Second to Fourth Digit Ratio in Women with Breast Cancer

Relación del Segundo al Cuarto Dígito en Mujeres con Cáncer de Mama

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SUMMARY: Digit ratio established in utero is positivelly correlated with intrauterine level of estrogen. Since the breast cancer is related to excessive and prolonged exposure to estrogen, digit ratio might be considered as useful marker in breast cancer risk assessment. The aim of the present study was to compare digit ratios in breast cancer patients and healthy controls. The study group consisted of 98 breast cancer patients aged between 29 to 84 years while the control group included 141 healthy women aged between 21 and 67 years. After collecting anamnestic data concerning menopausal status, the length of second and fourth fingers were measured and the digit ratios were calculated for both hands, as well as the difference between right and left digit ratio. Digit ratio was significantly higher on right hand in breast cancer patients compared to healthy controls (1.003 ± 0.05 vs. 0.990 ± 0.03). Right digit ratio showed better predictive capacity for the breast cancer development then the left (AUC:0.609 vs. 0.541). Negative statistically significant correlation between right digit ratio and the age of breast cancer diagnosis was observed ($r=-0.271$). Higher values of right digit ratio in women with breast cancer when compared to healthy women suggest their higher prenatal estrogen exposure that confirms the importance of digit ratio determination in breast cancer risk assessment.

KEY WORDS: Digit ratio; Breast cancer; Age of the breast cancer diagnosis.

INTRODUCTION

Breast cancer represents the most common malignancy in the women in developed countries. At the same time, it is considered to be one of the most usual causes of deaths in women. It is noticed that the number of women diagnosed with breast cancer has been increasing recently so it is estimated that 1 out of 8 women will be diagnosed with breast cancer during her lifespan (Eisemann *et al*., 2013).

Breast cancer is a multifactorial disease in whose etiology genetic as well as environmental factors play major role. It is well known that states providing excessive or long term estrogen stimulation such as early menarche, late menopause, hormonal therapy or the use of oral contraceptives multiply the risk of getting breast cancer (Muller *et al*., 2012; Haldosén *et al*., 2014). Today it is widely recognized that estrogen exerts proliferative effects on mammary gland cells and by increasing their mitotic activity it causes mutations. It also possess supportive role on the growth of these mutated cells (Preston-Martin *et al*., 1990, 1993; Yager & Davidson, 2006). Since the mammary gland

development starts prenatally and continues through the puberty, pregnancy and lactation time, it is believed that estrogen exposure in utero might affect the breast cancer development later in life. The impact of fetal exposure to estrogen is enlarged by the assumption that sex hormone display might have cumulative action in the risk of getting this malignant disease (Muller *et al*., 2012; Henderson & Feigelson, 2000).

Prenatal exposure to sex hormones – estrogen and testosterone might be assessed by the digit ratio (2D:4D) or the ratio between the lengths of the second and fourth finger (Manning *et al*., 1998; Manning & Leinster, 2001). It is supposed that the digit ratio is established early in utero and does not change throughout lifetime (Manning & Bundred, 2000). His value depends on the prenatal level of estrogen and testosterone, it is positively associated with the estrogen exposure, and negatively with testosterone (Hopp *et al*., 2014), two hormones that have impact on the genes engaged in its differentiation (Zheng & Cohn, 2011). The fact, that

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there are genes (WNTs, FGFR, HOX, SOX9) necessary for the differentiation of 2D:4D as well as mammary gland development and breast carcinogenesis, makes 2D:4D even more interesting predictive marker of breast cancer risk (Raman *et al.*, 2000; Manning *et al.*, 2003; Zhang *et al.*, 2003; Eblaghie *et al.*, 2004; Zheng & Cohn, 2011).

Being aware of the global burden of breast cancer in women nowadays, the aim of our study was to compare digit ratios in breast cancer patients and healthy controls, to determine their optimal cut-off value predicting the breast cancer development and to explore the association between the 2D:4D and the age of the onset of the illness.

MATERIAL AND METHOD

The study group consisted of 98 breast cancer patients aged from 29 to 84 years (average age 59.09±10.89 years) hospitalized at the Oncology Institute of Vojvodina with the histopathological confirmation of breast cancer. The control group included 141 healthy women aged between 21 and 67 years (average age 39.88±11.80 years). The research was approved by the Ethical Committee and Expert Council of Oncology Institute of Vojvodina located in Sremska Kamenica. All the participants signed the informed consent after being precisely informed about the aim of research.

The participants were of different menopausal status. Data regarding menopausal status was collected anamnestic and postmenopausal women were considered those with the absence of menstrual bleeding for more than 12 months. The study group consisted of 28 premenopausal and 70 postmenopausal women, while control group involved 108 premenopausal and 33 postmenopausal women.

After the anamnestic data was taken, all the subjects were measured. The length of second and fourth fingers on the both hand were measured by the nonius to the nearest 0.01 cm. The measurements were performed on the palmar side of the hand as the distance between the tip of the appropriate finger and palmar digital crease parallel to the longitudinal axis of the finger. Second to fourth digit ratio (2D:4D) was calculated on the basis of the obtained values of the length of the second and fourth finger separately for the right and the left hand. Afterwards, the difference between right and left second to fourth digit ratio was calculated (Dr-l).

The results were analyzed by statistic software program SPSS 24.0. In order to assess differences in right and left 2D:4D, as well as, Dr-l between study and control group multivariate analyses of variance (MANOVA) was used. Differences in observed variables were considered statistically significant if p-value was less than 0.05. Receiver operating characteristic (ROC) analyses was applied to determine the most appropriate cut-off value of the digit ratio on both hands in prediction of breast cancer development. The association between the values of right and left second to fourth digit ratio and difference between right and left second to fourth digit ratio and the age of breast cancer diagnosis was assed by bivariate correlation method by determining Pearson's correlation coefficient.

RESULTS

Comparison between the study and control group on the lengths of the index and ring fingers on the right and left hand and the difference between the right and left second to fourth digit ration is represented in Table I. Women with breast cancer had statistically higher 2D:4D only on the right hand when compared with the healthy controls.

Table I. Comparison of study and control group on right and left second to fourth digit ratio and difference between the right and left second to fourth digit ratioa

	Study group	Control group	p
Right 2D:4D	1.003±0.05	0.990±0.03	0.010*
Left 2D:4D	1.017±0.05	1.010±0.03	0.193
D_{r-l}	-0.013±0.07	-0.019±0.03	0.417

Receiver operating curve (ROC) analysis notified better predictive capacity of the right then the left second to fourth digit ratio for the breast cancer development (AUC 0.609). The cut-off value both of the right and the left 2D:4D associated with breast cancer was 1.012 (Table II, Figs. 1 and 2).

Table II. Assessment of the right and left second to fourth digit ration in the prediction of breast cancer development

	AUC	Cut-off	Sensitivity	1-Specificity
Right	0.609	1.012	0.480	0.234
Left	0.541	1.012	0.582	0.369

In Table III the association between the age of the onset of breast cancer and the right and left second to fourth digit ratio as well as the difference between right and left 2D:4D was shown. Weak statistically significant negative correlation between second to fourth digit ratio on the right hand and the age of breast cancer diagnosis was obtained (r=-0.271, p<0.05).
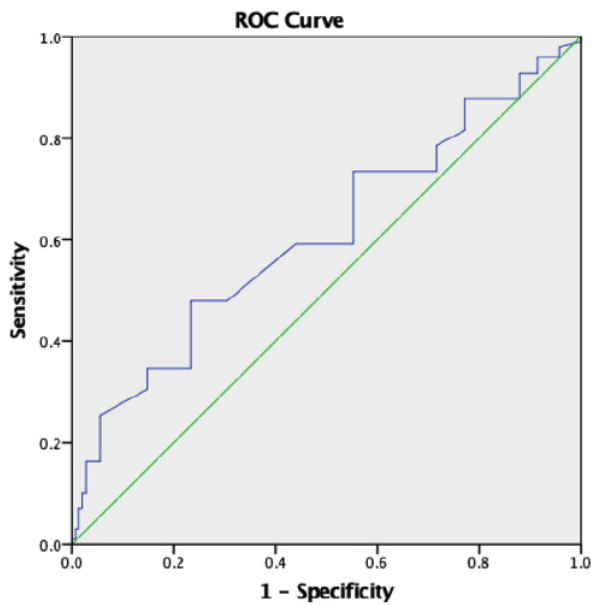
Fig. 1. Receiver operating characteristic (ROC) curve for the right second to fourth digit ratio in the prediction of breast cancer development.
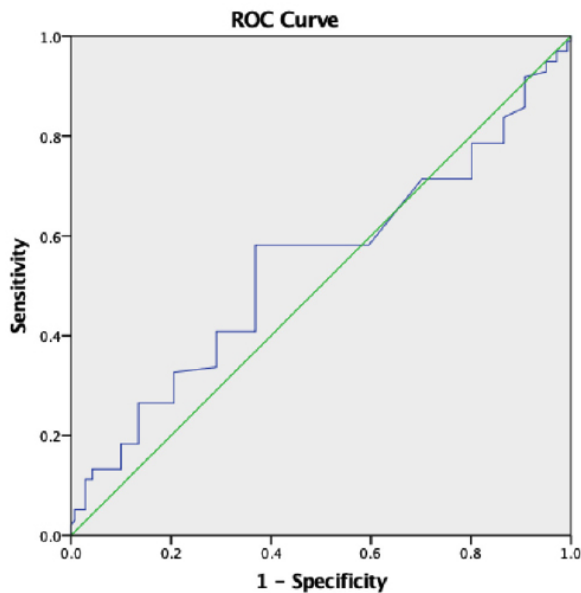

Fig. 2. Receiver operating characteristic (ROC) curve for the left second to fourth digit ratio in the prediction of breast cancer development.

Table III. Correlation of the right and left second to fourth digit ratio and difference between the right and left second to fourth digit ratio with the age of breast cancer diagnosis

	Right 2D:4D	Left 2D:4D	D_{r-l}
Age of breast cancer diagnosis	-0.271*	-0.080	-0.110
	0.007	0.433	0.283
Sig. (2-tailed)			

DISCUSSION

Breast cancer development is believed to be associated with the states providing long term or excessive estrogen stimulation (Muller *et al*., 2012; Haldosén *et al*., 2014). Since it is suggested that the exposure to this hormone might have cumulative effect on mammary gland tissue during lifetime (Henderson & Feigelson, 2000), the idea of the importance of intrauterine hormone display has been raised. The aim of our research was to compare digit ratios, as markers of hormonal exposure in utero, in breast cancer patients and healthy controls, as well as, to determine their optimal cut-off value in predicting the breast cancer development. Moreover, we analyzed the association between 2D:4D and the age of the illness onset. The results of our study showed that women with breast cancer had statistically significantly higher 2D:4D on right hand whose predictive capacity for breast cancer development was better when compared with left 2D:4D. We also noticed weak statistically significantly negative correlation between right 2D:4D and the age when breast cancer was diagnosed.

Digit ratio represents the ratio between the length of the second and fourth finger on each hand. Mouse models have shown that sex hormones, estrogen and testosterone, affect 2D:4D (Zheng & Cohn, 2011). Until nowadays 19 genes, influenced by intrauterine sex hormone exposure and being important for the differentiation of 2D:4D, have been described (Zheng & Cohn, 2011). Interestingly, some of these genes are also involved in mammary gland development (Eblaghie *et al*., 2004). Being determined in utero, effected by estrogen and testosterone, and unlikely to change during the lifetime, digit ratio might be considered as a long term signature of intrauterine sex hormones exposure. Since it is suggested that prenatal hormone exposure could impact breast cancer development later in life (Trichopoulos, 1990), digit ratio might be also regarded as the marker of breast cancer risk (Muller *et al*., 2012; Hopp *et al*., 2014; Hong *et al*., 2014; Mendes *et al*., 2016). In that respect, high 2D:4D has been associated with high intrauterine estrogen exposure (Muragaki *et al*., 1996) and positively correlated with the risk of breast cancer (Mendes *et al*., 2016). The assumption of this positive correlation firstly was proposed by Manning & Leinster (2001) in whose study was revealed that women with breast cancer had statistically significantly higher 2D:4D when compared to healthy controls. Succeeding studies done on this topic confirmed these results. Research carried out in Brazilian and Chinese population reported greater values of right as well as left 2D:4D in a study group (Hong *et al*., 2014; Mendes *et al*., 2016). The results of our investigation partially were in line with these studies since we described statistically significant difference in digit ratios between study and control group only on right hand, while

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Muller *et al*. (2012) noticed the difference on left hand. On the other hand, many authors observed the relationship between different types of malignant diseases and right hand digit ratio and related it to better sensitivity of right hand to intrauterine hormonal exposure (Jung *et al*., 2010; Hönekopp & Watson, 2010; Rahman *et al*., 2011; Hopp & Jorge, 2011, 2012; Waters *et al*., 2013). Moreover, receiver operating characteristic (ROC) analyses performed in our study also supported the previous assumption about better sensitivity of right hand to prenatal hormonal exposure since the AUC for right 2D:4D was bigger when compared to left 2D:4D. Although, with limited specificity and sensitivity, these results reveal better capacity of right digit ratio in prediction of breast cancer development. Unfortunately, in the literature we could not find any data associated to the determining optimal cut-off value and AUC of right and left 2D:4D related to breast cancer to compare with.

Besides digit ratio, the difference between right and left digit ratio was described as an indicator of intrauterine testosterone exposure (Hönekopp & Watson, 2010; Hurd *et al*., 2011). In that matter, higher Dr-l noticed by Mendes *et al*. (2016) in breast cancer patients was related to their lower prenatal testosterone and, on the other hand, higher estrogen exposure. This finding was not surprising since it is established that estrogen increases mitotic activity of mammary gland cells causing their mutation (Trichopoulos, 2003). On the other hand, the results of the study done by Muller *et al*. (2012) showed lower Dr-l in breast cancer patients and assumed it might had been the consequence of higher prenatal testosterone exposure which could had been converted to estrogen by aromatase activity and promoted mammary gland cells proliferation. Our research incompletely confirmed the results of Mendes *et al*. (2016) since breast cancer patients had higher Dr-l when compared to healthy controls but this difference did not reach the level of statistic significance.

Highly likely associated with intrauterine estrogen exposure, in our research right 2D:4D also showed weak statistically significantly negative correlation with the age of breast cancer diagnose. Our study verified the findings of Muller *et al*. (2012) who noticed inverse association between right 2D:4D, as well as, Dr-l with the age when breast cancer was diagnosed while Manning & Leinster (2001) and Hong *et al*. (2014) findings were related to the left 2D:4D. Although previously mentioned studies did not offer any possible explanation of the association of left digit ratio and the age of breast cancer presentation except of the ethnic differences and sample size (Hong *et al*., 2014), Mendes *et al*. (2016) regarded that their results should have pointed to the importance of considering digit ratio on both hands in relationship to the malignant diseases.

Although our study indicates to the significance of digit ratio in estimating breast cancer risk, its main disadvantages are related primarily to the sample size. The inclusion of larger number of respondents might strengthen our results and more clearly identify those with high risk of breast cancer development. Being non-invasive, cheap and simple determining digit ratio could contribute to breast cancer prevention.

UDICKI, M.; STARCEVIC, I.; SRDIC GALIC, B.; DRAGAN, T.; RADOVANOVIC, Z. Relación del segundo al cuarto dígito en mujeres con cáncer de mama. *Int. J. Morphol., 41(1)*:25-29, 2023.

RESUMEN: La proporción de dígitos establecida en el útero, se correlaciona positivamente con el nivel intrauterino de estrógeno. Dado que el cáncer de mama está relacionado con una exposición excesiva y prolongada a los estrógenos, la proporción de dígitos podría considerarse un marcador útil en la evaluación del riesgo de cáncer de mama. El objetivo del presente estudio fue comparar proporciones de dígitos en pacientes con cáncer de mama y controles sanos. El grupo de estudio consistió en 98 pacientes con cáncer de mama con edades comprendidas entre los 29 y los 84 años, mientras que el grupo de control incluyó a 141 mujeres sanas con edades comprendidas entre los 21 y los 67 años. Después de recopilar datos anamnésicos sobre el estado menopáusico, se midió la longitud de los dedos segundo y anular y se calcularon las proporciones de los dedos para ambas manos, así como la diferencia entre la proporción de los dedos derecho e izquierdo. La proporción de dígitos fue significativamente mayor en la mano derecha en pacientes con cáncer de mama en comparación con controles sanos (1,003 ± 0,05 frente a 0,990 ± 0,03). La proporción del dígito derecho mostró una mejor capacidad predictiva para el desarrollo de cáncer de mama que el izquierdo (AUC: 0.609 vs. 0.541). Se observó una correlación estadísticamente significativa negativa entre la proporción de dígitos derechos y la edad del diagnóstico de cáncer de mama (r=-0,271). Los valores más altos de la proporción de dígitos derechos en mujeres con cáncer de mama en comparación con mujeres sanas sugieren una mayor exposición prenatal a estrógenos que confirma la importancia de la determinación de la proporción de dígitos en la evaluación del riesgo de cáncer de mama.

PALABRAS CLAVE: Relación de dígitos; Cáncer de mama; Edad del diagnóstico de cáncer de mama

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