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ЛЕВШЕСТВО И РИСК РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ: ИЗОБИЛИЕ ПРОТИВОРЕЧИВЫХ ДАННЫХ

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The present short review summarizes controversial data regarding the putative association between left-handedness and breast cancer. Factors thought to be involved in the etiology and pathogenesis of breast cancer are outlined: prenatal and postnatal levels of sex steroids, maternal age, age at menarche and age at menopause. The same factors are discussed with regard to handedness and apparent conflicts are revealed.

Keywords: left-handedness, breast cancer, sex hormones, age at menarche, age at menopause

Convincing evidence suggests that functional brain asymmetry is spread over the neural control of autonomic physiologic functions (Neveu, 1992; Wittling, 1995; Fokin et al., 2011): the left and right hemispheres are differently involved in the control of cardiac activity, endocrine functions, and in neuroimmunomodulation. Against this background, it is reasonable to expect associations between the patterns of brain asymmetry and some somatic diseases.

It is widely accepted that manual asymmetry is a reflection of the general asymmetry of brain (Gutnik et al., 2010) and that left-handedness is associated with peculiarities in the patterns of brain lateralization (Llaurens et al., 2009). In the context of the above mentioned putative associations between brain

asymmetry and diseases, many researchers analyze the incidence of left-handedness in clinical populations (Geschwind and Behan, 1982; Coren, 1992; King and Nixon, 1995; Bryden et al., 2005; Gardener et al., 2009).

According to several publications, left-handed women should be included in the high-risk groups of breast cancer, the most common cancer in women (López-Otín and Diamandis, 1998; Armstrong et al., 2000; Persson, 2000). Titus-Ernstoff et al. (2000) found out a modest association between left-handedness and breast cancer risk in women over 60 years of age. Ramadhani et al. (2005) estimate that as a whole the risk of breast cancer is 39% higher in left-handed women. The same authors pointed out that in younger left-handed women (premenopausal ones) the risk is increased

more than twofold. Fritschi et al. (2007) replicated the finding of Titus-Ernstoff et al. (2000): the risk of developing postmenopausal breast cancer is significantly higher for left-handed women compared to right-handed. The authors of the articles cited above speculated that the origin of the association between left-handedness and breast cancer may lie (partly at least) in intrauterine hormonal milieu: exposure to sex steroids, which have been considered as aetiological factors for both left-handedness and breast cancer.

It should be noted, however, that contrary data exist. The study of Stellman et al. (1997) establishes that the risk of breast cancer is lower in left-handed women. The results of Stellman et al. (1997) are in accordance with the earlier ones of Olsson and Ingvar (1991): among breast cancer patients, left-handed are 1.5%, while the incidence of left-handedness in the observed referent population is 5%.

In their review on aetiology and pathogenesis of breast cancer López-Otín and Diamandis (1998) summarized: “1/ Breast cancer is not a purely genetic disease...; 2/ Environmental factors either acting alone or in association with genetic factors are likely to be very important; 3/ Endogenous and exogenous sex hormones appear to be linked to the pathogenesis. ...the endogenous hormonal milieu is very important especially early in life; 4/ It appears that the risk is established at a very early stage, e.g., during prenatal, neonatal, and pubertal life...”. The last two statements are the core of the hypothesis suggested by Trichopoulos (1990; 2003): that **intrauterine exposure to elevated concentrations of estrogens** increases the risk of breast

cancer in the offspring. As Trichopoulos (2003) acknowledges himself, “this hypothesis is very difficult to directly evaluate”. Some comparisons can, however, be made with conditions or anthropometric indicators (pregnancy toxemia, birth weight, second to fourth digit ratio), for which it is known that they correlate with the levels of pregnancy estrogens (Ekblom et al., 1997; Potischman and Troisi, 1999; Manning and Leinster, 2001; Park et al., 2008). It is accepted, for instance, that the ratio between the lengths of the 2nd and 4th digit of the hand (2D:4D ratio) correlates negatively with prenatal exposure to testosterone and positively with prenatal estrogens. The high ratio of testosterone/estrogens (relative low levels of estrogens) determines lower values of 2D:4D, and vice versa; that is, low testosterone/estrogens ratio (relative high levels of estrogens) is associated with higher values of 2D:4D (Lutchmaya et al., 2004). If high *in utero* exposure to estrogens predisposes to breast cancer, then 2D:4D ratios should positively correlate with cancer risk, suggested Manning and Leinster (Manning and Leinster, 2001). They found out that 2D:4D ratios in breast cancer patients were similar to ratios in controls. In a patients' group, however, women with high 2D:4D ratios (i.e., high prenatal estrogens) developed breast cancer earlier than women with low 2D:4D ratios (i.e. low prenatal estrogens).

If left-handed women are at higher risk to develop breast cancer and that can be attributed to specificity in the intrauterine hormonal environment and especially to relative high levels of estrogens, then 2D:4D ratios in left-handed women, as a rule, should be higher than 2D:4D ratios in right-handed

women. In one of our studies, however, we found out handedness-related peculiarities in the 2D:4D ratios, suggesting that left-handed women were not subjected to higher levels of estrogens *in utero*: right-hand 2D:4D ratio in left-handed women was lower than right-hand 2D:4D ratio in right-handed (Stoyanov et al., 2011). Our results are in concordance with the hypothesis of Geschwind and Galaburda (1985): that the high intrauterine levels of testosterone (relative low levels of estrogens respectively) impede the growth of certain regions of the left hemisphere, which leads to “anomalous cerebral dominance” and increase of left-handedness.

According to the results of some studies, the risk of breast cancer is to a certain extent higher in women born by **older mothers** (Ekbom et al., 1997; Park et al., 2008). On the other hand, there is data indicating increased incidence of non-right-handedness and left-handedness in the offspring of older mothers (Badian, 1983; McKeever et al., 1995; Ooki, 2006). Panagiotopoulou et al. (1990) and Zhang et al. (1995) associate older maternal age with high levels of pregnancy estrogens. In studies in primates, however, Hopkins et al. (2000) established a marked reduction of estrogen levels in older multipara and a correlation between that reduction and increased left-handedness among the offspring.

Early age at menarche (<12 years) and **late age at menopause** (≥ 55 years) are considered as predictors of increased breast cancer risk (Armstrong et al., 2000; Persson, 2000). The results of our study showed that the mean age at menarche in left-handed women (12 years 1 month of age) is significantly

lower than the mean age at menarche in right-handed (13 years 4 months of age) (Nikolova et al., 1994). That corresponds with the data for increased risk of breast cancer in left-handed women. Another of our studies, however, showed that left-handed women also have an earlier average age at menopause – 43 years 6 months of age against 50 years of age in right-handed women (Nikolova et al., 1996). Several publications reported similar to our data age at menarche (Orbak, 2005) and age at menopause in left-handers (Leidy, 1990; Dane et al., 1999), while other studies did not establish an association between handedness and these reproductive indices (Pavia et al., 1994; Kalichman and Kobylansky, 2008).

Based on findings from several studies, Epplein et al. (2010) concluded that early menarche contributes to increase of breast cancer risk in two ways: “by resulting in a greater lifetime number of menstrual cycles, leading to a greater cumulative exposure to endogenous estrogens; and through elevated circulating estrogen levels throughout the reproductive years”. Using our data for ages at menarche and at menopause, we can approximate the average reproductive life span for left- and right-handed women: it is 31 years 5 months for left-handed and 36 years 8 months for right-handed (Nikolova et al., 1994; Nikolova et al., 1996). We have established that the average length of menstrual cycle in left-handed women is shorter (27 days) as compared to right-handed (30 days) (Nikolova et al., 2003). Due to the shorter reproductive life span, however, the average lifetime number of menstrual cycles in left-handed is less – about 425 cycles, against approximately 444 cycles in right-handed. In regard to

elevated circulating estrogen levels throughout the reproductive years in women with early menarche, we have actually observed higher serum levels of estradiol in left-handed women of reproductive age as compared to right-handed (Negrev et al., 2001).

According to the suggested aetiological model for breast cancer (Persson, 2000), the probability of breast cancer developing depends on the amount of susceptible cells in the breast parenchyma. A number of mammatrophic hormones affect the cells at risk. Ovarian **estrogens** and **progesterone, prolactin** and **IGF-1*** increase the proliferation of breast epithelial cells and may determine breast cancer risk during adolescence and in adult life (Persson, 2000). It is interesting to note in this context that our data showed not only higher levels of estradiol in left-handed when compared to right-handed women, but of progesterone and prolactin as well (Negrev et al., 2001). Unfortunately, research on sex hormone levels and handedness are scarce (Tan, 1992) and it is difficult to make comparisons.

In conclusion, we think that the data presented, even if controversial, should be taken into account and discussed both by researchers who find an association between left-handedness and breast cancer, and by those who deny such a relation.

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