

Assessment of gynecological and lifestyle-related risk factors of ovarian cancer

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Abstract

Introduction: Ovarian cancer remains the most lethal gynecological cancer. Assessment of gynecological and lifestyle-related risk factors is essential to reduce the occurrence and the mortality rate of the disease.

Material and methods: Surveys were collected among 71 patients with ovarian cancer and 76 women without gynecological cancer. Questionnaires included questions about medical history and lifestyle in the past.

Results: The control group had breastfed longer ($p = 0.034$) and used hormonal contraception more often ($p = 0.00037$) than the study group. The patients in FIGO (French. *Fédération internationale de gynécologie et d'obstétrique*) stage III or IV had a higher number of lifetime ovulatory cycles ($p = 0.001$) than the control group. Women at FIGO stage IV slept significantly less than patients at other stages ($p = 0.0026$). Oncological patients reporting sedentary work more often were diagnosed at advanced stages ($p = 0.00328$). The risk of ovarian cancer was 0.046 times smaller for women who had given birth ($p = 0.025$), 0.94 times smaller for every one month longer breastfeeding ($p = 0.0428$), 0.677 times smaller for every one year older age at menarche ($p = 0.0152$), 0.106 times smaller for women who had used hormonal contraception ($p = 0.0019$), and 5.46 times higher for women who ever worked night shifts ($p = 0.0128$).

Conclusions: Our study proves the importance of both gynecological and lifestyle-related risk factors of ovarian cancer and their impact on its prevalence. Lifestyle-related risk factors cannot be ignored, as they might have a direct influence on the aggravation of the risk of this type of cancer. Promoting an adequate amount of physical activity and sleep, breastfeeding, and having children could improve the detection and treatment of ovarian cancer in general.

Key words: ovarian cancer, risk factors, lifestyle, oral contraceptives, parity, breastfeeding.

Introduction

Ovarian cancer remains the most lethal gynecological cancer. Due to the fact that there is no effective screening process available and the early symptoms are often non-distinctive, the diagnosis is usually made when cancer is advanced, at FIGO (French. *Fédération internationale de gynécologie et d'obstétrique*) stage III or IV, which results in a low survival rate. According to the Polish National Cancer Registry, ovarian cancer is the 4th leading cause of death from malignancies among women in Poland, following lung, breast, and colon cancer. Between 2010 and 2018, it caused 23,724 deaths [1]. High-grade serous carcinoma is the most commonly diagnosed form of ovarian cancer; however, other histological types include clear cell, endometrioid, mucinous, undifferentiated, and transitional cell tumor.

The pathogenesis of ovarian cancer remains unclear; however, many theories have been proposed. Fathall's theory on incessant ovulation explains the negative impact of ovulations on the ovaries due to the rupture

of the ovarian surface epithelium, which may promote mutations [2]. Another theory focuses on the constant inflammation of the ovaries due to their intraperitoneal location and the inflammatory character of the ovulation itself [3]. Based on these theories, several risk factors have been assessed. These include early menarche, late menopause, nulliparity, and lack of breastfeeding, which increase the number of lifetime ovulatory cycles (LOC). Genetic mutations such as *BRCA1* and *BRCA2* mutation, Lynch syndrome, and Peutz-Jeghers syndrome increase the risk as well [4].

The aim of the study was to identify new and assess already known risk factors of ovarian cancer among the Polish population as it is crucial to reduce the occurrence and the mortality of the disease.

Material and methods

Between February 2020 and July 2021, 71 women with the diagnosis of ovarian cancer and 76 women

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without gynecological cancer were recruited to the study and control group respectively (Table 1). Women were informed that the survey was anonymous and it was collected after receiving consent. Both groups received the same questionnaires. The control group's surveys were collected among women with vaginal prolapse or uterine fibroids. All women were interviewed at the Department of Gynecology, Obstetrics and Gynecologic Oncology at Poznan University of Medical Sciences.

The questionnaires included questions about medical history (e.g. body mass index – BMI, menarche, menopause, number of pregnancies and births, total duration of breastfeeding, the use of hormonal contraception or intrauterine device and the duration of therapy, chronic diseases, vaginal infections, blood type) and lifestyle, including profession, type of work (sedentary or standing), shifts at night, the amount of physical activity per week, average sleep duration, sleeping disorders, and the usage of painkillers. The data concerning the levels of CA125 and HE4 markers at the diagnosis, as well as FIGO stages (Table 2) and histological types of carcinomas (Table 3), were also collected.

Statistical analysis was performed using the Microsoft Excel program and the R language. Data obtained from the study group were compared with the control group. We performed the independent t-test and the test of proportions. The relationship between the potential risk factors and the risk of ovarian cancer was estimated by logistic regression. Odds ratios (ORs) and corresponding 95% confidence intervals (CI) were calculated (Table 4). The significance level of these tests was set at less than 0.05.

Results

The mean age of the study group was 61.0 ±10.6 years and the mean age of the control group was 59.7 ±12.7 years. The mean height of women in the study group was 1.61 m, in comparison to 1.63 m in the control group ($p = 0.032$). The mean BMI value of the study group was 26.2 and 27.4 in the control group ($p = 0.114$). 18.3% of women in the study group and 27.6% of the control group were obese (BMI > 30).

97.4% of women in the control group had given birth, in comparison to 87.3% of the women in the study group. The statistical significance of this result was confirmed in the proportion test performed in the R language ($p = 0.045$). The logistic regression analysis showed that the odds of having cancer for women who had given birth are 0.046 times smaller (OR = 0.046; 95% CI: 0.002–0.523; $p = 0.025$) than for women who had not given birth, holding all other variables constant.

The mean duration of breastfeeding among the control group was higher (14 months) than among the patients diagnosed with ovarian cancer (8 months). The difference was statistically significant both be-

Table 1. Characteristics of the study group and the control group

Variable	Study group	Control group
Number of patients recruited	71	76
Average age (years)	61.0 ±10.6	59.7 ±12.7
Average height (m)	1.61 ±0.10	1.63 ±0.10
Average weight (kg)	67.8 ±11.2	72.9 ±14.4
Average BMI	26.2 ± 4.1	27.4 ±5
Average age at diagnosis (years)	58.6 ±10.8	–
CA125 value above normal at diagnosis (%)	73.2	–
HE4 value above normal at diagnosis (%)	54.9	–

BMI – body mass index

Table 2. Distribution of FIGO stages among patients recruited to the study group

FIGO stage	n	%
I	11	15.5
II	3	4.2
III	44	62.0
IV	13	18.3

FIGO – French. *Fédération internationale de gynécologie et d'obstétrique*

Table 3. Distribution of histopathological types of ovarian cancer and FIGO stages among patients recruited to the study group

Histopathological type	n	%
Serous carcinoma	66	93
Clear-cell carcinoma	2	2.8
Endometrioid carcinoma	3	4.2

FIGO – French. *Fédération internationale de gynécologie et d'obstétrique*

Table 4. Assessment of odds ratios of particular risk factors in comparison to the control group

Variable	Odds ratio (95% CI)	p-value
Menarche (years)	0.677 (0.49–0.92)	$p = 0.0152$
Giving birth	0.046 (0.002–0.523)	$p = 0.025$
Breastfeeding (months)	0.94 (0.87–0.99)	$p = 0.0428$
Using hormonal contraception	0.106 (0.02–0.41)	$p = 1.9 \times 10^{-3}$
Ever working night shifts	5.46 (1.52–22.62)	$p = 0.0128$

tween the control and the study group ($p = 0.034$) and between the control group and the patients with advanced cancer (FIGO stages III and IV; $p = 0.049$). Also, among women who had not breastfed at all, more often there were patients with FIGO stage III or IV than patients with FIGO stage I or II ($p = 0.002$). The odds of having cancer were calculated as 0.94 times smaller for

Table 5. Comparison of gynecological variables between the study group and the control group

Variable	Average result of the variable	SD of the result	Average result of the variable	SD of the result	p-value
Age at the first delivery (years)	23.3	4.4	23.9	3.6	0.36
Number of deliveries	1.9	1.2	2.1	1.1	0.22
Duration of breastfeeding (months)	8	9.3	14	19.1	0.034
Duration of hormonal contraception use (months)	62	76.6	81	78.9	3.7×10^{-4}
Age at menarche (years)	13.4	1.7	13.5	1.7	0.78
Age at menopause (years)	48.5	6	49.6	4.8	0.27
Number of LOC	426	84	396	105	0.055

LOC – lifetime ovulatory cycles, SD – standard deviation

Table 6. Comparison of gynecological variables between the group of patients in FIGO stages III and IV and the control group

Variable	Patients in FIGO stage III or IV		Control group		p-value
	n	%	n	%	
Gave birth	62	87.3	74	97.4	0.045
Gave birth once	18	25.4	21	27.6	0.90
Breastfed	41	71.9	56	73.7	0.05
Suffered from painful menstruation	34	47.9	31	40.8	3.7×10^{-5}
Used hormonal contraception	6	10.5	29	38.2	1.0×10^{-3}
Suffered from endometriosis	5	7	8	10.5	0.65
Had a miscarriage	11	15.5	12	15.8	1.0
Used intrauterine device	6	8.5	11	14.5	0.38
Reported having frequent or recurrent vaginal infections	17	23.9	13	17.1	0.41

FIGO – French. Fédération internationale de gynécologie et d'obstétrique, SD – standard deviation

every one month increase in the duration of breastfeeding, holding all other variables constant (OR = 0.94; 95% CI: 0.87–0.99; $p = 0.0428$).

The mean age at menarche was estimated at 13 years both in the study and control group. However, performing the logistic regression analysis allowed us to assume that for every one year increase in the age at menarche, developing ovarian cancer is 0.677 times less likely, holding all other variables constant (OR = 0.67; 95% CI: 0.49–0.92; $p = 0.0152$).

Among women in the study group who reported having painful menstruation throughout their life, more often there were patients with advanced cancer ($p = 3.7 \times 10^{-5}$).

38.2% of women in the control group had used hormonal contraception, with the mean duration of the therapy being 81 months. Only 11.3% of patients with ovarian cancer took hormonal contraception, with the mean duration of the therapy estimated at 62 months. This outcome was statistically significantly different between these groups ($p = 3.7 \times 10^{-4}$), as well as between the control group and the patients with FIGO stages III and IV ($p = 1.0 \times 10^{-3}$). The odds for developing ovarian cancer for women who took hormonal contraception are 0.106 times smaller than for women who did not take hormonal contraception, holding all other variables

constant (OR = 0.106; 95% CI: 0.02–0.41; $p = 1.9 \times 10^{-3}$). Out of all oncological patients who did not use hormonal contraception, those diagnosed in the third or fourth FIGO stage were more frequent ($p = 3.024 \times 10^{-11}$).

There was a statistically significant difference in LOC between the control group and the patients with advanced cancer (FIGO stages III and IV; $p = 0.0304$) (Tables 5, 6).

49.3% of women in the study group had blood type A, in comparison to 35.5% in the control group ($p = 0.128$). Among all patients with ovarian cancer who had blood type A, statistically significantly more often these were women diagnosed at FIGO stage III or IV ($p = 1.7 \times 10^{-5}$) (Table 7).

39.5% of women in the study group reported having sedentary work (vs. 55.3% in the control group, $p = 0.08$). 35.1% of women with advanced cancer (at FIGO stage III and IV) reported having sedentary work, which is significantly less than in the case of the control group ($p = 0.03$). However, patients who had sedentary work more often had cancer at FIGO stage III or IV rather than at stage I or II ($p = 3.3 \times 10^{-3}$). 29.6% of women in the study group performed physical activity regularly (at least 150 minutes of moderate-intensity activity per week), in comparison to 35.5% in the control group ($p = 0.55$). Women who did not exercise more often had

Table 7. Comparison of the distribution of blood types between the study group, the control group, and the distribution of blood types in Polish society

Blood type	Study group		Control group		p-value	Polish society %
	n	%	n	%		
A	35	49.3	27	35.5	0.128	38
B	12	15.5	16	21.1	0.667	17
AB	9	12.9	5	6.6	0.328	7
0	14	19.7	25	32.9	0.105	37

Table 8. Comparison of lifestyle-related variables between the study group and the control group

Variable	Study group		Control group		p-value
	n	%	n	%	
BMI > 30	13	18.3	21	27.6	0.25
Sedentary job	28	39.4	42	55.3	0.08
Night shifts	16	22.5	12	15.8	0.41
Regular exercise	21	29.6	27	35.5	0.55
Sleeping problems	20	28.2	32	42.1	0.11
Analgesics usage	12	16.9	22	28.9	0.13
	Average result of the variable	SD of the result	Average result of the variable	SD of the result	p-value
BMI	26.2	4.1	27.4	5.0	0.11
Time seated at work per day (hours)	7.1	1.1	6.8	1.4	0.45
Night shifts per week	2.4	0.7	2.6	0.9	0.55
Time spent on physical activity per week (hours)	1.7	2.8	2.1	3.9	0.521
Sleep duration (hours)	6.8	1.4	7.1	1.1	0.128

SD – standard deviation, BMI – body mass index

advanced cancer (at FIGO stage III or IV) than at stage I or II ($p = 6.7 \times 10^{-8}$).

22.5% of patients in the study group reported having night shifts during their lifetime in comparison to 15.8% in the control group ($p = 0.406$). The mean value of shifts per week was 2.5 in both control and study groups. Among women who reported ever working night shifts, more often these were women with FIGO stages III and IV ($p = 1.0 \times 10^{-3}$). Moreover, working night shifts was associated with a 5.46 times greater risk of cancer than for women who did not work night shifts, holding all other variables constant (OR = 5.46; 95% CI: 1.52–22.62; $p = 0.0128$).

The mean duration of sleep per day was 6.8 hours in the study group and 7.1 hours in the control group ($p = 0.128$). The median duration of sleep at FIGO stage IV was 5 hours, in comparison to 7 hours at FIGO stages I and III and 8 hours at FIGO stage II. Women with advanced cancer at FIGO stage IV slept significantly less than at other stages ($p = 2.6 \times 10^{-3}$). 28.2% of women in the study group reported having sleeping disorders, whereas in the control group 42.1% of women reported having sleeping disorders ($p = 0.111$). Women with sleeping disorders more often had advanced cancer (at FIGO stage III or IV) than at stage I or II ($p = 3.9 \times 10^{-5}$).

Among interviewed women, 16.9% of the whole study group and 17.5% of women with advanced cancer at FIGO stages III and IV reported using painkillers every week (vs. 28.9% in the control group, $p = 0.125$). However, women who did not use analgesics at all more often had cancer at FIGO stage III or IV than at stage I or II ($p = 9.0 \times 10^{-10}$) (Tables 8–10).

Discussion

There have been many attempts at trying to determine what the exact risk factors of ovarian cancer are. One theory is that every ovulation causes damage to the epithelium of the ovary, subsequently leading to the healing process, during which genetic mutations can occur. Furthermore, each ovulation is accompanied by inflammation, being a source of oxidative stress. That is why it is acknowledged that women who have not given birth, breastfed or used hormonal contraception and also women who had their menarche early and menopause late are at significantly greater risk of developing ovarian cancer. The mentioned variables have a direct impact on LOC, which, when increased, might generate a higher risk of a cancerous process [2]. The results of our study confirmed this assumption and

Table 9. Comparison of lifestyle-related variables between the group of patients in FIGO stages III and IV and the control group

Variable	Patients in III	FIGO stage or IV	Control	group	p-value
	n	%	n	%	
BMI > 30	11	19.3	21	27.6	0.36
Sedentary job (%)	20	35.1	42	55.3	0.03
Night shifts (%)	13	22.8	12	15.8	0.42
Regular exercise (%)	18	31.6	27	35.5	0.77
Sleeping problems (%)	17	29.8	32	42.1	0.21
Analgesics usage (%)	10	17.5	22	28.9	0.188
	Average result of the variable	SD of the result	Average result of the variable	SD of the result	p-value
BMI	26.34	4.2	27.4	5.0	0.1
Time seated at work per day (hours)	7.4	1.9	6.8	1.4	0.257
Night shifts per week	2.4	0.7	2.6	0.9	0.62
Time spent on physical activity per week (hours)	1.8	2.7	2.1	3.9	0.64
Sleep duration (hours)	6.8	1.4	7.1	1.1	0.145

BMI – body mass index, FIGO – French. *Fédération internationale de gynécologie et d'obstétrique*, SD – standard deviation

Table 10. Comparison between patients with FIGO stage I or II with patients with stage III or IV

Variable	FIGO stages I and II	FIGO stages III and IV	p-value
	%	%	
Not given birth	44.4	55.6	1
Not breastfed	23.8	76.2	2.03 × 10 ⁻³
Suffered from painful menstruation	23.5	76.5	3.73 × 10 ⁻⁵
Not used hormonal contraception	19.4	80.6	3.02 × 10 ⁻¹¹
Had a miscarriage	36.4	63.6	0.4
Reported having frequent or recurrent vaginal infections	11.8	88.2	4.0 × 10 ⁻⁵
Has blood type A	22.9	77.1	1.7 × 10 ⁻⁵
Variable	FIGO stages I and II	FIGO stages III and IV	p-value
	%	%	
Had sedentary job	28.6	71.4	3.3 × 10 ⁻³
Had night shifts	18.7	81.3	1.0 × 10 ⁻³
Did not exercise regularly	22.0	78.0	6.7 × 10 ⁻⁸
Sleeping problems	15.0	85.0	3.9 × 10 ⁻⁵
Did not use analgesics	20.7	79.3	9.0 × 10 ⁻¹⁰

FIGO – French. *Fédération internationale de gynécologie et d'obstétrique*

brought to light more data on these and other potential risk factors for this type of carcinoma.

The correlation between LOC and the risk of ovarian cancer has already been discussed. It was calculated that every year of ovulation increases the risk of the illness by as much as 2.6–6% [5]. The histological types most closely associated with this factor are serous and endometrioid carcinomas [6]. Nevertheless, there is still a lack of research comparing the number of cycles between women with different FIGO stages. On the basis of the

results obtained during the study, it was observed that LOC differed significantly between women interviewed as a control group and patients treated for advanced ovarian cancer ($p = 0.0304$). More research is needed in order to find out whether LOC can also have an influence on the severity of the disease, not only on its occurrence.

Researchers are inconsistent as regards the age at menarche being a risk for ovarian cancer (OC). Some stated that generally a younger age at menarche decreases the odds of developing OC by 15% [7]. The

results of the study conducted in our facility do not confirm this calculation. Although the mean age at menarche was similar for both groups (13.4 years in the study group and 13.5 years in the control group), the logistic regression showed that every one year increase in the age at menarche reduces the odds of OC 0.677 times (95% CI: 0.49–0.92; $p = 0.0152$). The age at menarche remains one of many variables taken into account when calculating the LOC; therefore it should be suggested to consider this aspect together with others, directly influencing LOC.

Pregnancy is unquestionably one of the most important factors having an impact on preventing ovarian cancer, as well as on the LOC. It was even found to be more beneficial than older age at menarche or younger age at menopause [8]. Troisi *et al.* reported that women who had given birth had a 30–40% lower risk of developing OC than nulliparous women and that the mentioned protective effect increases with each subsequent pregnancy [9]. Similar findings were presented in other studies. One calculated the risk of OC decreasing 8% with every pregnancy [10] and another one calculated a decline of 18%, 26%, 33%, and 42% for the first, second, third, and fourth pregnancy respectively [11]. Our results confirm that giving birth has a positive influence on the prevalence of ovarian cancer. The probability of developing OC for women who had given birth was 0.046 times lower than for nulliparous women (95% CI: 0.002–0.523; $p = 0.025$). 87.3% of interviewees in the study group had been pregnant at least once, while in the control group it was 97.4% of women. This difference was statistically significant ($p = 0.0456$). However, the median number of births did not differ between the groups, and for both of them, the result was 2 childbirths per woman. The mean age at the first birth was also similar (23.3 years in the study group and 23.9 years in the control group) and no statistically significant difference or correlation was found regarding this aspect. That is why the subject of pregnancy, perinatal and reproductive factors should be further explored, especially in larger study groups.

The influence of breastfeeding on the occurrence of ovarian cancer appears to be incontrovertible. Multiple studies confirm the reduced risk of this carcinoma among women who have breastfed, but there are no explicit data on how long women should breastfeed in order to decrease their risk of OC effectively. It was discovered that the long duration of all breastfeeding episodes combined, a higher number of breastfeeding episodes, and relatively younger age during the first episode of breastfeeding are additional factors increasing the efficiency of breastfeeding in preventing OC [12]. Luan *et al.* claim that any breastfeeding history is a preventive factor itself and its efficiency only grows with the extension of the lactation period [13]. A three-month-long breastfeeding episode was considered to

be profitable by two independent studies [12, 14] and another one reported that a year-long episode can decrease the risk of ovarian cancer by as much as 35% in comparison to women who have never breastfed [15]. One hypothesis explaining why breastfeeding is this beneficial states that oxytocin, which is closely associated with breastfeeding, limits the expression of matrix metalloproteinase-2 and vascular endothelial growth factor and this helps to avoid angiogenesis and the growth of cancer cells [16]. The most successful prevention was observed in relation to high-grade serous and endometrioid carcinomas [17]. In this single-center study, statistically significant differences were noted in the duration of women's lactation between the control and study groups ($p = 0.034$) and between the control group and the group of patients classified as FIGO stage III or IV ($p = 0.049$), which suggests that breastfeeding in fact provides beneficial effects in terms of ovarian cancer prevention. According to the results obtained in logistic regression, every additional month of breastfeeding reduces the risk of the disease 0.94 times, holding all other variables constant (95% CI: 0.87–0.99; $p = 0.0428$), which supports available research on the influence of breastfeeding on the risk of ovarian cancer.

Hormonal contraception is considered one of the most successful ways of preventing ovarian cancer. Abundant research has proved that using this type of contraception effectively minimizes the risk of OC [18, 19]. The protective effect lasts for 25 to 30 years, even if the therapy was only 1–4 years long [20] and was similar regardless of the dose of estrogens and progestins [21]. The difference between the analyzed groups was considerable – 38.2% of women in the control group reported using oral contraception, whereas only 11.3% of all oncological patients and 10.5% of patients in FIGO stage III or IV did so. Both comparisons were statistically significant ($p = 3.7 \times 10^{-5}$ and $p = 1.0 \times 10^{-3}$). The analysis showed that the risk of OC for women who took oral contraception is 0.106 times lower than for the women who did not use this type of contraception (95% CI: 0.02–0.41; $p = 1.9 \times 10^{-3}$) [3]. These results confirm the importance of hormonal contraception as a preventive tool against OC.

Some research has revealed that painful menstruation could also increase the risk of ovarian cancer. A correlation was observed between moderate and severe pain and epithelial ovarian cancer [22]. According to the results of our study, the patients diagnosed in FIGO stage III or IV stated more frequently than women diagnosed in stages I or II that their periods were, in fact, painful. However, suffering from a painful menstrual period is a common complaint, so this aspect should be investigated on larger groups of patients to assess whether it could have an impact on developing ovarian cancer.

The collected data were also assessed for the prevalence of endometriosis in both the control and study

groups, as this disease is a well-known risk factor of endometrioid and clear-cell ovarian cancer. Five out of 71 patients were diagnosed with these histological types of carcinomas (2 patients with clear-cell carcinoma and 3 patients with endometrioid carcinoma), but none of them reported suffering from endometriosis before being diagnosed with cancer. In the control group, 10.5% of women ($n = 8$) had endometriosis. These numbers were too small to conduct any conclusive statistics and provide reasonable data; however, the subject of endometriosis and ovarian cancer should be further explored.

Blood type can have a direct influence on the risk of cancer, as it has been proven for pancreatic and gastric cancer. Some research has shown that women with blood type A are more likely to develop ovarian cancer [23, 24], whereas those with blood type O have a lower risk of this kind of cancer [23]. According to Björkholm *et al.*, this blood type increases the risk of the serous type of ovarian cancer by 15% [23]. A possible explanation for this particular connection was presented by Henderson *et al.*, who claimed that ovarian cancer cells release the Forssman antigen, which is very similar to the determinant of blood type A antigen [25]. This way people who have anti-A antibodies are less subject to developing ovarian cancer because these antibodies tend to damage already existing cancerous cells and therefore prevent the growth of the neoplasm. In the study conducted in our facility, the women diagnosed at FIGO stage III or IV had blood type A more often than women diagnosed in FIGO stage I or II ($p = 1.7 \times 10^{-5}$). There is no research yet considering the potential influence of blood type on the stage of ovarian cancer on larger study groups. The comparison between the distribution of blood types in the study group, the control group, and in Polish society brought results that would confirm the mentioned studies. Blood type A was present more often in patients with ovarian cancer than in the control group and Polish society, and blood type O was present more often among women in the control group, as well as among Polish society. However, this outcome was not statistically significant and should be confirmed in larger study groups, as noted above.

As it is commonly known, obesity is a risk factor for many malignancies. It has been estimated that in Europe as many as 5% of all malignancies may be related to being overweight [26]. Higher levels of IGF-1, insulin, or leptin may promote the growth of cancer cells. Adipose tissue produces pro-inflammatory factors such as TNF- α , IL-6 [27] or C-reactive protein [28] that, according to the theory of constant inflammation [3], may contribute to the process of carcinogenesis in ovaries. Many studies have already proven that obesity is a risk factor for ovarian cancer occurrence. It is also associated with a poorer prognosis [29]. Increased risk has been observed when obesity occurred up to 5 years before the diagnosis, in

youth [30] and also during the perimenopausal period [31]. Moreover, the diet itself affects the time of menarche and menopause. A high energy diet promotes early menarche and late menopause; therefore, it increases LOC and hence the risk of ovarian cancer [32]. The mean BMI value of the study group was 26.2 and of the control group 27.4. Both of these values exceed the norm and correspond to being overweight. However, only 18.3% of women in the study group were obese (vs. 27.6% of women in the control group). Therefore, a 5-year follow-up must be performed in order to evaluate the impact of obesity on the survival of these women.

It has been proven that physical activity reduces constant inflammation [3]. Moreover, regular, heavy workouts can inhibit ovulation, which was observed in athletes [33]. Therefore, physical activity decreases the number of LOC and the risk of ovarian cancer. According to the analysis conducted by Minlikeeva *et al.* [34], all three factors together – lack of any physical exercise, obesity, and smoking – have a negative effect on the survival of patients suffering from ovarian cancer. Only 29.6% of patients in the study group reported performing physical activity regularly, in comparison to 35.5% of women in the control group. Women who did not exercise more often had advanced cancer at FIGO stage III or IV than at stage I or II ($p = 6.7 \times 10^{-8}$). These data prove the effect of lifestyle-related factors on the prevalence of ovarian cancer. It is, therefore, essential to motivate patients to exercise and live a healthy lifestyle in order to prevent the occurrence of ovarian cancer.

Working night shifts has already been classified as a possible carcinogenic factor. It has been suggested that melatonin, produced at night time and suppressed by light, may affect ovarian function [35]. 22.5% of women in the study group reported having worked night shifts in comparison to 15.8% in the control group. Among women who reported ever working night shifts, more often these were women with FIGO stage III or IV than I or II ($p = 1.0 \times 10^{-3}$). Published research provided information about 1.24 times greater risk among women who had worked night shifts in comparison to women who had never worked night shifts. However, after performing logistic regression analysis on the data obtained from this study, the OR of developing ovarian cancer was estimated as 5.46 times greater than for women who had not worked night shifts, holding all other variables constant (OR = 5.46; 95% CI: 1.52–22.62; $p = 0.0128$). Therefore, both of these results are consistent and must be taken into consideration, especially due to the character of medical professions.

Having a sedentary job is extremely common, especially during the COVID-19 pandemic. There are no consistent data about the impact of sedentary jobs on ovarian cancer occurrence. This factor must be analyzed along with obesity and lack of physical activity, as they are closely connected. Exercise should be performed

in leisure time in order to prevent both cardiovascular diseases and malignancies. Surprisingly, women in the control group more often had sedentary jobs than women with advanced cancer – 55.3% vs. 35.1% respectively ($p = 0.033$). However, patients who had sedentary work more often had advanced cancer (at FIGO stage III or IV) rather than at stage I or II ($p = 3.3 \times 10^{-3}$). It is possible that women in the control group were more active during their leisure time than the study group. Another reason for this may be that night shifts, which are more common in the study group, increase the risk more than sedentary jobs. Considering the results presented above, definitely more emphasis should be put on the importance of a healthy lifestyle and regular exercise.

Sleeping disorders and chronic fatigue are associated with the poor quality of life of women suffering from ovarian cancer. However, there are no consistent data about the effect of sleeping disorders and lack of a proper amount of sleep on the occurrence of ovarian cancer. Recent research suggested that there is no correlation between sleep and ovarian cancer occurrence after menopause. Nevertheless, restful sleep quality is associated with a lower risk of invasive serous ovarian cancer, whereas insomnia is associated with a higher one [36]. 28.2% of patients in the study group reported having sleep disorders prior to diagnosis (vs. 42.1% in the control group). However, these women were more often diagnosed with advanced cancer (at FIGO stage III or IV) than at stage I or II ($p = 3.9 \times 10^{-5}$). Moreover, the median duration of sleep of women with cancer at FIGO stage IV was only 5 hours. It was significantly less than in the case of other stages ($p = 2.6 \times 10^{-3}$). Based on this result, it can be assumed that sleep duration may have an impact on ovarian cancer occurrence and more emphasis should be put on getting a proper amount of rest per day.

Analgesic drugs, commonly known as painkillers, are frequently used; therefore, their possible impact on carcinogenesis has been evaluated in order to prove their long-term safety. The pathogenesis of ovarian cancer may be associated with constant inflammation [3]. Non-steroidal anti-inflammatory drugs (NSAIDs), especially aspirin, have been proven to reduce the ovarian cancer risk by 44% in the case of aspirin (OR = 0.56) and 26% (OR = 0.74) in the case of non-aspirin NSAIDs [37]. The impact of another common drug, paracetamol, on ovarian cancer occurrence was analyzed in a Danish study [38]. As well as NSAIDs, it has been proven to reduce the incidence of ovarian cancer (OR = 0.82). The odds ratio continued to decrease in the case of long-term (above 10 years) and high-intensity use (OR = 0.45). 16.9% of the entire study group and 17.5% of women with advanced cancer at FIGO stages III and IV reported using painkillers at least once a week in comparison to 28.9% of women in the control group. Women who did not use analgesics more often had cancer at FIGO stage III or IV than at stage I or II ($p = 9.0 \times 10^{-10}$).

Therefore, the usage of aspirin as prophylaxis seems not only beneficial in terms of cardiovascular diseases but also gynecological ones and requires further research.

Conclusions

Ovarian cancer is still one of the most puzzling gynecological cancers. As there is no effective screening available and the symptoms are not visible and specific enough, this disease is diagnosed far too often in advanced stages, which equates to limited treatment possibilities. This study confirms well-known and openly discussed gynecological risk factors of ovarian cancer, such as nulliparity, lack of breastfeeding, lack of hormonal contraception use, and an increased number of LOC, as well as pointing out the importance of lifestyle as a complex but potentially very significant risk factor for this malignancy. Medicines taken throughout life, sleep quality, profession, and its character, and work shifts at night are other aspects that should be considered relevant in the context of the risk of ovarian cancer. Some of the outcomes presented in this study suggest that there might be a direct connection between the occurrence of the factors and the stage of the disease at diagnosis. Acknowledging and gaining more insight on the subject could reduce the prevalence and mortality rate of this carcinoma. Being aware of the limitations of this study, such as the relatively small number of patients recruited, the authors suggest that the topic of gynecological history and lifestyle as a source of risk factors of ovarian cancer should be further explored, especially in multiple centers and in larger study and control groups.

Disclosure

The authors report no conflict of interest.

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