

A REVIEW OF STUDIES ASSESSING THE INFLUENCE OF DIETARY FACTORS ON THE LEVEL OF LNCRNA EXPRESSION, WHOSE EPIGENETIC MECHANISMS CAN POTENTIALLY PARTICIPATE IN THE COURSE OF OVARIAN CANCER

PRZEGLĄD BADAŃ OCENIAJĄCYCH WPŁYW CZYNNIKÓW ŻYWIENIOWYCH NA POZIOM EKSPRESJI LNCRNA, KTÓRYCH MECHANIZMY EPIGENETYCZNE POTENCJALNIE MOGĄ BRAĆ UDZIAŁ W PRZEBIEGU RAKA JAJNIKA

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ABSTRACT

Research suggests that increased expression of long noncoding RNAs is a factor that can affect tumour size, and the level of their expression may depend on the increased fat intake, which can lead to obesity.

The aim of this work was assessment of the impact of nutritional intervention on the level of lncRNA expression. The PubMed and ScienceDirect bases were searched from December 31, 2018 to January 23, 2019 in order to find works that concern the effect of nutrition on the level of lncRNA expression. The following keywords were used: lncRNA + *high fat diet* (720 publications), lncRNA + *obesity* (142 publications), lncRNA + *dietary* (480 publications). 1342 works were found. No studies with the participation of people were found. The study excluded the works in which information was not provided on how to divide groups of test animals, prepare feed or measure the expression of lncRNA after the introduction of a specific diet. The review included 4 animal studies, in which a nutritional intervention was used and its impact on the level of lncRNA expression was assessed, and information about the duration of the study and the level of expression of the studied lncRNA were included.

Research shows that the use of high fat food (25% of fat) may contribute to a statistically significant increase or decrease in the level of the lncRNA.

Studies indicate that higher fat content in food intake may affect the level of lncRNA expression lacking the protein coding potential.

KEYWORDS: lncRNA, expression, high fat, obesity, dietary.

STRESZCZENIE

Badania sugerują, że zwiększona ekspresja długich niekodujących RNA jest czynnikiem, który może wpływać na rozmiar nowotworu, a poziom ich ekspresji może być uzależniony od zwiększonego spożycia tłuszczu, który może prowadzić do otyłości.

Celem pracy była ocena wpływu interwencji żywieniowej na poziom ekspresji lncRNA. Przeszukiwano bazę PubMed i ScienceDirect w okresie od 31 grudnia 2018 do 23 stycznia 2019 roku w celu znalezienia prac, które dotyczą wpływu żywienia na poziom ekspresji lncRNA. Użyto następujących słów kluczowych: lncRNA + *high fat diet* (dieta wysokotłuszczowa) (720 publikacji), lncRNA + *obesity* (otyłość) (142 publikacje), lncRNA + *dietary* (dieta) (480 publikacji). Znaleziono 1342 prace. Nie znaleziono badań z udziałem ludzi. Z przeglądu badań wykluczono prace, w których umieszczono informacje na temat sposobu podziału grup badanych zwierząt, przygotowania karmy bądź pomiaru ekspresji lncRNA po wprowadzeniu określonego sposobu żywienia. Do przeglądu włączono 4 badania z udziałem zwierząt, w których zastosowano interwencję żywieniową i oceniono jej wpływ na poziom ekspresji lncRNA, a także zawarto informacje o czasie trwania badania i poziomie ekspresji badanych lncRNA.

Badania wskazują, że zastosowanie karmy wysokotłuszczowej (25% tłuszczu) może przyczynić się do istotnego statystycznie zwiększenia lub obniżenia poziomu ekspresji lncRNA. Wyższa zawartość tłuszczu w spożywanym pokarmie może wpływać na poziom ekspresji lncRNA nieposiadających potencjału kodowania białek.

SŁOWA KLUCZOWE: rak jajnika, lncRNA, ekspresja, żywienie, otyłość.

Introduction

Obesity is not one of the most frequently mentioned risk factors for developing ovarian cancer, however, some literature data list it as a factor of increased risk

of developing ovarian cancer. In the case of neoplastic diseases of the digestive system, obesity is one of the main factors increasing the risk of cancer [1]. Kornafel et al. [2] list the following as the risk factors in the on-

colological recommendations: mutations BRCA1, BRCA2, childlessness, hereditary ovarian cancer syndromes. The following are listed as risk factors that reduce the incidence: use of hormonal contraception, occlusion of the fallopian tubes, removal of the fallopian tubes, breastfeeding [2, 3]. In a study conducted by Fong PC et al. [4] among 50 patients with ovarian cancer who had a mutation in the BRCA 1 and BRCA 2 gene, the mutation of BRCA1 c.185 del AG (14%, n = 7), BRCA 1 c. 5386 ins C (8%, x = 4), BRCA 1 c. 4184 del. TCAA (6%, n = 3), BRCA 2 .6174 del T (6%, n = 3) took place most often [4]. According to literature data for women with ovarian cancer, there is an increase or decrease in the level of lncRNA expression, such as, e.g. MALAT, HO-TAIR, GAS5. Increased expression in relation to healthy ovarian tissue is associated with increased tumour size ($p < 0,05$) [5, 6, 7], and one of the factors mentioned as affecting its expression is the diet. In the research conducted so far, only the effect of a high fat diet on the level of their expression was evaluated and the tests were carried out on animals [8, 9, 10, 11].

Obesity and hormonal management and ovarian cancer

According to FIGO classification, ovarian cancer can be classified according to the stage I (tumour limited to the ovary), II (tumour of one or both ovaries with occlusion of the minor pelvis), III (tumour of one or both ovaries, intraperitoneal metastasis outside the minor pelvis, metastases do retroperitoneal nodes) and IV (tumour of one or both ovaries, distant metastases). In the study conducted by Erond CO et al. [12] it was observed that in the study group cancer was classified more often to the III and IV stage of advancement for women with higher BMI. 34 women with BMI 30–25 kg/m² and 32 with BMI > 35 kg/m² and 25 women with BMI < 25 kg/m² were qualified to the III stage [2, 12]. In the study of Bae et al. HS (2014), an assessment of the effect of the body mass on the size of ovarian cancer was made based on patient cards from 5 different hospitals that came from January 2000 to February 2009. Finally, 236 patient cards were included that underwent surgery and at least 6 cycles of chemotherapy. Data on body mass and height come from the day of cancer diagnosis, which is three months before surgery. The studied group included 5 women with underweight, 86 with normal body mass, 69 with overweight, 64 women with obesity and 13 with the second degree obesity. There was no influence of body mass on the size of ovarian cancer and its histological type ($p < 0,05$) [13]. Obesity is a factor that increases the level of leptin (a hormone that informs about the feeling of fullness) in the blood, whose increased level may be involved in the cancer

process. Another hormone that is involved in the regulation of satiety and hunger is ghrelin, but it is not mentioned as a factor that is related to the cancer process. Slomian GI et al. [14] observed the impact of BMI on leptin concentration in patients with ovarian cancer and that its concentration decreased after chemotherapy ($p < 0,05$). Initially, the concentration was ($16,89 \pm 15,54$ ng/ml), and after chemotherapy ($21,77 \pm 14,69$ ug/ml) [14]. In a study carried out by Chin YT et al. (2017), in which artificial cancer cells were used and treated with leptin in various doses (0–100 nM) and OB3 (0–100 μ M), the level of gene expression and the number of tumour cells were determined. It was observed that the treatment of the SKOV-3 cell lines with leptin and OB3 affected their number. The number of cells after treatment of SKOV 3 with leptin at a dose of 1 nM and 10 nM was about 20×10^6 and in the case of the leptin dose of 100 nM about 55×10^6 . Such a difference was also observed in OVCAR-3 cell lines ($p < 0,05$). Treatment with a 10 nM leptin dose increased the number of cells to about 39×10^5 in relation to the initial number (about 37×10^5), on which leptin was not used. The insulin dose of 100 nM increased the number of cells to about 70×10^5 . The study assessed, among others, the level of HIF-1 α gene expression (hypoxia-induced factor), VEGF (vascular endothelial growth factor), ER α (alpha receptor oestrogen), OB-R (leptin receptor). It was observed that leptin and OB3 increased the expression of HIF-1 α , OB-R, ER α , VEGF genes [15]. According to Kurzyk A [16], tumour tissues are responsible for the production of VEGF, and its production is responsible for increasing the vascularization of the tumour and its size [16]. The research results collected so far do not provide information about the degree of malignancy characterized by ovarian cancer with a higher degree of vascularization. The angiogenesis test carried out by Laforga JB et al. [17] among 210 women with nipple cancer aged 23–87 showed that with a tumour size of 0–2 cm, the average number of vessels was 66/mm² (160/1000 cells), and in the case of > 5,0 cm 70/mm² (220/1000 cells). Laforga JB et al. [17] do not describe the accurate method for evaluating the number of vessels. There is no accurate data on the number of vessels with different tumour sizes among women with ovarian cancer [17]. The share of leptin in increasing the number of cancer cells (ovarian cancer) is indicated by Kasiappan R et al. [18], however, there are no specific figures [18]. According to the review of Mardas M et al. [19], there is one study that examines the effect of body weight on the survival of patients with ovarian cancer. The paper included in the review by Hess LM et al. [20] shows that during chemotherapy, no significant changes in body weight were observed and the survival time is predicted according to the Kaplan

Meier curve, which indicates a shorter survival time for patients with BMI 30 kg/m² in relation to patients with BMI < 25 kg/m² [19, 20]. In the study of Jin JH et al. [21], the level of leptin was assessed in a group of 52 women with ovarian cancer (BMI 23,34 kg/m²) and 18 healthy women (BMI 23,77 kg/m²). A higher level of leptin was observed in the group of healthy women (11,44 ± 1,13 ug/ml) in relation to the ovarian cancer group (8,25 ± 0,97 ug/ml) (p < 0,05) [21]. In the study of Chin YT et al. [15], ten-week mice were divided (n = 15) weighing 20 ~ 25 g into three groups and leptin (80 µg/kg), saline or OB3 (1 mg/kg) were administered intraperitoneally. Blood samples were collected one week before and 2 days after the injection. It was observed that leptin affects the concentration of phytotropin (FSH) and lutropin (LH) in mice blood (p < 0,05). Higher concentration of FSH and lower LH were observed in the leptin group compared to the control group [15]. The FSH hormone is considered to be the hormone which stimulates the growth of the number of cancer cells, however, there are no detailed data on this subject and research involving humans [22].

Nutrition and ovarian cancer

The changes in taste sensation, oral mucositis, nausea, vomiting, diarrhoea or constipation occurring during chemotherapy treatment adversely affect the nutritional status of patients. Constipation occurs in about 40% of patients and are mainly associated with the use of Vinca alkaloids. Treatment regimens containing entogenous cytostatics, such as cisplatin, cyclophosphamide intensify nausea and vomiting, reducing food supply, which may contribute to a reduction in food supply and, consequently, to malnutrition, which occurs in 70% of patients with ovarian cancer [23]. In the study by Mardas M et al. [24] in the group of women suffering from ovarian cancer of 44 women, in whom vomiting occurs during chemotherapy sometimes in 6%, often in 3% of women and very often in 0%. It has been observed that the consumption of lower total fat during chemo-

therapy is associated with vomiting (-0,47, p < 0,001) and nausea (-0,43, p < 0,01). A reverse correlation was observed between the occurrence of vomiting and the intake of chows with higher calories (-0,56; p < 0,001) and the carbohydrate content (-0,36, p < 0,05) and protein (-0,49, p < 0,001) in diet [24]. According to Mardas M et al. [25], based on a 7-day observation, cancer is associated with the fact that women with ovarian cancer change their eating habits. 44 women participated in the study, the nutrition method of whom was evaluated on the basis of the nutritional diary and the FFQ questionnaire. Women after using the first chemotherapy changed their way of eating and began to eat rye bread, vegetables, fruits, oils, nuts and sea chow more often. The diet was not different in terms of energy and nutritional value [25]. The same conclusions were reached by Dąbrowska O et al. [26]. In a study conducted on a group of 100 people with cancer aged 21–72, who had a short questionnaire assessing the correctness of eating habits, it was observed that despite social beliefs that health care is important, the declaration of people with cancer regarding caring for the state of health does not positively correlate with health practices [26].

Methodology

The PubMed and ScienceDirect bases were searched for in the period from December 31, 2018 to January 21, 2019 in order to find papers on the effect of nutrition on the level of lncRNA expression. The following keywords were used: lncRNA + high fat diet (720 publications), lncRNA + obesity (142 publications), lncRNA + dietary (480 publications). In total, 1342 works were found. The study review excluded works that had no accurate information on the conduct of the study, i.e. the method of dividing research groups and preparing chow for mice or measuring the lncRNA expression after the introduction of a specific diet. The review included 4 animal studies that used nutritional interventions and evaluated its effect on the level of the lncRNA expression and information on its duration.

Table 1. Summary of studies included in the review

Author	Study group	Duration	Methodology	Dietary intervention	Blood test results	Level of lncRNA expression
Huang BB et al. [8]	Mice on the 21 st day of life	14 weeks of chow intervention	Collection of white adipose tissue and ovary and measurement of 8 lncRNA expression (labelled as 1–8) and 13 genes (18 srRNA, Apof, Fads 2, Fam213b, Hsd17b7, Crim 1, Srebf 1, Aacsm5, Aacsm5, Aacs, Fapb5)	Group I (HFD) – fed with a high fat diet that consisted of 41% carbohydrates, 24% fats and 24% proteins Group II (Control) – Kaoxetel chow	HDL (mmol/l) (p < 0.05) Control group: about 2 HFD group: about 3 LDL (mmol/l) (p < 0.05) Control group: about -0.45 HFD group: about 0.6 Cholesterol (mmol/l) (p < 0.05) Control group: about 2.3 HFD group: about 3.0 Triglycerides (mmol/l) (p < 0.05) Control group: about 1.45 HFD group: about 1.5 Glucose (mmol/l) (p < 0.05) Week 9 Control group about 7 HFD group about 9 Week 11 Control group about 6 HFD group about 9 Week 13 Control group about 7 HFD group about 9	Ovary lncRNA 1: Control about 0.00001, HFD about 0.0035 lncRNA 2: Control about 0.0015, HFD 0.0035 lncRNA 3: Control about 0.01, HFD about 0.10 lncRNA 4: Control 0.12, HFD 0.07 Fat tissue lncRNA 5: Control about 0.0015, HFD about 0.0004 lncRNA 6: Control about 0.001, HFD about 0.003 lncRNA 7: Control about 0.002, HFD about 0.005 lncRNA 8: Control about 0.0006, HFD about 0.00001 Differences in the level of the lncRNA expression and genes (18 srRNA, Apof, Fads 2, Fam213b, Hsd17b7, Crim 1, Srebf 1, Aacsm5, Aacs, Fapb5) in the HFD group and control group fed with Kaoxetel chow (p < 0.05)
Bao MH et al. [9]	Mice males	8 weeks of chow intervention	Collection of blood and aorta to evaluate the measurement of the lncRNA expression	Group I (Control) – conventional chow Group II (HFD) – chow with a high fat content (20% of fat, 2.5% of cholesterol). Fat composition: 5% of soy oil 10% of pig lard 10% of rapeseed oil	Higher level of LDL, cholesterol, HDL, triglycerides in the group fed with conventional chow and high-fat chow (p < 0.05) Lipid profile (mM) Control group HDL about 3 LDL about 1 Cholesterol about 19 Triglycerides about 2 HFD group HDL about 3 LDL about 4 Cholesterol about 17 Triglycerides about 20	The level of lncRNA expression in the group fed with conventional chow: FR375488 (about 4.9 1.0), n418283 (about -1.0), n419646 (about 1.0), FR331566 (about 1.0), n297428 (about 1.0), n297428 (about 1.0), n297368 (about 1.0), FR384764 (about 1.0), FR334236 (about 1.0), Spp1 (about 1.0), AKNA (about 1.0), TNK1 (about 1.0), Lrp 1 (about 1.0) The level of lncRNA expression in the group fed with high-fat chow: FR375488 (about 0.25), n418283 (about 0.25), n419646 (about 0.25), FR331566 (about 0.25), n297428 (about 7.0), n297428 (about 7.0), n297368 (about 5.5), FR384764 (about 1.0), FR334236 (about 6.0), Spp1 (about 10.0), AKNA (about 0.8), TNK1 (about 7.0), Lrp 1 (about 6.0) The level of lncRNA expression in the two groups was statistically different (p < 0.05)

Author	Study group	Duration	Methodology	Dietary intervention	Blood test results	Results
Lin Y et al. [10]	n = 73 pregnant rats L-L n = 15 L-H n = 16 H-L n = 14 H-H n = 18 Age: 3 months	7-day preparation for laboratory conditions and application of a 4-week nutritional intervention	Evaluation of the level of lncRNA H19 expression and genes in the nutrient transporters of the placenta at 13.5 and 17.5 weeks of pregnancy	Group I (LL) – Low fat (5%)/ low fibre (2.46%) diet. Group II (LH) – Low fat (5%)/high fibre (13.4%) diet. Group III (HL) – High fat (25%) and low fibre (2.46%) diet. Group IV (HH) – High fibre (25%), high fat (13.4%) diet.	none	Level of the lncRNA H19 expression in the 13.5 week of pregnancy: LL about 1.0, LH about 0.4, HL about 0.25, HH about 0.3 17.5 week of pregnancy LL about 1.0, LH about 0.8 HL about 0.45, HH about 0.75 It was observed that the way of feeding significantly affects the expression level of lncRNA H19 and the studied genes. The difference is statistically significant in the groups in which different dietary patterns were applied (p < 0.05)
Huang C et al. [11]	Pregnant mice n = 11	No data	Evaluation of the level of expression of lncRNA and mRNA in the fat tissue and the gonadal tissue	Chow intervention High-fat diet (HFD, n = 5) 45% of fat or standard chow (Chow; n = 6), which contained 10% of fat	none	Change in the expression of lncRNA and mRNA under the influence of a change in diet. Fat tissue – lnc RNA NONMMUT068206 Chow about 1.0 HFD about 2.0 * NONMMUT068202 Chow about 0.9 HFD about 3.8 * NONMMUT068204 Chow about 1.1 HFD about 2.1 Fat tissue – genes PRAP 1 Chow about 1.0 HFD about 5.8 * Serpina 3 Chow about 1.0 HFD about 8.0 * Guca 2b Chow about 1.0 HFD about 4.0 * Muc16 Chow about 1.0 HFD about 4.0 * Pn7b1 Chow about 1.0 HFD about 0.5 * Adh1a3 Chow about 1.0 HFD about 0.8 Circ1b Chow about 1.2 HFD about 0.4 * Pn7c1 Chow about 1.3 HFD about 0.6 * The Chow about 1.0 HFD about 0.5 * NONMMUT073434 Chow about 1.1 HFD about 2.2 * NONMMUT062807 Chow about 1.0 HFD about 2.2 * XR_140468 Chow about 1 HFD about 0.5 * NONMMUT021632 Chow about 1.2 HFD about 0.4 * ENSMUST000000826823 Chow about 1.0 HFD about 0.3 * Gonadal tissue – lncRNA XR_141088 Chow about 1.3 HFD about 0.2 * XR_141492 Chow about 1.0 HFD about 0.7 * Gonadal tissue – genes Mest Chow about 0.6 HFD about 10.0 * 110059M11RIK Chow about 0.5 HFD about 8.0 * Vcn1 Chow about 0.7 HFD about 7.8 * Vnn1 Chow about 0.7 HFD about 0.8 * Elov6 Chow about 0.5 HFD about 0.3 * Gys2 Chow about 0.8 HFD about 0.3 * Achy Chow about 0.8 HFD about 0.3 * GM64B4 Chow about 0.7 HFD about 0.3 * Slc15a5 Chow 0.7 about HFD about 0.2 * NONMMUT 016106 Chow about 1.0 HFD about 3.2 * NONMMUT040834 Chow about 1.0 HFD about 3.3 * ENSMUST 000000121379 Chow about 1.0 HFD about 0.2 * ENSMUST0000012178 Chow about 1.0 HFD about 0.5 * ENSMUST0000009869 Chow about 1.0 HFD about 0.6 *

lncRNA – long non-coding RNA, LL – low fat and fibre diet, LH – low fat and high fibre diet, HL – high fat and low fibre diet, HH – high fat and high fibre diet, HFD – high fat diet, * – a significant change in the level of expression

Source: author's own analysis

Summary

The studies carried out so far assessing the impact of diet and specifically the fat content in chow on the level of the lncRNA expression collected in table 1 show that the diet can influence the level of the lncRNA expression, the overexpression of which is included in the epigenetic mechanisms mentioned as affecting the size of ovarian cancer. Based on the PubMed and Gene NCBI base, it is impossible to determine whether lncRNA H19 and those studied by Huang BB et al. [8], Bao MH et al. [9], Lin Y et al. [10] and Huang C et al. [11] are included to lncRNA, whose change of expression can increase the size of the tumour. Available data concerning the effect of the lncRNA H19 expression level on the size of ovarian cancer are residual, however, the study by Tanos V et al. [27] observed various levels of expression in tumours of various malignancies [27]. In order to evaluate the effect of nutrients, e.g. on the level of folate synthesis by microbiome, bacterial cultures are conducted in the presence of the PABA acid. Current data do not provide information on the effect of tissue culture in the presence of different amounts of fat in the medium to assess the effect of fat content on the level of the lncRNA expression. Nutritional recommendations for women suffering from ovarian cancer should be in accordance with the guidelines of the Polish Cancer Association for people with cancer [28]. On the basis of the collected literature, it can be concluded that women suffering from ovarian cancer should maintain normal body weight and observe the basic principles of healthy eating.

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