© Curr Gynecol Oncol 2020, 18 (2), p. e46–e56
DOI: 10.15557/CGO.2020.0010

Received: 06.04.2020
Accepted: 12.10.2020
Published: 31.12.2020

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The role of long non-coding RNA (lncRNA) in the development of ovarian cancer

Rola długich niekodujących RNA (lncRNA) w raku jajnika

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Abstract

The aim of this study was to review research on the role of long non-coding RNA (lncRNA) in ovarian cancer. This article analyses studies on the effect of increased lncRNA expression on the size of ovarian cancer and the incidence of metastasis. The review covers a period from October 15, 2018 to August 22, 2020, and comprises 23 studies in which a total of 1,580 women with ovarian cancer participated, and an undetermined number of control groups where healthy tissue samples were collected. A review of the studies indicates that increased lncRNA expression is associated with elevated ovarian cancer size and metastatic risk. The most studied lncRNA include *HOTAIR*, *CCAT2*, *GAS5*, *MALAT-1*, *UCA1*. Studies assessing the expression levels of *HOTAIR* lncRNA and *CCAT2* in normal and cancer tissue showed varying levels of expression in studies of different authors, which indicates that the expression of the same lncRNA may vary individually or is a result of study errors.

Keywords: lncRNA, ovarian cancer, expression, FIGO

Streszczenie

Celem pracy był przegląd badań dotyczących oceny roli długiego, niekodującego RNA (*long non-coding RNA*, lncRNA) w raku jajnika. W artykule dokonano przeglądu badań dotyczących wpływu zwiększonej ekspresji lncRNA na rozmiar raka jajnika i występowanie przerzutów. Przeglądu badań dokonano w okresie od 15 października 2018 do 22 sierpnia 2020 roku. W przeglądzie uwzględniono 23 badania, w których łącznie wzięło udział 1580 kobiet z rakiem jajnika oraz nieokreślona liczba osób z grup kontrolnych, od których pobrano zdrowe tkanki. Przegląd badań wskazuje, że zwiększona ekspresja lncRNA jest związana ze zwiększonym rozmiarem raka jajnika oraz przerzutami. Najczęściej badane lncRNA to: *HOTAIR*, *CCAT2*, *GAS5*, *MALAT-1*, *UCA1*. Badania, które oceniły poziom ekspresji lncRNA *HOTAIR* oraz *CCAT2* w tkance zdrowej i nowotworowej, wykazały różne poziomy ekspresji u różnych autorów, co świadczy o tym, że ekspresja tego samego lncRNA może być zmienna osobniczo lub jest wynikiem błędów w przeprowadzonym badaniu.

Słowa kluczowe: lncRNA, rak jajnika, ekspresja, FIGO

INTRODUCTION

An important achievement of biology in the second half of the twentieth century was the understanding of the molecular processes underlying the expression of genetic information. Information created at that time seemed to be precise and completely describe the scheme of living organisms. The information was mainly focused on deoxyribonucleic acid (DNA) as an information carrier and proteins, i.e. the final product. Ribonucleic acid (RNA) molecules were attributed with the secondary role as an intermediary in protein biosynthesis. RNA is a polymer consisting of nucleotides composed of ribose, a phosphate residue, and one of four nitrogen bases: adenine, guanine, cytosine or uracil. Today, the knowledge about the functioning of RNA is much wider. It is known that RNA is not only a skeleton that binds proteins or an adapter that enables translation. The current state of knowledge warrants the conclusion that RNA is directly involved in the synthesis of proteins, and is a cofactor involved in many biochemical processes or affecting the structure of the genome[1]. Biology textbooks divide RNA into messenger (mRNA) and non-coding RNA (ncRNA). Among ncRNA, housekeeping RNA and regulatory RNA are distinguished. Housekeeping RNA includes rRNA, tRNA, snoRNA. Regulatory RNA is divided into short ncRNA (<200 base pairs), long ncRNA (lncRNA) (>200 base pairs), and very long ncRNA (>100,000 base pairs). Short-coding RNA includes miRNA, siRNA, piRNA, tsRNA (Fig. 1)[2]. The amount of lncRNA outweighs the amount of short ncRNA. Most lncRNA is present in the nucleus and cytoplasm[3]. Recent research results indicate that lncRNA may be involved in the development of ovarian cancer. An increased level of lncRNA expression is associated with increased tumor size[4] as well as lower predicted survival outcomes[5]. Studies reveal that the level of lncRNA expression is not dependent on the histological type[6]. The World Health Organization (2014) distinguishes the following histological types of ovarian cancer: serous cancer, mucous carcinoma, endometrioid cancer, clear cell carcinoma, transitional cell carcinoma, Brenner tumor, squamous cell carcinoma, mixed cancer, undifferentiated cancer, sarcoma carcinoma, and granulomatosis[7].

ETIOLOGY OF OVARIAN CANCER

Over 95% of malignant ovarian tumors have epithelial origin. The most important risk factors include *BRCA1* and *BRCA2* mutation carriers, hereditary ovarian cancer syndromes, childlessness, hereditary ovarian and breast cancer syndromes, hereditary ovarian cancer, and familial

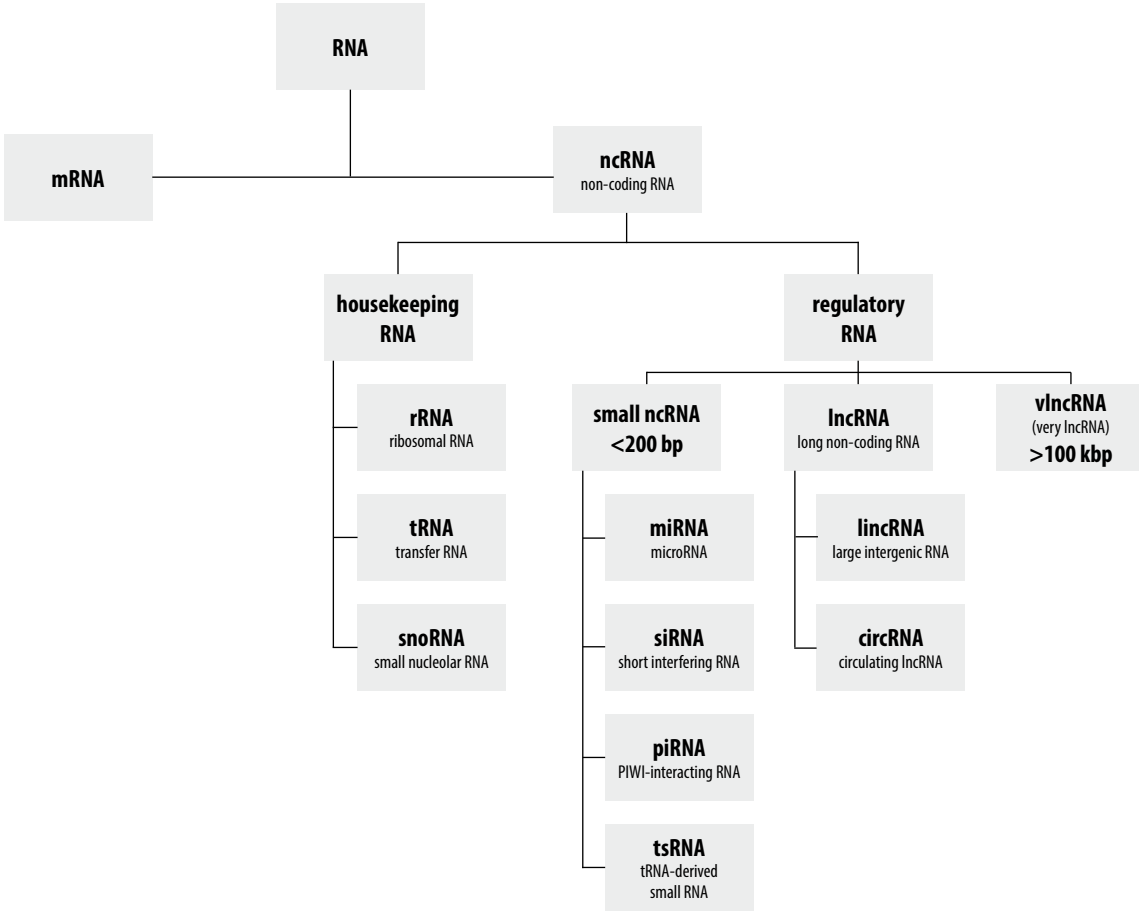

Fig. 1. RNA division[2]

 DOI: 10.15557/CGO.2020.0010

occurrence of non-globular colorectal cancer. Factors that reduce the risk of ovarian cancer include hormonal contraception, fallopian tube occlusion, uterus excision, and breastfeeding[8].

HISTOLOGICAL TYPES OF OVARIAN CANCER AND THEIR CHARACTERISTICS

Nowak-Markwitz and Spaczyński divide ovarian cancer into two types. Type I is characterized by a diagnosis at a less advanced stage, slow growth and low sensitivity to chemotherapy, and good prognosis. Type I comprises serous, endometrial, mucosal, clear cell carcinomas and Brenner cancers. Type II of ovarian cancer is diagnosed at stages III and IV. Type II is characterized by rapid growth and high sensitivity to chemotherapy, and poor prognosis. Type II comprises serous, endometrial, undifferentiated and sarcoma carcinomas[9] (Tab. 1).

EFFECT OF LNCRNA EXPRESSION ON THE SURVIVAL OF PATIENTS WITH OVARIAN CANCER

LncRNA does not have the translation potential due to the presence of multiple stop codons in mature transcripts[13]. However, the lack of protein coding and the absence of translation potential does not mean that lncRNA does not carry any information or perform any function[1]. The available literature does not contain precise information on the role of lncRNA in the process of protein biosynthesis and their exact function in the cancerous process. Studies conducted so far have focused on associations between increased expression of lncRNA and tumor development and its increased size or involvement in the proliferation and migration of tumor cells[14]. siRNA potentially contributes to lower expression of lncRNA *NONRATT021972* as with other epigenetic mechanisms. Liu et al. (2016) observed that as a result of siRNA activity, the expression may be lowered by 0.5 in relation to the expression in which siRNA transfection was not applied[15]. In the majority of studies conducted to date, the exact impact of siRNA on the level of lncRNA expression has not been assessed, and the moment at which it is joined is not known. According to the literature data, some of them may have a prognostic value. Ning et al. (2018) conducted a meta-analysis to determine the impact of lncRNA expression on the survival of patients. A total of 15 studies evaluating 1,333 patients were included in the analysis. The results of the study predict a higher risk of death for patients with its increased level ($p > 0.05$). Another meta-analysis evaluated the effect of lncRNA expression on the survival time of patients based on its exact formula. A total of 14 studies were included in the study, with 1,276 participating patients. The results predict a higher risk of death in patients with its increased level ($p > 0.05$). The presented studies included the work of Xia et al. (2017) with the Kaplan–Meier curve, which presents the prognosis of survival of people at low and high level of lncRNA *ZFAS1* over consecutive months. The Kaplan–Meier curve predicts that a high level of lncRNA may be associated with the death of 35% of patients 60 months after surgery ($p < 0.05$), and in the case of women with its low level, 40% of patients may die after approximately 65 months. Similar data was reported in the paper by Cheng et al. (2015). According to their results, 55% of patients with a high level of lncRNA *AB073614* are expected to die after ca. 35 months ($p < 0.05$), and in the case of its low level, 50% of patients after 50 months are expected to die. The results obtained by Li et al. (2017) suggest a statistically significant difference between the predicted survival time of patients with low and high levels of lncRNA *SPRY 4-IT1* expression. The death of 25% of patients with high levels of expression is expected after ca. 50 months, and approximately 55% with low levels after ca. 50 months[5,16–21]. The results reported in the paper by Ning et al. (2018) indicate a very poor survival prognosis of patients who participated in the studies included in the meta-analysis.

Histological type of ovarian cancer	Characteristics	Accompanying molecular changes
Serous cancer	The glandular epithelium differentiates towards the phenotype of oviduct epithelial cells. In serous adenocarcinoma, a variety of glandular weaving is found depending on the stage of cancer.	Mutations in the *KRAS* gene (protooncogene Kristen rat sarcoma viral oncogene homolog) or *BRAF* (protooncogene B-Raf proto-oncogene)
Endometrioid cancer	The group of endometrioid ovarian tumors includes phenotypically equivalent proliferations of all types of cancer that may develop in the endometrial mucosa. In order to make an endometrial tumor diagnosis, no histological diagnosis of endometriosis is necessary.	Mutations of the *PTEN* gene (phosphatase, suppressor protein), *PIK3CA* (gene coding the PI3K kinase catalytic subunit), *CTNNB1* (gene coding β-catenin)
Mucosal tumor	They have glandular epithelium in their woven cells, containing neutral glucosamine (mucins) in the cytoplasm. Glandular epithelial cells are phenotypically similar to cells of different mature epithelia producing mucus (intestinal, glandular cells of the pylorus of the pyloric part).	Mutations in the *KRAS* gene and *HER2* overexpression (superficial growth factor receptor)
Clear cell carcinoma	Dispatch through epithelium, cells which have a clear cytoplasm or sometimes take on the hobnail appearance.	Mutations in the *TGF-β RII* gene (transforming the growth factor, receptor β II)
Sarcoma	Non-epithelial origin derived from connective tissue	Mutations in *TP53*
Undifferentiated ovarian cancer	-	-

Tab. 1. Characteristics of different histological types of ovarian cancer[10–12]

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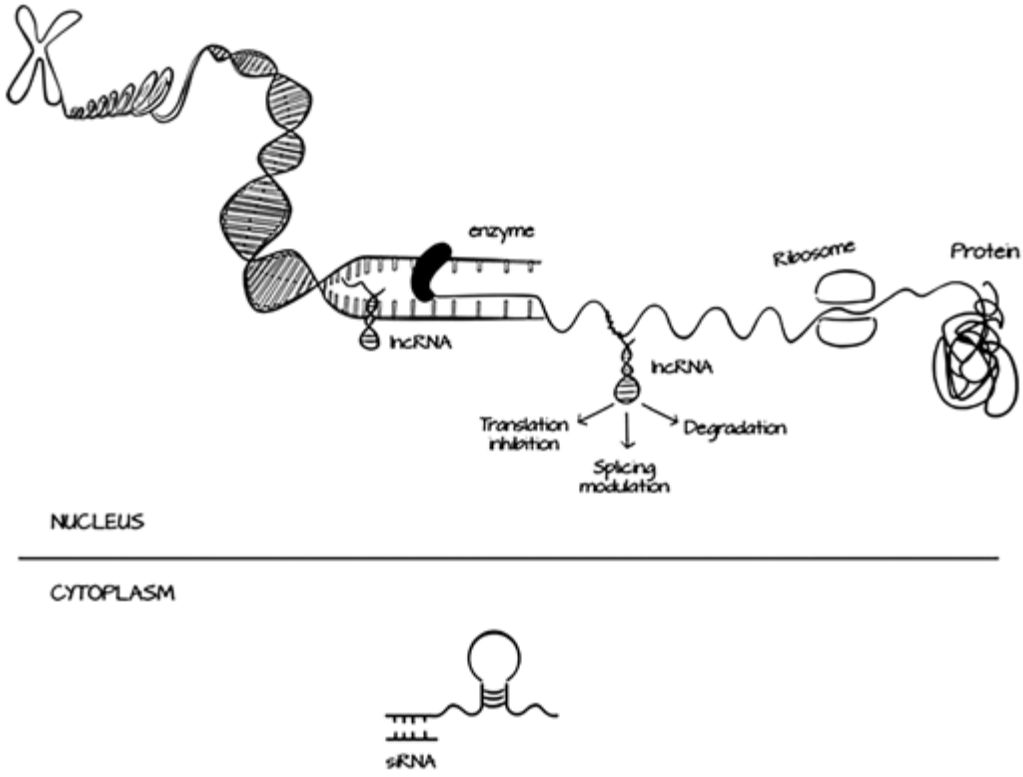

Fig. 2. Molecular function of lncRNA[26,27]

On the basis of only predicted values, it cannot be determined whether and to what extent an increased expression of lncRNA affects the survival time of patients[5]. Worku et al. (2017) in their study compiled 20 lncRNA and attributed the role they play in the cancer process. The analysis compared studies involving humans and animals, demonstrating that increased or decreased expression of ovarian cancer in lncRNA contributes to increased cell proliferation and migration, but there is no description of the underlying mechanism that is responsible for this observation[20].

ROLE OF lncRNA IN THE TRANSCRIPTION AND TRANSLATION PROCESS

According to high school textbooks, the process of protein biosynthesis begins with the attachment of polymerase to the gene promoter and dehydration of the DNA double helix. RNA polymerase moves along the DNA strand and unravels it, adding subsequent nucleotides to the mRNA strand[2,21]. In the next step of protein biosynthesis (translation), at first the ribosomal subunit attaches to the end of 5' mRNA, and the START (AUG) codon is attached with tRNA (transporting RNA). During the elongation and termination step, tRNA is carried by consecutive codons until the STOP codon is provided (at the termination stage) by tRNA to terminate the production of the polypeptide chain. In the biosynthesis process, miRNA proteins are responsible for regulating gene expression by joining this 6 nucleotide strand to mRNA and matching their nucleotides, as in the case to tRNA and mRNA, provided that the degradation of the mRNA strand is an effect of miRNA attachment to mRNA. When the complementarity is incomplete, the process of protein biosynthesis is blocked. siRNA is also responsible for the silencing of gene expression. siRNA at the time of connection with the complementary strand of mRNA contributes to the fact that the mRNA strands are cleaved, which prevents the formation of coded protein[21,22]. At the time when the splicing of intronic regions takes place in the transcription process, after it ends there may be degradation of genetic material by the enzyme or protein that has been synthesized. The RNA types mentioned in school textbooks include ribosomal RNA (rRNA), whose molecules are a component of ribosomes – structures where proteins are synthesized, and small nuclear RNA (snRNA), which are involved in the pre-mRNA assembly process the main stage of maturation – transforming the primary transcript of genes encoding mRNA proteins. School textbooks do not describe the exact mechanism of ribosome formation from rRNA, and how it goes into their construction. According to the data reported by de la Cruz et al. (1999) DNA, as a result of rRNA transcription, leads to the formation of mRNA of which the polypeptide chain is biosynthesized, from which ribosomes are then biosynthesized[23]. The literature data indicates that the mechanism of protein biosynthesis is in fact more complicated, and more types of RNA are involved in it. Numerous studies were published, attempting to describe the functions of lncRNA in this process. Osielska and Jagodziński (2018)

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indicate that the epigenetic mechanism of lncRNA action depends on its potential attachment to tRNA in the translation process, however, their study shows that the attachment of lncRNA occurs when tRNA is connected to three ribosomes[2]. Usually, one ribosome is involved in the translation process[21]. Carpenter (2016) argues that lncRNA may play a role in the transcription process. The author does not discuss whether lncRNA is transcribed into mRNA and is a non-coding fragment of an exon that is included in the process of translation into protein biosynthesis or is an intron not transmitted to mRNA and under the influence of polymerase the lncRNA section is separated from the mRNA fragment, and lncRNA thus created participates in epigenetic mechanisms[24]. mRNA may be reverse-transcribed, resulting in the re-formation of DNA that can be stored in the form of chromosomes by wrapping into histones. Despite the lack of accurate information on whether lncRNA is prescribed for mRNA and is subject to the transcription and translation process like the other genes, or the translation process takes place, lncRNA is an intron and is excreted in the transcription process. Based on the information contained in the gene bank, it can be assumed that lncRNA ultimately undergoes reverse transcription and is found on one of the chromosomes[24,25] (Fig. 2).

CHARACTERISTICS OF lncRNA IN OVARIAN CANCER

HOTAIR is located on chromosome 12. According to the Gene Bank database, even though it is a non-coding region, no protein products are attributed to it, and the effect of increased *HOTAIR* lncRNA expression is the binding of lysine demethylase (LSD 1) and repulsive complex 2 Polycomb (*PRC2*) and it serves as scaffolding to connect these regulators to the *HOXD* gene cluster. The available literature lacks data on the method of binding of the above-mentioned compounds.

MALAT is located on chromosome 11. According to Gene Bank, it controls the transcription process and is stored in the nucleus, where it forms a framework for ribonucleoprotein complexes (which include miRNA), which are responsible for blocking the translation process. It can be assumed that this segment is subject to the process of splicing before the translation process, due to the formation of ribonucleoprotein complexes. The available literature lacks a description of the exact mechanism that leads to the incorporation of lncRNA *MALAT* into these complexes.

GAS5 is located on chromosome 6, and the product of this gene is lncRNA. According to Gen Cards, the component of this lncRNA is snoRNA.

HOXA11 according to Gene Bank, is located on chromosome 6 and the result of its action is the impact on the rate of expression of other chromosome 6 genes, the product of which is a protein. According to the Gen Cards data *HOXA11* encodes a protein, but there are no literature reports that would address the product of its expression. There is no data about the functions of some lncRNA in the Gene Bank, including *ANRIL*, *UCA1*, *CCAT2*, *BC200*, *TUG1*, *LNCRSR*, *RAD51-AS1*, *DARS-AS1*, *LSINCT5*, *AFAP-1AS1*, *lncSOX4*, *SNHG20*[28] (tab. 2).

METHODOLOGY

The PubMed database was systematically searched to identify studies that assessed the role of lncRNA in ovarian cancer. The effect of lncRNA expression on tumor size was evaluated. The following phrases were searched: ovarian cancer lncRNA (350 publications), lncRNA ovarian cancer review (36 publications), lncRNA ovarian cancer meta-analysis (11 publications), *MALAT* lncRNA ovarian cancer (4 publications), lncRNA ovarian cancer *H19* (32 publications), lncRNA ovarian cancer *HOTAIR* (23 publications), lncRNA ovarian cancer *HOST2* (2 publications), lncRNA ovarian cancer *UCA1* (15 publications), lncRNA ovarian cancer *PVT1* (1 publication), lncRNA *SNHG20* ovarian cancer (3 publication), and lncRNA *RAD51-AS1* ovarian cancer (1 publication), covering a period from October 15, 2018 to 22 August, 2020. The review included studies conducted among women with ovarian cancer that included information about the size of the study and control groups, which consisted of tissue samples collected from women with cancer involving sites that were not covered by the disease process, and the level of lncRNA expression in cancer tissue and healthy tissue. The review excluded studies conducted on animals and humans which provided no information about the size of the study group and the level of lncRNA expression. Also, the review did not include studies in which the control group consisted of women with benign ovarian cancer or the study group comprised patients with varying degrees of sensitivity to cisplatin.

SUMMARY

Previously conducted reviews of studies and meta-analyses concerned with the assessment of the role of lncRNA in ovarian cancer did not comprise all studies, and there are no exact data on the impact of different lncRNA on tumor size. The most frequently studied lncRNA included *HOTAIR*, *CCAT2*, *GAS5*, *MALAT*, *MALAT-1*, *UCA1*. In the studies carried out to date, the differences in lncRNA expression in healthy and cancerous tissue were typically evaluated without assessing the difference between lncRNA expression in the healthy and cancerous tissues with varying FIGO (International Federation of Gynecology and Obstetrics) stages. The results of eleven studies indicate that increased expression of lncRNA contributes to tumor growth ($p < 0.05$), and the findings obtained in eight studies indicate that increased lncRNA expression is related to metastases. Research carried out to date lacks accurate data that would indicate to what extent increased or decreased expression of lncRNA increases the size of the tumor. Studies evaluating the expression level in the *HOTAIR* or *CCAT2* lncRNA gene in

Author	Type of lncRNA	Population	Age [years]	Type of cancer and size of tumor	Treatment method	Level of lncRNA expression	Results
Zhang et al. (2016)[4]	*HOTAIR*	Study group: $n = 30$ Control group: $n = 30$***	45.8 ± 10.5	No data	Surgical treatment	Healthy tissue: 1.00** Ovarian cancer tissue: 3.00–9.00** <5 cm: 2.00** >5 cm: 4.00–13.00**	A statistically significant difference was observed in the level of *HOTAIR* lncRNA expression in the healthy tissue in relation to ovarian cancer tissue ($p < 0.05$) A statistically significant difference was observed in the level of *HOTAIR* lncRNA expression of the ovarian cancer size <5 cm in relation to ovarian cancer >5 cm ($p < 0.05$)
Qiu et al. (2015)[29]	*HOTAIR*	Study group: $n = 68$ Control group: $n = 30$	<50: $n = 26$ ≥50: $n = 42$	FIGO classification: • FIGO I/II: $n = 19$ • FIGO III/IV: $n = 49$ Tumor size: • <1 cm: $n = 46$ • ≥1 cm: $n = 22$	Surgical treatment	Healthy tissue: 0.000–0.001** Ovarian cancer tissue: 0.000–0.005**	Statistically significant difference in the level of *HOTAIR* lncRNA expression in the healthy tissue in relation to ovarian cancer tissue ($p < 0.05$)
Chang et al. (2018)[30]	*HOTAIR* *CCND1* *CCND2*	Study group: $n = 92$ Control group: $n = 92$***	≤55: $n = 41$ >55: $n = 51$	FIGO classification: • I + II: $n = 60$ • III + IV: $n = 32$ Histological type: • well: $n = 27$ • moderate: $n = 48$ • poor: $n = 17$	Surgical treatment	*HOTAIR*: • healthy tissue: 0.1–3.9** • cancer tissue: 0.3–7.2** *CCND1*: • healthy tissue: w0.1–1.5** • cancer tissue: 0.6–2.0** *CCND2*: • healthy tissue 0.1–2.3** • cancer tissue: 1.0–6.0**	Statistically significant difference in *HOTAIR* lncRNA expression, *CCND1* and *CCND2* between the healthy and cancerous tissue ($p < 0.05$) Relationship between *HOTAIR* lncRNA and *CCND1* expression ($r = 0.6784$, $p < 0.001$) Relationship between *HOTAIR* lncRNA and *CCND2* expression ($r = 0.4884$, $p < 0.001$)
Huang et al. (2016)[19]	*CCAT2*	Study group: $n = 109$ Control group: $n = 45$	<55: $n = 50$ ≥55: $n = 59$	FIGO classification: • I/II: $n = 33$ • III/IV: $n = 76$ Histological type: • serous cancer: $n = 78$ • mucinous: $n = 7$ • endodermal cancer: $n = 8$ • clear cell: $n = 9$ • others: $n = 7$ Tumor size: • ≤10 cm: $n = 62$ • >10 cm: $n = 47$	Surgical treatment and chemotherapy paclitaxel (135 mg/m^2) and cisplatin (75 mg/m^2) or paclitaxel (175 mg/m^2) and carboplatin (AUC 6) administered for 3 weeks in 6 cycles	Healthy tissue: 0.0–1.0** Ovarian cancer tissue: 0.0–4.8**	No statistically significant difference in *CCAT* lncRNA expression between groups of different histological types ($p > 0.05$) Statistically significant difference in the level of *CCAT* lncRNA expression between groups with different FIGO classification ($p < 0.05$)
Hua et al. (2018)[31]	*CCAT2*	Study group: $n = 31$ Control group: $n = 31$***	No data	No data	Surgical treatment	Healthy tissue: 0.01–0.09** Ovarian cancer tissue: 0.03–0.13**	Statistically significant difference in the level of *CCAT2* lncRNA expression in the healthy and cancerous tissue ($p < 0.05$)
Yim et al. (2017)[32]	*HOXA11*	Study group: $n = 129$ Control group: $n = 38$	Low expression: average of 54.7 years High expression: average of 54.6 years	FIGO classification: • I: $n = 6$ • II: $n = 5$ • III: $n = 87$ • IV: $n = 31$ Tumor size: • ≤1 cm: $n = 108$ • >1 cm: $n = 21$	Surgical treatment. Exclusion from the study group of patients who received surgical chemotherapy	Healthy tissue: 0** Cancer tissue: 0–800**	*HOXA11* lncRNA expression in cancerous tissue was 77 times higher than in the healthy tissue ($p < 0.05$)

Tab. 2. Summary of tests included in the review

DOI: 10.15557/CGO.2020.0010

Wu et al. (2016)[33]	*BC200*	Study group: $n = 22$ Control group: $n = 10$	No data	Histological type: • serous cancer: $n = 8$ • endometrial cancer: $n = 2$ • mucosal cancer: $n = 2$	No data	Healthy tissue: 0.01–2.50** Cancer tissue: 0.00–0.02**	The expression level *BC200* lncRNA is reduced in ovarian cancer tissue
Li et al. (2016)[34]	*GAS5*	Study group: $n = 63$ Control group: $n = 63$	≤55: $n = 29$ >55: $n = 34$	FIGO classification: • I: $n = 8$ • II: $n = 22$ • III: $n = 27$ • IV: $n = 6$ Tumor size: • <5 cm: $n = 33$ • ≥5 cm: $n = 21$	Surgical treatment. No data about the use of chemotherapy	Healthy tissue: 0.5–3.0** Cancer tissue: 0.0–2.0**	Statistically significant difference in the level of *GAS5* lncRNA expression in the healthy and cancerous tissue ($p < 0.05$)
Li et al. (2018)[35]	*GAS5*	Study group: $n = 20$ Control group: $n = 20$***	No data	No data	Surgical treatment	Healthy tissue: 0.5–3.2** Cancer tissue: 0.2–2.3**	Statistically significant difference in the level of *GAS5* lncRNA expression in the healthy and cancerous tissue ($p < 0.05$)
Ma et al. (2018)[36]	*GAS5* *SPRY2*	Study group: $n = 53$ Control group: $n = 53$***	Average of 58.3 years: 37–69 <55: $n = 22$ ≥55: $n = 31$	FIGO classification: • I–II: $n = 32$ • III–IV: $n = 21$ Histological type: • well/moderate: $n = 38$ • poor: $n = 15$	Surgical treatment	GAS5: • healthy tissue: 0.1–5.8** • cancer tissue: 0.0–3.0** SPRY2: • healthy tissue: 0.5–12.0** • cancer tissue: 0.0–7.00**	Statistically significant difference in the level of *GAS5* lncRNA expression in the healthy and cancerous tissue ($p < 0.05$) Statistically significant difference in the level of *SPRY2* lncRNA expression in the healthy and cancerous tissue ($p < 0.05$)
Zou et al. (2016)[37]	*MALAT*	Study group: $n = 20$ Control group: $n = 20$	27–69	No data	Surgical treatment. No use of chemotherapy	Healthy tissue: 0.8–1.3** Cancer tissue: 1.6–2.8**	Statistically significant difference in the level of *MALAT-1* lncRNA expression between the healthy and cancerous tissue ($p < 0.05$) Significant relationship between the level of *MALAT* lncRNA expression and the tumor size (in cm) ($r^2 = 0.78$; $p < 0.05$)
Jin et al. (2017)[38]	*MALAT*	Study group: $n = 64$ Exclusion of women with borderline ovarian cancer who have two or more tumors Control group: $n = 30$	No data	No data	Surgical treatment. Patients were given hormone therapy, radiotherapy or chemotherapy before surgery	Healthy tissue: 5–18** Ovarian cancer tissue: 10–27**	Statistically significant difference in the level of *MALAT-1* lncRNA expression between the healthy and cancerous tissue ($p < 0.05$)
Lei et al. (2017)[39]	*MALAT-1*	Study group: $n = 30$ Control group: $n = 30$***	No data	No data	Surgical treatment	Healthy tissue: 0.1–4.0** Cancer tissue: 4.3–13.0**	Statistically significant difference in the level of *MALAT-1* lncRNA expression between the healthy and cancerous tissue ($p < 0.05$)
Zhou et al. (2016)[6]	*MALAT-1*	Study group: $n = 45$ Control group: $n = 37$	<50: $n = 19$ >50: $n = 26$	Histological type: • serum: $n = 21$ • mucous: $n = 24$ FIGO classification: • I/II: $n = 21$ • III/IV: $n = 24$	Surgical treatment	Cancer tissue: • FIGO I/II: 1.009 • FIGO III/IV: 7.189 • serous cancer: 5.537 • mucous cancer: 3.227 Healthy tissue: 0.0–6.0** Cancer tissue: 0.0–100**	Statistically significant difference between *MALAT-1* lncRNA expression in tumor tissue, which was classified to different sizes according to the FIGO classification ($p < 0.05$) No statistically significant difference between *MALAT-1* lncRNA expression in cancer tissue that has been classified to various histological types (serous or mucosal) ($p > 0.05$) Statistically significant difference in the level of *MALAT-1* lncRNA expression in the healthy and cancerous tissue ($p < 0.05$)

Tab. 2. Summary of tests included in the review (cont.)

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Qiu et al. (2016)[40]	*ANRIL*	Study group: $n = 102$ Group with low *ANRIL* expression: $n = 51$ Group with high *ANRIL* expression: $n = 51$ Control group: $n = 30$	Group with low *ANRIL* expression <50: $n = 18$ ≥50: $n = 33$ Group with high *ANRIL* expression <50: $n = 23$ ≥50: $n = 28$	FIGO classification: • I–II: ◦ low *ANRIL* expression: $n = 25$ ◦ high *ANRIL* expression: $n = 8$ • III–IV: ◦ low *ANRIL* expression: $n = 26$ ◦ high *ANRIL* expression: $n = 43$ Tumor size: • <1 cm: ◦ low *ANRIL* expression: $n = 24$ ◦ high *ANRIL* expression: $n = 18$ • ≥1 cm: ◦ low *ANRIL* expression: $n = 27$ ◦ high *ANRIL* expression: $n = 33$ Type of cancer: • serous cancer: ◦ low *ANRIL* expression: $n = 31$ ◦ high *ANRIL* expression: $n = 37$ • other cancer: ◦ low *ANRIL* expression: $n = 20$ ◦ high *ANRIL* expression: $n = 14$	Surgical treatment	Healthy tissue: 0.000–0.001** Cancer tissue: 0.000–0.009**	Statistically significant difference in *ANRIL* lncRNA expression in the healthy and cancerous tissue ($p < 0.05$)
Yang et al. (2016)[41]	*UCA1*	Study group: $n = 53$ Control group: $n = 29$	<50: $n = 24$ ≥50: $n = 29$	FIGO classification: • I–II: $n = 21$ • III–IV: $n = 32$ Tumor size: • <8 cm: $n = 28$ • ≥8 cm: $n = 25$ Histological type: • mucous: $n = 21$ • other: $n = 32$	Surgical treatment	Healthy tissue: 0.0–0.25** Cancer tissue: 0.0–0.45**	Statistically significant difference in the level of *UCA1* lncRNA expression between healthy and cancerous tissue ($p < 0.05$)
Zhang et al. (2016)[42]	*UCA1*	Study group: $n = 117$ Control group: $n = 117$***	≤60: $n = 43$ >60: $n = 74$	Tumor size: • <3 cm: $n = 57$ • ≥3 cm: $n = 46$ Histological type: • serous: $n = 60$ • other: $n = 52$	Surgical treatment. Before the surgery, chemotherapy, immunotherapy, radiotherapy treatment were not used	Healthy tissue: 0.0–0.5** Ovarian cancer tissue: 0.0–5.8** FIGO classification: • I + II: 0.0–4.5** • III + IV: 0.0–6.5** No metastases to lymph nodes: 0.0–5.5** Metastases to lymph nodes: 0.0–7.5**	Statistically significant difference in the level of *UCA1* lncRNA expression between healthy tissue and ovarian cancer tissue ($p < 0.05$) Statistically significant difference in the level of *UCA1* lncRNA expression between women who had metastases to lymph nodes and women in whom they were not observed ($p < 0.05$) Statistically significant difference in the level of *UCA1* lncRNA expression between women diagnosed with ovarian cancer classified as FIGO I + II and FIGO III + IV ($p < 0.05$)
Yang et al. (2016)[43]	*AFAP-1AS1*	Study group: $n = 130$ Control group: $n = 65$	≤60: $n = 48$ >60: $n = 82$	Tumor size: • <3 cm: $n = 70$ • ≥3 cm: $n = 60$ FIGO classification: • I + II: $n = 64$ • III + IV: $n = 66$ Histological type: • serous: $n = 86$ • other: $n = 44$	Surgical treatment. No treatment with chemotherapy and radiotherapy before surgical treatment	Healthy tissue: 0.0–1.5** Ovarian cancer tissue: 0.0–7.8**	Statistically significant difference between *AFAP-1AS1* lncRNA expression in the cancerous tissue and tissue of ovarian cancer ($p < 0.05$)

Tab. 2. Summary of tests included in the review (cont.)

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Liu et al. (2018)[44]	*lncSOX4*	Study group: $n = 30$ Control group: $n = 18$	46.2 ± 12.4 ≤55: $n = 17$ >55: $n = 13$	FIGO classification: • I–II: $n = 14$ • III–IV: $n = 16$ Tumor size: • <5 cm: $n = 14$ • ≥5 cm: $n = 16$	Surgical treatment	Healthy tissue: 0.15–2.3** Cancer tissue: 3.5–5.0**	Statistically significant difference in the level of *lncSOX4* lncRNA expression between the healthy tissue and cancerous tissue ($p < 0.05$)
He et al. (2018)[45]	*SNHG20*	Study group: $n = 30$ Control group: $n = 30$***	No data	No data	Surgical treatment	Healthy tissue: 0.3–1.2** Cancer tissue: 0.6–2.3**	Statistically significant difference between the level of *SNHG20* lncRNA expression in the healthy tissue and cancerous tissue ($p < 0.05$)
Kuang et al. (2016)[46]	*TUG1*	Study group: $n = 62$ Control group: $n = 62$***	≤51: $n = 20$ >51: $n = 42$	FIGO classification: • I/II: $n = 25$ • III/IV: $n = 37$ Tumor size: • ≤2 cm: $n = 45$ • >2 cm: $n = 17$	Surgical treatment	Healthy tissue: 0.0–22.0** Cancer tissue: 0.0–35.0**	Statistically significant difference in the level of expression lncRNA *TUG1* in the healthy and cancerous tissue ($p < 0.05$)
Zhang et al. (2017)[47]	*RAD51-AS1*	Study group: $n = 163$	No data	FIGO classification: • I/II: $n = 67$ • III/IV: $n = 62$	Surgical treatment	FIGO classification: • I: 0.7–4.0** • II: 0.7–4.0** • III: 1.8–4.0** • IV: 2.2–4.0**	Statistically significant difference in the level of *RAD51-AS1* lncRNA expression in the healthy and cancerous tissue ($p < 0.05$)
Long et al. (2018)[48]	*LSINCT5*	Study group: $n = 40$ Control group: $n = 30$	≤50: $n = 17$ ≥50: $n = 23$	FIGO classification: • I–II: $n = 17$ • III–IV: $n = 23$ Tumor size: • <1 cm: $n = 28$ • ≥1 cm: $n = 12$	Surgical treatment	Healthy tissue: 0.00–40** Cancer tissue: 1.00–80.00**	Statistically significant difference in the level of *LSINCT5* lncRNA expression in the healthy and cancerous tissue ($p < 0.05$)

FIGO – International Federation of Gynecology and Obstetrics;
n – group size;
p – statistical significance level ($p < 0.05$ – statistically significant difference, $p > 0.05$ – no statistical significance).

** Approximate value read from the graph.
*** No data on the exact size of the control group.

Tab. 2. Summary of tests included in the review (cont.)

DOI: 10.15557/CGO.2020.0010

ovarian cancer tissue and healthy tissue showed varying levels of expression in papers published by different authors, indicating that the expression of the same lncRNA can be variable individually or is attributable to study errors. Currently, there is no cytotoxic drug with an effect on lncRNA available on the market.

Conflict of interest

The author declares no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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DOI: 10.15557/CGO.2020.0010 CURR GYNECOL ONCOL 2020, 18 (2), p. e46–e56