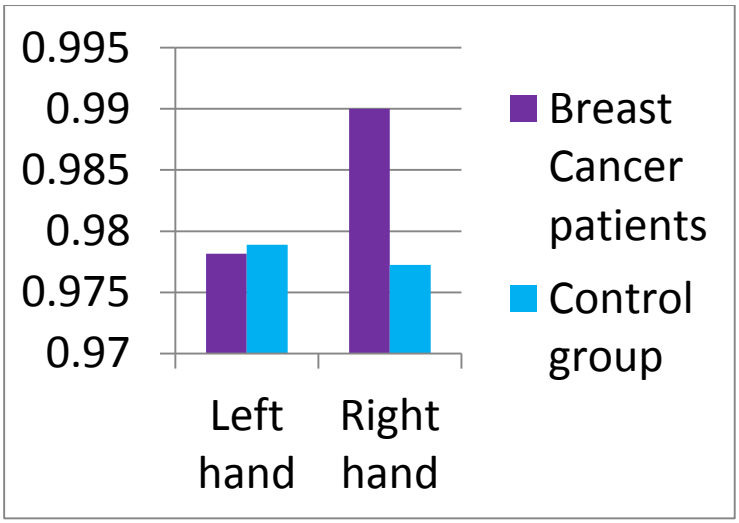

Figure 4**: Bar graph showing values of 2D:4D ratios of both hands of Patients and Controls.**

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