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Original research

LncRNA SRA gene polymorphisms and risk of gynecological pathology development among Ukrainian women with proliferative type of benign breast disease without atypia

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Benign breast disease is a group of all noncancerous mammary lesions with a risk of breast cancer (BC) development. BC is the most common cancer in the world; therefore, it is necessary to find new biomarkers and targets for early diagnosis, treatment, prediction of prognosis and survival. Long non-coding RNA SRA could play this role, thus further studies of its impact on the precancerous lesion pathogenesis are needed.

The aim. To analyze the association between *SRA1* rs801460 and rs10463297 SNPs and the occurrence of gynecological pathology among Ukrainian women with the proliferative type of benign breast disease without atypia.

Materials and methods. This study included 115 patients with proliferative type of benign breast disease without atypia: 55 – with gynecological pathology and 60 – without it. Polymerase chain reaction-restriction fragment length polymorphism analysis (PCR-RFLP) was used for polymorphism genotyping.

Hematoxylin and eosin, toluidine blue and van Gieson's picrofuchsin methods were applied for staining of sections. Statistical analysis was carried out using Statistical Package for the Social Sciences software (SPSS, version 25.0, Chicago, IL, USA).

Results. Significant differences were found in the rs10463297 frequency of alleles ($P = 0.032$), but not in the rs801460 ($P > 0.05$), in groups with and without gynecological pathology, while the distribution of both single nucleotide polymorphism (SNPs) genotypes was similar between these groups ($P > 0.05$). Statistically significant association was detected between *SRA1* rs10463297 polymorphism and gynecological pathology occurrence in both dominant ($P_a = 0.023$; $OR_a = 2.638$, 95 % CI = 1.145–6.076) and additive ($P_a = 0.034$; $OR_a = 2.489$, 95 % CI = 1.069–5.794) models of inheritance.

No association was found between *SRA1* rs801460 SNP and gynecological pathology development among Ukrainian women with proliferative type of benign breast disease without atypia ($P > 0.05$).

Conclusions. It was revealed that *SRA1* rs10463297 TT carriers had 2.6 times higher risk of gynecological pathology development than C allele carriers and 2.48 times than TC carriers.

Key words: breast disease, lncRNA, SRA, single nucleotide polymorphism.

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Поліморфізми гена днРНК SRA та ризик виникнення гінекологічної патології серед українських жінок із проліферативним типом доброякісної дисплазії молочної залози без атипії

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Доброякісна дисплазія молочної залози – це група всіх доброякісних захворювань із ризиком розвитку раку молочної залози (РМЗ). РМЗ – найбільш поширене онкологічне захворювання у світі, тому важливо знайти нові біомаркери та мішені для ранньої діагностики, лікування, визначення прогнозу та виживання. Довга некодувальна РНК SRA може відіграти цю роль, а отже необхідні дальші дослідження її впливу на патогенез передракових уражень.

Мета роботи – проаналізувати зв'язок між rs801460 та rs10463297 поліморфізмами та виникненням гінекологічної патології серед українських жінок із проліферативним типом доброякісної дисплазії молочної залози без атипії.

Матеріали та методи. У дослідження ввійшли 115 пацієнток із проліферативним типом доброякісної дисплазії молочної залози без атипії: 55 – із гінекологічною патологією та 60 – без неї. Полімеразна ланцюгова реакція з аналізом довжини рестрикційних фрагментів (PCR-RFLP) використана для генотипування поліморфізмів.

Для фарбування зрізів застосовували гематоксилін, еозин, толуїдиновий синій і пікрофуксин за ван Гізоном. Статистичний аналіз здійснили з використанням програми для статистичного опрацювання даних SPSS 25.0.

Результати. Встановили суттєві відмінності в частоті алелей rs10463297-поліморфізму ($p = 0,032$), але не rs801460 ($p > 0,05$) у групах із гінекологічною патологією та без неї. Водночас розподіл генотипів обох поліморфізмів статистично не відрізнявся ($p > 0,05$). Суттєвий зв'язок виявили між *SRA1* rs10463297-поліморфізмом та виникненням гінекологічної патології в домінантній ($p_a = 0,023$; $OR_a = 2,638$, 95 % CI = 1,145–6,076) та адитивній ($p_a = 0,034$; $OR_a = 2,489$, 95 % CI = 1,069–5,794) моделях.

Не встановлено зв'язку між *SRA1* rs801460-поліморфізмом та розвитком цієї патології ($p > 0,05$).

Висновки. Виявлено, що носії *SRA1* rs10463297 TT-генотипу мають у 2,6 раза вищий ризик розвитку гінекологічної патології, ніж носії С-алеля, та у 2,48 раза – ніж ТС-гетерозиготи.

Ключові слова: доброякісна дисплазія молочної залози, днРНК, SRA, однонуклеотидний поліморфізм.

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Ключевые слова: доброкачественная дисплазия молочной железы, днРНК, SRA, однонуклеотидный полиморфизм.

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Полиморфизмы гена днРНК SRA и риск развития гинекологической патологии среди украинских женщин с пролиферативным типом доброкачественной дисплазии молочной железы без атипии

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Доброкачественная дисплазия молочной железы – это группа всех доброкачественных заболеваний с риском развития рака молочной железы (РМЖ). РМЖ – самое распространённое онкологическое заболевание в мире, поэтому важно найти новые биомаркеры и мишени для ранней диагностики, лечения, определения прогноза и выживаемости. Длинная некодирующая РНК SRA может исполнить эту роль, следовательно нужны дальнейшие исследования её влияния на патогенез предраковых поражений.

Цель работы – проанализировать связь между rs801460 и rs10463197 полиморфизмами и возникновением гинекологической патологии среди украинских женщин с пролиферативным типом доброкачественной дисплазии молочной железы без атипии.

Материалы и методы. В исследование вошли 115 пациенток с пролиферативным типом доброкачественной дисплазии молочной железы без атипии: 55 – с гинекологической патологией и 60 – без нее. Полимеразная цепная реакция с анализом длины рестрикционных фрагментов (PCR-RFLP) использована для генотипирования полиморфизмов. Для окраски срезов использовали гематоксилин и эозин, толуидиновый синий и пикрофуксин по ван Гизону. Статистический анализ проведен с использованием программы для статистической обработки данных SPSS 25.0.

Результаты. Установлены существенные различия в частоте аллелей rs10463297-полиморфизма ($p = 0,032$), но не rs801460 ($p > 0,05$) в группах с гинекологической патологией и без нее. В то время как распределение генотипов обоих полиморфизмов статистически не различалось ($p > 0,05$).

Существенная связь обнаружена между *SRA1* rs10463297-полиморфизмом и возникновением гинекологической патологии в доминантной ($p_a = 0.023$; $OR_a = 2,638$, 95 % CI = 1,145–6,076) и аддитивной ($p_a = 0,034$; $OR_a = 2,489$, 95 % CI = 1,069–5,794) моделях. Не установлена связь между *SRA1* rs801460-полиморфизмом и развитием данной патологии ($p > 0,05$).

Выводы. Выявлено, что носители *SRA1* rs10463297 TT-генотипа имеют в 2,6 раз выше риск развития гинекологической патологии, чем носители С-аллеля, и в 2,48 раз – чем TC-гетерозиготы.

Since the large-scale genomic projects FANTOM and ENCODE revealed that only 2 % of the human genome is protein-coding and the genome products are predominantly transcribed into non-coding RNAs (ncRNA), a lot of scientists began their efforts to create a catalogue of these RNAs [1,2]. Long non-coding RNAs (lncRNA) were found to have more than 200 nucleotides in length, secondary and three-dimentional structures and regulate the target gene expression [3,4]. A lot of data on the involvement of dysregulated lncRNAs in the oncological processes were presented. Therefore, they can be used as biomarkers and targets to provide the cancer early diagnosis and treatment, predict the prognosis and survival [2,3].

In 1999, the steroid receptor RNA activator (SRA) lncRNA was characterized by Lanz et al. They revealed that SRA specifically transactivates steroid receptors and is encoded by the *SRA1* gene [5,6]. A few years ago, they reported SRA overexpression in human tumors of steroid-responsive tissues and SRA-mediated stimulation of proliferation as well as apoptosis in SRA-transgenic mouse models [7].

There is no evidence of an association between any lncRNA and benign breast disease (BBD) development. Given the fact that SRA can coactivate ERα- and Erβ-receptors of the breast tissue and stimulate proliferation through the paracrine signaling, it can be assumed that SRA can be involved into the proliferative type of BBD pathogenesis [8,9]. In our previous paper, we defined the link between *SRA1* rs801460 and rs10463197 single nucleotide polymorphisms (SNP) and proliferative type of BBD with atypia. We have established the positive association between *SRA1* rs801460 SNP and this pathology development (not published).

Aim

To analyze the association between *SRA1* rs801460 and rs10463297 SNPs and the occurrence of gynecological pathology among Ukrainian women with the proliferative type of benign breast disease without atypia.

Materials and methods

Study population. Whole venous blood of 115 Ukrainian females with proliferative type of BBD without atypia was used for the study. The study group included 55 subjects with gynecological pathology (mean age [±SD] 31.80 ± 9.13) and the control group – 60 subjects without it (mean age 29.17 ± 9.27). Gynecological pathology comprised all dyshormonal disorders of reproductive organs. Each patient with proliferative type of BBD was examined by a licensed surgeon (license AG No. 600519) on an outpatient basis and underwent surgical treatment at clinical sites of the Department of Surgery with a Course of Pediatric Surgery and Urology of Sumy Regional Oncology Center. All morphological samples were investigated at the Scientific Center of Pathomorphological Researches of Sumy State University. The Scientific Laboratory of Molecular Genetic Research of Sumy State University performed molecular genetic testing.

The study involved solely individuals with genetic predisposition to the breast diseases, proliferative lesions without atypia and without nonproliferative lesions.

The study design corresponded to the current orders of the Ministry of Health of Ukraine No. 690 from 23.09.2009 and No. 616 from 03.08.2012, the European Convention of Human Rights and Biomedicine, and the World Medical Association Declaration of Helsinki on the Ethical Principles

for Medical Research Involving Human Subjects. Written informed consents were obtained from all participants.

Genotyping. DNA extraction was done from the whole venous blood of 115 BBD patients using the GeneJET Whole Blood Genomic DNA Purification Kit (Thermo Fisher Scientific, USA). Polymerase chain reaction-restriction fragment length polymorphism analysis (PCR-RFLP) was used for the *SRA1* rs801460 and rs10463297 genotyping. The PCR reaction mixture included 5 μL of FastDigest Green Buffer (10X) (Thermo Scientific™, USA), 0.5 μL dNTP Mix (10mM of each deoxynucleotide) (Thermo Scientific™, USA), 0.75U DreamTaq DNA Polymerase (5 U/μL) (Thermo Scientific™, USA), 0.1 μL of each primer, 75–100 ng DNA, and bidistilled water added up to 25 μL. the next sequences were used the specific primers: forward – 5`-GTC CAT TCT GTC TTC ACT TAG-3`, reverse – 5`-GGT GGC TCT CCT CTA CTT-3`for rs10463297; 5`-TTT TTA GTA GAG ACA GGG TTT TGC C-3` and 5`-ACT CTA CGC CAG ACA ATA TGC TAT G-3` for rs801460, respectively. Amplification was conducted using Thermocycler GeneAmp PCR System 2700 (Thermo Fisher Scientific, USA).

The reaction mixture for the restriction included 2U of restriction enzyme, 0.8 μL of 10X Buffer R (Thermo Scientific™, USA) and bidistilled water added up to 2 μL. The compound of amplification product (6 μL) and reaction mixture (2 μL) was incubated at 37°C for 20 hours. *Nsi*I restriction enzyme (Thermo Fisher Scientific, USA) was used for *SRA1* rs801460 SNP. It cut the amplicon (178bp) into 155 bp and 23 bp fragments in the case of cytosine (C) to thymine (T) replacement at the -5749th position of the *SRA1* gene [10]. The *SRA1* rs10463297 SNP restriction analysis was carried out using *Eco*47I (Thermo Fisher Scientific, USA). The primary amplicon (483bp) was splitted into two fragments of 317 bp and 166 bp by *Eco*47I in case of T to C substitution at the -1440th position of the *SRA1* gene [10].

Horizontal electrophoresis (10 V/cm) in 2.5 % agarose gel with the ethidium bromide (10 mg/mL) addition was applied for restriction fragments separation with further visualization using ultraviolet transillumination.

Histology. The mammary tissue obtained was used for histology. It was fixed in 10 % phosphate buffered formalin for 48 hours and then embedded in paraffin. Paraffin series were sliced at a thickness of 8–10 μm and incubated at 37 °C for 12 hours with the subsequent deparaffinization. Hematoxylin and eosin, toluidine blue or van Gieson's picrofuchsin were used for sections staining.

Statistical analysis. The informative samples were selected (115 cases) to find the possible association between *SRA1* rs801460 and rs10463297 SNPs and gynecological pathology development among patients with proliferative type of BBD without atypia. The statistical analysis was done using Statistical Package for the Social Sciences software (SPSS, version 25.0, Chicago, IL, USA). The distribution for normality was verified according to the Kolmogorov–Smirnov test. Continuous variables were presented as the mean ±SD; categorical variables – as absolute number and percentage value. Chi square (χ^2) test was used for the comparison of categorical variables. The mean values for two groups were compared using two-tailed Student's t-test, for three – ANOVA test with subsequent Bonferroni post hoc test. Logistic regression was used to estimate the odds ratio (OR) and 95 % confidence interval (CI) for the four models of inheritance: dominant, recessive, over-dominant and additive. The adjustments for age, BMI, oral contraceptives intake, abortions and smoking were used for multivariable logistic regression. A P value < 0.05 was considered as significant.

Table 1. General characteristics of the studied groups

Parameters, units	With gynecological pathology (n = 55)	Without gynecological pathology (n = 60)	P
Age, years	31.80 ± 9.13	29.17 ± 9.27	0.785
Weight, kg	59.91 ± 11.30	58.33 ± 8.99	0.281
Height, cm	166.53 ± 6.48	166.62 ± 7.15	0.913
BMI, kg/m^2	21.57 ± 3.63	20.98 ± 2.63	0.097
Height of the glandular part of the breast, mm	14.80 ± 3.73	15.87 ± 4.42	0.446
Height of the fibroglandular part of the breast, mm	18.93 ± 4.33	19.78 ± 4.37	0.785
Age at menarche, years	13.42 ± 1.62	13.48 ± 1.38	0.217
Abortions, n (%)	24 (43.6)	18 (30.0)	0.129
Oral contraceptive intake, n (%)	16 (29.1)	8 (13.3)	0.038
Smokers, n (%)	19 (34.5)	18 (30.0)	0.602

Categorical variables were compared by χ^2 test, continuous variables – by t-test.

Results

The general characteristics of the study groups are shown in *Table 1*. The studied groups were matched by mean age, weight, height, BMI, height of the glandular and fibroglandular parts of the breast, age at menarche, abortions and smoking (P > 0.05). The significant difference was found only in oral contraceptives intake (P = 0.038).

Table 2 contains the results of the *SRA1* rs801460 and rs10463297 alleles and genotype distribution. The frequency of *SRA1* rs10463297 alleles, but not genotypes (P = 0.052), in patients with gynecological pathology significantly differed from the group without it (P = 0.032), while the distribution of *SRA1* rs801460 alleles and genotypes was similar between these groups (P > 0.05).

The results of *SRA1* rs801460 and rs10463297 genotypic association with gynecological pathology development among women with proliferative type of BBD without atypia are presented in *Table 3*. Statistically significant association was found between *SRA1* rs10463297 polymorphism in both dominant (P_c = 0.024; OR_c = 2.437, 95 % CI = 1.127–5.271) and additive (P_c = 0.040; OR_c = 2.277, 95 % CI = 1.037–4.998) inheritance models, as well as after adjustment for age, body mass index, abortions, oral contraceptive intake and smoking (dominant (P_a = 0.023; OR_a = 2.638, 95 % CI = 1.145–6.076), additive (P_a = 0.034; OR_a = 2.489, 95 % CI = 1.069–5.794) models). There was no association between rs801460 and gynecological pathology occurrence (P > 0.05).

Discussion

BBD is a group of all noncancerous mammary lesions. It is classified into nonproliferative type, proliferative type with and without atypia. The latter two have a high risk of breast cancer (BC) development [11]. BC is the most common cancer in the world; therefore, it is very important

Table 2. Distributions of genotypes and alleles in compared groups

Gene	SNP		With gynecological pathology		Without gynecological pathology		χ^2	P
			n	%	n	%		
SRA1	rs801460	Genotypes						
		CC	15	27.3	24	40.0	2.731	0.255
		CT	34	61.8	28	46.7		
		TT	6	10.9	8	13.3		
		Alleles						
		C	64	58.2	76	63.3	0.639	0.424
		T	46	41.8	44	36.7		
	rs10463297	Genotypes						
		TT	16	29.1	30	50.0	5.921	0.052
		TC	34	61.8	28	46.7		
		CC	5	9.1	2	3.3		
		Alleles						
		T	66	60.0	88	73.3	4.612	0.032
		C	44	40.0	32	26.7		

SNP: single nucleotide polymorphism; categorical variables were compared by χ^2 test

Table 3. Analysis of *SRA1* rs801460 and rs10463297 genotypic association with gynecological pathology development among women with proliferative type of BBD without atypia

SNP	Model	P_c	OR_c (95 % CI)	P_a	OR_a (95 % CI)
rs801460	Dominant	0.152	1.778 (0.809–3.904)	0.093	2.088 (0.884–4.928)
	Recessive	0.692	0.796 (0.258–2.459)	0.782	0.843 (0.253–2.811)
	Over-dominant	0.105	1.850 (0.880–3.893)	0.081	2.012 (0.917–4.417)
	Additive[1]	0.111	1.943 (0.859–4.395)	0.073	2.237 (0.927–5.399)
		0.773	1.200 (0.347–4.145)	0.590	1.450 (0.376–5.598)
rs10463297	Dominant	0.024	2.437 (1.127–5.271)	0.023	2.638 (1.145–6.076)
	Recessive	0.215	2.900 (0.539–15.605)	0.234	2.923 (0.500–17.093)
	Over-dominant	0.105	1.850 (0.880–3.893)	0.102	1.919 (0.878–4.192)
	Additive[1]	0.040	2.277 (1.037–4.998)	0.034	2.489 (1.069–5.794)
		0.083	4.687 (0.816–26.934)	0.076	5.417 (0.838–35.002)

SNP: single nucleotide polymorphism; **CI:** confidence interval; **Pc:** crude P value; **ORc:** crude odds ratio; **Pa:** P value adjusted for age, body mass index, abortions, oral contraceptive intake and smoking; **ORa:** adjusted odds ratio. [1]Upper row in the additive inheritance model – comparison between Aa and AA genotypes; lower row – between aa and AA genotypes.

to find new biomarkers and targets for early diagnosis, treatment, prediction of prognosis and survival [12,13]. In our previous paper, we found the positive link between *SRA1* rs801460 SNP and proliferative type of BBD with atypia development (not published). This paper considered the association between *SRA1* rs801460 and rs10463297 polymorphisms and the occurrence of gynecological pathology among women with the proliferative type of BBD without atypia.

A few papers reported on the *SRA1* polymorphisms. Rui Yan et al. studied the association between *SRA1* rs801460 and rs10463297 SNPs and BC development. They found that rs10463297 TC genotype increased BC risk compared to the CC genotype. However, they did not reveal a significant link between *SRA1* rs801460 SNP and BC development [14]. At the same time, Jifan Tan et al. disclosed that the *SRA1* rs10463297 polymorphism was associated with polycystic ovary syndrome susceptibility [15].

Our results have shown significant differences in the rs10463297 frequency of alleles in groups with and without gynecological pathology. Statistically significant association has been found between *SRA1* rs10463297 polymorphism and gynecological pathology occurrence in dominant and additive inheritance models. Consequently, TT-carriers had 2.6 times higher risk of gynecological pathology development than C-allele carriers; at the same time, they had 2.48 times higher risk of gynecological pathology occurrence than TC genotype carriers.

Conclusions

1. The frequency of *SRA1* rs10463297 alleles in patients with gynecological pathology is significantly different from the group without it ($P = 0.032$).

2. Statistically significant association between *SRA1* rs10463297 polymorphism and gynecological pathology occurrence in both dominant and additive models of inheritance ($P > 0.05$) has been found.

3. No association has been detected between *SRA1* rs801460 SNP and gynecological pathology development ($P > 0.05$).

4. *SRA1* rs10463297 TT carriers have 2.6 times higher risk of gynecological pathology development than C allele carriers and 2.48 times compared with TC carriers.

Prospects for future research. Further studies are necessary to expand the comparison groups and confirm results. Moreover, the association analysis between other *SRA1* SNPs and proliferative type of BBD development are needed for better understanding the lncRNA SRA role in BBD.

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References

[1] Djebali, S., Davis, C. A., Merkel, A., Dobin, A., Lassmann, T., Mortazavi, A., Tanzer, A., Lagarde, J., Lin, W., Schlesinger, F., Xue, C., Marinov, G. K., Khatun, J., Williams, B. A., Zaleski, C., Rozowsky, J., Röder, M., Kokocinski, F., Abdelhamid, R. F., Alioto, T., … Gingeras, T. R. (2012). Landscape of transcription in human cells. *Nature, 489*(7414), 101-108. https://doi.org/10.1038/nature11233

[2] Sanchez Calle, A., Kawamura, Y., Yamamoto, Y., Takeshita, F., & Ochiya, T. (2018). Emerging roles of long non-coding RNA in cancer. *Cancer Science*, *109*(7), 2093-2100. https://doi.org/10.1111/cas.13642

[3] Chi, Y., Wang, D., Wang, J., Yu, W., & Yang, J. (2019). Long Non-Coding RNA in the Pathogenesis of Cancers. *Cells, 8*(9), Article 1015. https://doi.org/10.3390/cells8091015

[4] Anastasiadou, E., Jacob, L. S., & Slack, F. J. (2018). Non-coding RNA networks in cancer. *Nature Reviews Cancer, 18*(1), 5-18. https://doi.org/10.1038/nrc.2017.99

[5] Lanz, R. B., McKenna, N. J., Onate, S. A., Albrecht, U., Wong, J., Tsai, S. Y., Tsai, M. J., & O'Malley, B. W. (1999). A Steroid Receptor Coactivator, SRA, Functions as an RNA and Is Present in an SRC-1 Complex. *Cell, 97*(1), 17-27. https://doi.org/10.1016/s0092-8674(00)80711-4

[6] Leygue, E. (2007). Steroid Receptor RNA Activator (SRA1): Unusual Bifaceted Gene Products with Suspected Relevance to Breast Cancer. *Nuclear Receptor Signaling, 5*(1), Article e006. https://doi.org/10.1621/nrs.05006

[7] Lanz, R. B., Chua, S. S., Barron, N., Söder, B. M., DeMayo, F., & O'Malley, B. W. (2003). Steroid Receptor RNA Activator Stimulates Proliferation as Well as Apoptosis In Vivo. *Molecular and Cellular Biology, 23*(20), 7163-7176. https://doi.org/10.1128/MCB.23.20.7163-7176.2003

[8] Clarke, R. B. (2004). Human breast cell proliferation and its relationship to steroid receptor expression. *Climacteric, 7*(2), 129-137. https://doi.org/10.1080/13697130410001713751

[9] Sheng, L., Ye, L., Zhang, D., Cawthorn, W. P., & Xu, B. (2018). New Insights Into the Long Non-coding RNA SRA: Physiological Functions and Mechanisms of Action. *Frontiers in Medicine*, *5*, Article 244. https://doi.org/10.3389/fmed.2018.00244

[10] Sherry, S. T., Ward, M. H., Kholodov, M., Baker, J., Phan, L., Smigielski, E. M., & Sirotkin, K. (2001). dbSNP: the NCBI database of genetic variation. *Nucleic Acids Research, 29*(1), 308-311. https://doi.org/10.1093/nar/29.1.308

[11] Calhoun, B. C., Grobmyer, S. R., & Simpson, J. F. (2018). 8 – Benign, High-Risk, and Premalignant Lesions of the Breast. In K. I. Bland, E. M. Copeland, V. S. Klimberg & W. J. Gradishar (Eds.), *The Breast* (pp. 116-129.e3). Elsevier. https://doi.org/10.1016/b978-0-323-35955-9.00008-8

[12] International Agency for Research on Cancer. (n.d.). CANCER TODAY. Data visualization tools for exploring the global cancer burden in 2020. https://gco.iarc.fr/today/home

[13] Sasaki, J., Geletzke, A., Kass, R. B., Klimberg, V. S., Copeland, E. M., & Bland, K. I. (2018). 5 – Etiology and Management of Benign Breast Disease. In K. I. Bland, E. M. Copeland, V. S. Klimberg & W. J. Gradishar (Eds.), *The Breast* (pp. 79-92.e5). Elsevier. https://doi.org/10.1016/b978-0-323-35955-9.00005-2

[14] Yan, R., Wang, K., Peng, R., Wang, S., Cao, J., Wang, P., & Song, C. (2016). Genetic variants in lncRNA SRA and risk of breast cancer. *Oncotarget, 7*(16), 22486-22496. https://doi.org/10.18632/oncotarget.7995

[15] Tan, J., Hao, X., Zhao, T., Ying, J., Li, T., & Cheng, L. (2020). Association between long-chain non-coding RNA SRA1 gene single-nucleotide polymorphism and polycystic ovary syndrome susceptibility. *Journal of Assisted Reproduction and Genetics, 37*(10), 2513-2523. https://doi.org/10.1007/s10815-020-01922-3