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Age differences of morbidity of a right and left sided breast cancer: influence of chronic pathology of internal genitals and reproductive organs surgery.

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Introduction

Influence of chronic pathology of internal genitals and reproductive organs surgery (ROS) on a breast cancer (BC) morbidity is actively studied. However results are ambiguous. Especially it concerns ROS [1-4]. Most of researchers consider that with some slip of the tongue of ROS reduces a BC risk [5-10]. But there is no full understanding of fundamental mechanisms of this phenomenon yet. In the context of the vast majority epidemiological and case-control of researches the role of internal genitals in an BC etiology is reduced only to a hormonal factor. However on this aspect there are contradictions too. So, Davelaar et al. using at patients with ROS an estradiol as replacement therapy did not find increase in risk of BC [11].

Nevertheless, influence of ROS is not limited only to change of the hormonal status. By numerous experiments it is shown that ROS leads to functional and morphological changes of a peripheral and central nervous system [12-16]. Thus, considering only a hormonal factor as the main effect of ROS, we unreasonably exclude other important mechanisms of antitumoral resistance.

The tumor laterality remains inexplicable aspect of a BC epidemiology [17-24]. By results of numerous researches it was shown that BC mainly unilateral process (frequency of the bilateral BC only 1-5%). As the BC in many respects has the genetic nature and distinctly depends on a hormonal factor, naturally there is a question: why the tumor arises only in one mammary gland if both mammary glands have equal risk? It is possible to answer this question, having only defined how symmetry of risks is broken and what can promote it.

By experiments it was determined that ROS can influence on mechanisms of functional asymmetry of a brain. These reactions have lateral specificity and depend on age of experimental animals [25-31]. By other remarkable works of neurophysiologists has been determined the dependence of BC from brain functional asymmetry [32-34].

The theory about possible influence of the status of internal genitals on BC laterality lack clinical confirmation. I.e. in literature we did not find clinical researches with such design. We try to progress in studying of this question. The purpose of this research is an assessment of age differences of morbidity of a right-sided and left-sided BC (i) at the considerable chronic pathology of internal genitals demanding surgical treatment and (ii) after ROS.

Materials and Methods

The retrospective analysis of sampling of patients with BC (n=2060) is carried out. From them 120 (5.8%; CL 95%: 3.8-7.7%) patients with BC which manifested before of ROS, and 83 (4.02%; CL 95%: 2.0-5.9%) patients with BC which manifested after ROS. ROS had not 1857 patients (90.1%; CL 95%: 86.7-93.4%). The age structure of morbidity of BC which manifested before ROS (BC-ROS group; n=120) and after ROS (ROS-BC group; n=83) were compared. Patients without ROS formed the control group (n=1857). The BC laterality and age at the moment of BC verification were considered.

The statistical analysis is carried out with use of the programs "Statistica 8.0", "SPSS Statistics 23", "Excel". Comparison of ranks of data was carried out by the Kruskal-Wallis test. Value $p<0.05$ was considered as the statistically significant.

In group BC-ROS the most often there was a hysterectomy with ovaries - 96 (80.0%) cases, a bilateral ovariectomy was more rare - 24 (20.0%) cases. We have studied reasons of ROS. The bilateral ovariectomy (n=24) and hysterectomy with ovaries (n=24) were carried out with the purpose of surgical castration (n=52; 43.3%); at 41 of them at postoperative histologic research benign diseases of a uterus and ovaries are revealed (polycystic ovary syndrome, uterine fibroids, etc.). In 14 (11.6%) cases the reasons of ROS were malignant tumours of a uterus (n=8) and ovaries (n=6). In other cases the reasons of ROS were benign diseases of a uterus and ovaries (uterine fibroids, endometriosis, polycystic ovary syndrome, etc.) - 54 (45.0%) cases.

In group ROS-BC most often there was a hysterectomy with ovaries - 45 (54.2%) cases. A hysterectomy without ovaries was more rare - 16 (19.3%) cases. The hysterectomy with unilateral ovariectomy - 14 (16.8%) cases. The only unilateral ovariectomy - 8 (9.6%) cases. Thus, hysterectomy was done to 90.3% of the patients of this group, bilateral or a unilateral ovariectomy - 80.6% of patients. The reasons of ROS were

mainly benign diseases of a uterus and ovaries - uterine fibroids, polycystic ovary syndrome, adenomatous hyperplasia of endometrium, dermoid cysts of ovaries, etc. In 9 cases the reasons of ROS were malignant tumours of a uterus (n=5) and ovaries (n=4).

Due to the retrospective character of the research we had no possibility to receive the full information on a state of internal reproductive organs of the patients of control group. Quite possibly, these patients also had pathology of a uterus and ovaries. But as it did not demand surgical treatment, it is empirically possible to assume that this pathology was considerably less expressed, than at patients of BC-ROS and ROS-BC groups.

Results

In the group BC-ROS the left-sided BC was manifested significantly at younger age, than the right-sided BC (p=0.009). The morbidity median (Me [25%; 75%]) of the left-sided BC (n=53) was 42.0 [38.0; 47.0] years, the right-sided BC (n=67) - 46.0 [41.7; 52.0] years. In control group the age structure of left-sided and right-sided BC did not differ (p=0.86); the median of age both in that and in other case was 57.0 [47.0; 66.0] years (Figure 1).

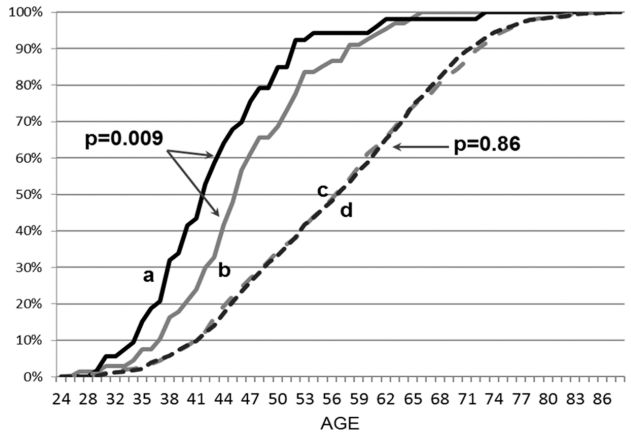

Figure 1. Age structure of morbidity of BC which manifested before ROS (BC-ROS group): a – left-sided cancer of BC-ROS group; b – right-sided cancer of BC-ROS group; c and d – right-sided and left-sided cancer of control group.

In the group ROS-BC the patients had ROS aged from 33 till 68 years; the median was 45.0 [41.5; 52.5] years. At patients with right-sided BC the ROS was carried out significantly earlier, than at patients with the left-sided BC (p=0.003). So, patients with the right-sided BC had ROS at 43.0 [39.0; 49.0] years, patients with the left-sided BC - at 48.5 [43.3; 56.0] years. The assessment of statistical dependence of such variables as age during ROS and BC laterality has shown, what the earlier ROS was carried out, the higher was a probability of right-sided BC, the later - the higher was the probability of left-sided BC (p=0.017). The time interval between the ROS and manifestation of the BC at patients with a right-sided and left-sided cancer did not differ (p=0.56), the median was there and there 108.0 [48.0; 175.5] months.

In this group the manifestation of left-sided BC (n=40) happened much later, than among patients of control group (p=0.015). It is also necessary to note, that after 65 years the difference of age structure disappeared (Figure 2). At right-sided BC the age structure of the patients of the group ROS-BC (n=43) and control group formally did not differ (p=0.39). However, the attitude of cumulative curves to each other forms "scissors" crossing in the point corresponding to 50 years that allows to single out two periods with a boundary in 50 years. I.e. in the age period before 50 years among the patients of the group ROS-BC the manifestation of the BC occurred significantly later, than among the patients of the control group (p=0.007). However in the age periods after 50 years the manifestation of the BC occurred significantly earlier, than among patients of control group (p=0.03). As a result we see, that at the group ROS-BC the patients with right-sided BC were significantly younger than the patients with left-sided BC (p=0.025). The median of a morbidity of right-sided cancer was 53.0 [47.7; 61.0] years, left-sided cancer - 61.0 [53.0; 65.0] years.

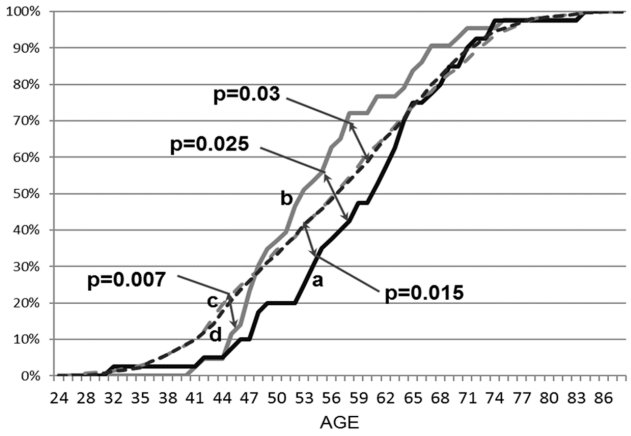

Figure 2. Age structure of morbidity of BC which manifested after ROS (ROS-BC group): a – left-sided cancer of ROS-BC group; b – right-sided cancer of ROS-BC group; c and d – right-sided and left-sided cancer of control group.

Thus, it is possible to formulate the main conclusions of research:

At the considerable chronic pathology of internal genitals the BC diagnosing in the left breast happens at younger age, than in the right breast.

After ROS because of the considerable chronic pathology of internal genitals the BC diagnosing in the left breast happens at later age, than in the right breast.

The considerable chronic pathology of internal genitals and its surgical treatment is a factor of age differences of morbidity of right and left-sided BC.

Discussion

The results of analysis of the group BC-ROS allow to assume, that the left breast directly or is indirectly more sensitive to negative influence of a considerable chronic pathology of

internal genitals, than right breast. Perhaps, there is a physiological state at which the combination of systemic and local factors defines unilateral decrease of antitumoral resistance of mammary glands and internal genitals are involved in it. Anyhow, as a result we observe that among the women having a considerable pathology of internal genitals, the deficiency of antitumoral resistance in the left breast is formed earlier, than in the right breast.

According to the results of comparative analysis in the group ROS-BC it is possible to assume, what the ROS changes antitumoral resistance of an organism too. Apparently, the influence of ROS on the existing right-sided and left-sided deficiency of antitumoral resistance has a different orientation: increase of antitumoral resistance at presence of left-sided deficiency and additional decrease of antitumoral resistance at presence of right-sided deficiency. Actually, the patients with the right-sided BC was significantly younger, than the patients with the left-sided BC. I.e. after ROS the left-sided cancer is diagnosed significantly later in comparison with the control group and right-sided cancer. Perhaps, ROS softens the left-sided deficiency of antitumoral resistance. This effect of ROS was observed only till 65 years. In the subsequent (in an involution phase), perhaps, the role of internal genitals in formation of lateral deficiency of antitumoral resistance is little significant.

In 1993 model of disturbance of symmetry of antitumoral resistance was offered [35]. According to this model, unilateral oncological process in breasts is the sign of disparity of antitumoral resistance of didymous elements of a functional system. As reason of genesis and growth of tumoral illness, the model envisage the presence of unilateral structurally functional deficiency of nervous control as a result of pathological functioning of a hypothalamic-ovarian axis. The model is based on an assumption, that the factors of unilateral decrease of antitumoral resistance have the immediate attitude to features of female generative processes and brain asymmetries. In fact, this model of disturbance of symmetry of antitumoral resistance is a continuation of fundamental works by Balitsky and Volegov dedicated to studying of antitumoral resistance of an organism [36,37]. Researches of these scientists convincingly showed modulating influence of the nervous system on mechanisms of antitumoral resistance.

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Conflicts of Interest

The author declares that he has no conflict of interests.

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