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Original Articles

Risk assessment for ovarian cancer

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Summary

Introduction: Ovarian cancer (OC) is the most common malignancy among women and epidemiological data report the trends in OC incidence to steadily increase. *Objectives:* The aim of the study was to analyze selected, non-genetic risk factors for OC, and to design a mathematical model and a risk assessment tool for it. *Materials and Methods:* The study included healthy women with no focal changes in the breast and ovaries (control group) and patients with OC (study group). A total of 1346 women, aged from 18 to 80, were included in the study. An original questionnaire, designed especially for the purpose of the study and comprising of 40 questions, was used as one of the evaluation tools. All respondents underwent a clinical psychological evaluation. *Results:* Risk Assessment for Ovarian Cancer Chart (RAFOCC) was designed on the basis of the odds ratio (OR) analysis for individual parameters and revealed that women who scored >31.5 points on a scale from 0 to 72, with a 72% test sensitivity (95% confidence interval (CI) 0.656-0.783) and 75% specificity (95% CI 0.718-0.770), face a statistically significantly increased risk for OC. *Conclusions:* RAFOCC is a useful screening tool for identifying women with increased risk for OC. Women who scored >31.5 points face a statistically significantly increased risk for OC. High-risk patients should be offered timely medical care and undergo further diagnostic testing.

Key words: Ovarian cancer; Risk assessment; RAFOCC.

Introduction

Ovarian cancer (OC) is a common malignancy among women, with high mortality rates (114,000 women/year) and steadily increasing morbidity. Epidemiological data from Europe report the highest incidence in the Czech Republic, Great Britain, Austria, Ireland and Island, while the lowest rates are noted in Spain and Italy. Globally, OC is the most common carcinoma in the South America and Israel and the least common in Asia and Africa. Poland belongs to the group of countries with average morbidity rates, nevertheless 3,300 women were diagnosed with OC in 2008 alone, accounting for 5% of the overall neoplasm incidence among women that year [1, 2]. OC affects mostly middle-aged women (52% of cases), with a 40%-incidence rate in women over 65. A slight decline in morbidity and mortality has been observed since 1990s, what might be attributed to a wider use of oral contraceptives and more effective treatment. On the other hand, the absence of early and specific symptoms, together with ineffective screening programs, are the reason why too many women are diagnosed in advanced stages of the disease. Over 75% of the cases are diagnosed with FIGO Stage III or IV [1-3]. Therefore, it is a matter of great importance to design a plan to fight this type of cancer at every stage of development. Preventive measures that aim to avoid morbidity have a more beneficial effect on health and life expectancy than treatment of neoplastic processes. Primary prevention aims to popularize heath-related behaviors, knowledge of the epidemiology, and causes of OC [4-6].

Numerous factors may be monitored as the majority of cancer-related risk factors are affected by individual decisions regarding lifestyle. Most malignancies (70%) are estimated to result from the harmful influence of bad diet, lifestyle, and environmental factors [7, 8].

It is possible to assess the relative risk of disease in the event of exposure to known harmful factors, but it remains challenging to precisely determine the role of a single factor in the process of carcinogenesis. Also, the hierarchy of the factors has not been fully elucidated and, what is more, their impact differs considerably among various populations of women [7, 8].

The aim of the study was to analyze selected, non-genetic risk factors for OC, as well as to design a mathematical model and risk assessment chart for it.

Materials and Methods

The study included healthy women with no focal changes in the breast and ovaries (controls) and patients diagnosed with OC (study group). Tests were conducted between September 2007 and November 2011 among the patients of the Gynecologic Oncology Hospital. In total, 1346 women, aged from 18 to 80, were included in the study. Due to considerable age differences the study group was further subdivided into: group 1 (18-45 years of age) and group

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2 (46-80 years of age). The division was the result of the analysis of the following factors: parity, oral contraceptives, HRT, and age at first clinical manifestations connected with perimenopause. Also, the authors took into account the fact that screening tests are intended mostly for women over the age of 45.

The inclusion criteria for controls (n=1144) were: normal result of the physical examination performed by a specialist, unremarkable anamnesis, normal mammogram, and/or breast ultrasound, and familial anamnesis excluding genetic risk factors. The inclusion criterion for the study group (n=202) was a positive histopathologic result of a surgery or a biopsy.

An original questionnaire, designed especially for the purpose of the study and comprising of 40 questions, was used as one of the evaluation tools. Data pertaining to socio-economic data, menstrual and obstetric details, breastfeeding and puerperium, age at first and last oral contraceptives, and/or HRT, were collected. Also, the respondents provided information about their lifestyle and health behaviors, including physical activity, coffee consumption, alcohol use, cigarette smoking, and breast self-examination.

All respondents underwent a clinical psychological evaluation and the Hospital Anxiety and Depression Scale (HADS) was used for the assessment of the results. The scale consists of two subscales: anxiety and depression. HADS is a 14-item scale with four possible answers: 'yes, definitely'; 'yes, sometimes'; 'no, not much'; 'no, not at all'. The items are scored from 0-3, what amounts to 21 points for each part of the test.

The odds ratio (OR) with a 95% confidence interval (CI) was calculated for individual risk factors. On the basis of the OR analysis, significant parameters were assigned points, depending on their weight. The results of the HADS depression sub-scale were graded as follows: 0-7 points: no signs of depression; 8-10 borderline depression, 11-21 depression. The anxiety sub-scale was graded in the same way.

The following parameters: age, BMI, age at first menarche, age at first pregnancy, age at first delivery, and age at first mammogram, were expressed as arithmetic mean ± standard deviation in the studied groups. The Shapiro-Wilk test was used for normal distribution. Student's *t*-test for dependent variables or the Welch test were used for normally distributed samples for comparison between two groups (after homogeneity of variance was confirmed). Otherwise, non-parametric Mann-Whitney test for independent samples was applied.

Two parameters – miscarriage and intervention during puerperium – were expressed on nominal scale in size and corresponding percentage. Chi^2 test, Fisher's exact test or Fisher-Freeman-Halton test were used to determine the correlation between the above mentioned variables and group association. OR was calculated for individual risk factors.

The following parameters: age, BMI, time to weaning, number of cigarettes, and parity were divided into confidence intervals and OR was calculated for intervals of increase. On the basis of the OR analysis, significant parameters were assigned points, depending on their weight.

Sensitivity, specificity, negative, and positive predictive values with a 95% CI were calculated for the diagnostic tests.

STATISTICA v.8, Instat v.3.00, Analyze-it v.2.2, and StatXact-8 were used for statistical analysis. The level of statistical significance was estimated at $p \leq 0.05$.

All participants voluntarily agreed to participate in the study. Data confidentiality and survey procedures were reviewed with each participant before the questionnaire. Researchers assured participants that the contents of the questionnaire would be used solely for research purposes. The patients gave written obtained consent for this study. Ethics committees approved this consent procedure. This study was specifically approved only for this study by the Bioethics Commission at the Poznan University of Medical Sciences No 574/2011.

Table 1. — *Age-adjusted OR for OC women and controls.*

Age (years)	OR	CI 95%
46-55	4.62	2.88-7.39
56-65	10.45	6.47-16.89
>65	20.00	10.86-36.82

Table 2. — *BMI-adjusted OD for OC women and controls.*

BMI	OR	CI 95%
25-29.9	1.85	1.30-2.63
>30	4.28	2.88-6.36

Table 3. — *Smoking-adjusted OR for OC women and controls.*

Number of cigarettes (cigarettes/day)	OR	CI 95%
<5	2.5	1.0- 5.26
>5	1.5	0.90-2.25

Table 4. - *Frequency of physical activity-adjusted OR for OC women and controls.*

Frequency of physical activity	OR	CI 95%
Once every two weeks	1.4	0.52-3.4
Once a week	1.1	0.58-2.5
Three times a week	1.3	1.36-4.0

Results

The authors analyzed which parameters influenced the OR for OC and in which intervals the OR statistically significantly increases or decreases.

Age in the following age groups: 46-55 years, 56-65 years, and > 65 years in comparison to < 45 years, was the first parameter to be analyzed. The ORs were OR=4.62; 95% CI 2.8-7.3, and OR=10.45; 95% CI 6.47-16.89 and OR=20.00; 95% CI 10.86-36.82 in the first, second, and third age groups, respectively. The differences between the groups were statistically significantly $p = 0.0000$. The results are presented in Table 1.

BMI was analyzed in the following ranges: 25-29.9 and > 30. The OR was OR=1.85; 95% CI 1.30-2.63, and OR=4.28; 95% CI 2.88-6.36, respectively, in comparison to women with normal BMI (18.5-24.9). The differences between the groups were statistically significantly $p = 0.0000$. The results are presented in Table 2.

A significantly increased risk for OC was observed among women up to 45 years of age in case of obesity or BMI > 30 when compared to same age peers with normal BMI. The OR for obese women was OR=6.7; 95% CI 2.53-

Table 5. - *Risk Assessment for Ovarian Cancer Chart (RAFOCC) form.*

RISK ASSESSMENT CHART FOR OVARIAN CANCER

Parameter	Suggested score (points)	Score (points)	Comments
AGE			
≤ 45	0		
46-55	5		
56-65	10		
> 65	20		
BMI			
19-24.9	0		
25-29.9	2		
≥ 30	7		
EDUCATION			
VET	3		
SECONDARY	1.5		
TERTIARY	0		
RESIDENCE			
≤ 10.000	2		
10-50.000	3		
50-100.000	3		
>500.000	0		
FIRST MENSES			
≤11 YEARS OF AGE	1		
>11 YEARS OF AGE	0		
LAST MENSES			
≤50	0		
>51	1.5		
PARITY			
'0'	1		
>1	0		
AGE AT FIRST PREGNANCY			
≤35	0		
>35	2		
AGE AT FIRST LABOR			
≤35	0		
>35	2		
AGE AT MISCARRIAGE			
≤35	0		
>35	1.5		
BREASTFEEDING			Breastfeeding = for > 1 month
YES	0		
NO	2		
COFFEE			At least 1 cup/day
NO	2		
YES	0		
SMOKER			At least 1 cigarette/day for at least 1 year
N0	2		
YES	0		
PHYSICAL ACTIVITY			Physically active = women who exercise
NO	1		three times/week for 30 minutes
YES	0		
ALCOHOL CONSUMPTION			Alcohol consumption = 1/month or more frequent
NONE	2		consumption of 20-25 g of pure ethanol
SPORADICALLY	2		
OFTEN	0		
CONTRACEPTIVES			Contraceptives for >1 year
NO	15		
YES	0		
HRT			Hormonal Replacement Therapy (HRT) for >1 year
NO	2		
YES	0		
ANXIETY			
NO	1.5		
YES	0		
DEPRESSION AT AGE < 45			
NO	0		
YES	4		
TOTAL	0-72		SCORE > 31.5 POINTS – significantly increased risk for ovarian cancer

Table 6. — Sensitivity and specificity test was performed for RAFOCC.

Test	Area	95% CI	SE	Z	P	Ovarian cancer = 1
Total	0.81	0.78 to 0.84	0.015	20.46	<0.0001	have higher values

18.14.

The OR for women >45 years of age and with BMI > 30 was OR=2.5; 95% CI 1.6-3.9 when compared to same age peers with normal BMI.

Primary and VET education constitutes a high-risk parameter for OC. The OR for that group of women was OR=3.3; 95% CI 2.00-5.00 when compared to women with tertiary education. Secondary education proved to not be statistically significant and the OR for that group of women was OR=0.7; 95% CI 0.54-1.1 when compared to peers with primary and VET education.

The risk for OC proved to increase twofold for inhabitants of small towns (population: < 10,000), and was OR= 2.0; 95% CI 1.4-3.3 when compared to peers from large cities (population: > 500,000).

In case of women from larger towns (population 10-50,000 or 50-100,000 inhabitants), the risk is slightly elevated, OR=1.1; 95% CI 0.7-1,6, and OR= 1.2; 95% CI 0.7-1.8, respectively, when compared to peers from small towns (population: < 10,000).

Early age at first menarche and late age at last menarche negatively influenced the risk for OC. Women who had their first menarche < 11 years of age are at a 1.6 higher risk of disease when compared to women who had their first menarche at the age of 13 (OR= 1.66; 95% CI 0.9-3.3). Women who continued to menstruate > 55 years of age were at a 1.4 higher risk of disease (OR=1.42; 95% CI 0.48-4.18) than women who ceased to menstruate < 55.

The risk for OC increased by 2.7-fold for women who were pregnant after 35 years of age (OR=2.72; 95% CI 1.05-7.05) when compared to women who conceived before the age of 25. Also, the authors analyzed the correlation between parity and OR, taking into account women over 45, regardless of whether the pregnancy resulted in a miscarriage or a live term birth. Nulliparas were at a slightly higher risk of disease (OR=1.1; 95% CI 0.5-2.5) when compared to primiparas, biparas, and tertiparas and at a significantly higher risk (OR=1.4; 95% CI 0.6-3.3) when compared to multiparas (>3 pregnancies). In case of a miscarriage, the risk of disease lowers (OR=0.8; 95% CI 0.53-1.28), when compared to nulliparas.

Age at first live birth is also an important factor. First birth at > 35 years of age was connected with elevated risk for OC (OR=1.7; 95% CI 0.66-4.5), when compared to women who give birth to their first child < 25. The risk was not significantly higher for women who delivered first time between 26 and 34 years of age.

Women who did not breastfeed their children were at a 1.7-fold higher risk for OC (OR=1.73; 95% CI 1.22-2.45) when compared to breastfeeding mothers.

The influence of time to weaning on OR was evaluated among breastfeeding women. Mothers who were breastfeeding their children for less than one month were at a slightly higher risk of disease (OR=1.11; 95% CI 0.13-1.42) than women who were breastfeeding for six months or more.

Women who never took contraceptives were at a 13.59-fold higher risk of disease (OR=13.59; 95% CI 6.63-27.88) when compared to women who have used or currently use contraceptives. Duration of oral contraceptive use is also an important factor. The OR for women who received contraceptives for one to three years was OR=0.09; 95% CI 0.03-0.2, for four to six years was OR=0.04; 95% CI 0.005-0.30, whereas for > six years it was OR=0.16; 95%CI 0.04-0.6, when compared to patients who used contraceptives for < one year.

Women who never received HRT were at a 1.9-fold higher risk for OC (OR=1.9; 95% CI 1.04-3.58) when compared to women who have received or currently receive HRT. The OR for women who used HRT for < one year was OR=2.5; 95% CI 0.30-20.00, when compared to women used HRT for one to six years.

The OR for non-smokers was OR=2.5; 95% CI 1.0-5.26 when compared to women who smoked between one to five cigarettes a day and OR=1.5; 95% CI 0.90-2.25 for smokers of > five cigarettes a day. The results are presented in Table 3. The risk for non-smokers at the age of > 45 years rises (OR=2.12; 95%CI 1.42-5.00), when compared to same age smokers of > five cigarettes a day.

The OR for women > 45 years of age who do not drink coffee was OR=2.0, 95% CI 1.42-3.33 when compared to women who drank between one to three cups of coffee and OR=1.5, 95% CI 0.31-8.33 compared to women who drank > three cups of coffee a day.

The OR for women who do not drink alcohol was OR=3.3, 95% CI 0.76-8.33 when compared to women who consumed 20-25 grams of pure ethanol once every two weeks, and OR= 2.0, 95% CI 0.83-5.00 when compared to women who drank more alcohol.

The OR for women who lead a sedentary lifestyle was OR=1.4, 95% CI 0.52-3.4 when compared to women who exercised once every two weeks and OR=1.1, 95% CI 0.58-2.5 when compared to women who exercised once a week. The OR for women who exercised three times a week was OR=1.3, 95% CI 1.36-4.0 compared to women who led a sedentary lifestyle. The exact data are presented in Table 4.

Women < 45 years of age, suffering from major depression, were at an increased risk for OC (OR=4.8, 95% CI

0.52-45.1) in comparison to women who do not reveal signs of depression.

RAFOCC was designed on the basis of the OR analysis for the selected parameters. The results are presented in Table 5.

The analysis of test sensitivity and specificity revealed that women who scored > 31.5 on a scale from 0-72, with 72% sensitivity (95%CI 0.656-0.783) and 75% specificity (95% CI 0.718-0.770), faced a statistically significantly increased risk for OC.

Discussion

The etiology of OC has not been fully elucidated. Numerous factors take part in the process of carcinogenesis. Undoubtedly, genetic, hormonal and environ- mental interactions are responsible for the neogenesis of OC cells. Ovarian carcinoma affects women of all ages - in 2002 there were 19 OC cases among very young women (<19 years of age) in Poland, but about 80-90% of the neoplasms are diagnosed in women > 40 years of age. In the present study, mean age at diagnosis was 56 years and the youngest patient was 20 years. Mean ages at diagnosis were 38 and 59 years in the group of women ≤ 45 and > 45, respectively. OR analysis revealed a tendency for OC risk to increase with age. Women over 65 are at a 20-fold higher risk of disease.

Among all patients with OC, early-stage carcinoma is detected most often in younger, up to 45 years of age, women (51%), while Stages III and IV are diagnosed predominantly in women > 55 years of age (75%) [2].

Regional, ethnic, and racial differences in OC occurrence have been reported. Low standardized incidence ratio (SIR) of Japanese women in the Oceania (OR=9.8) and high SIR of white inhabitants of that same region (OR=14.4), are the best examples of racial differences. The influence of environmental factors may be confirmed by higher OC incidence in Jewish women who were born in the USA or Europe but live in Africa, than in Jewish women born and living in Africa [5-8]. Also, immigration from low- to high-incidence geographical regions causes the ratio to reach values typical for inhabitants of a given region in just a few generations. White women are affected by OC significantly more often than their Black peers. Moreover, studies proved that large city dwellers with tertiary education suffer from cancer more frequently than women with lower education residing in rural areas (OR=1.3 *vs*. OR=1), what might be connected with dietary differences, especially with the fact that the former eat less fresh fruit and vegetables but more processed foods than the latter. [7]. However, the present authors observed a tendency that was contrary to most literature reposts as far as place of inhabitance and education were concerned. The greatest number of OC patients had secondary education (45.54%), followed by VET (34.16%), and tertiary (20.30%) education. Almost half of the respondents (45%) lived in small towns (≤ 10,000 inhabitants) and only 18.81% were large city dwellers. It might have been connected with the place where the data was collected, as well as access to commercial prevention, diagnostic and medical services in other Poznań centers.

Obesity constitutes to be an important cause of morbidity and mortality. According to Sekhon *et al.*, [9], obese women are at a increased risk for OC, what was also confirmed by the present study. Mean BMI in OC patients was 26.3 and was higher than mean BMI of controls. It ought to be emphasized that obese women with BMI > 30 are at a four-fold higher risk for OC than their peers with normal BMI. Most importantly, the risk rises by seven-fold in young (< 45 years of age) obese women.

The dependence between physical activity and the risk of malignant neoplasms has been the topic of numerous studies and investigations [10-14]. It seems safe to conclude that regular physical activity reduces the risk of colon, breast, endometrial, and prostate cancers. In order to maintain proper BMI (18.5-25 kg/m^2) if a person leads sedentary lifestyle, moderate level of physical activity (30 minutes three times per week), is recommended, whereas more intense exercise is advised to prevent cancer [10].

The influence of regular, moderate level physical activity on declining risk for OC has its roots in the beneficial effect of physical activity on the immune system and hormonal regulation. Excessive physical exercise may delay first menses, cause irregularity of menstrual cycles, primary or secondary amenorrhea resulting from the decline of ovulatory cycles. The production of steroid hormone-binding globulins, leading to decreased estrogen activity, also declines [11, 14, 15].

Tobacco smoking is the main, together with diet, environmental risk factor for OC. In the developed countries about 25%-30% of all cancer deaths are connected with smoking [10]. Analysis of the connection between tobacco smoking and alcohol use as risk factors for OC failed to demonstrated such a correlation. Paradoxically, some studies demonstrated that alcohol use may in fact lower the OC risk by decreasing the level of gonadotropins which, in physiological conditions, may stimulate tumor growth in the ovaries. The present study demonstrated a decreased risk for OC in respondents who smoked, used alcohol, and/or consumed coffee.

On average, OC patients consumed one and controls had two cups of coffee a day. Mean number of cigarettes among OC women was 1.3, with the maximum of 20 cigarettes a day, while mean number of cigarettes a day in the control group was two, with significantly higher maximum number of 45 cigarettes a day. The OR analysis for OC reveals that women > 45 years of age who do not drink coffee have a two-fold higher risk than peers who consume coffee. Regardless, large amounts of coffee are not recommended to people before 45 years because the risk in that age group after drinking three cups of coffee a day is slightly elevated

and increases the OR by 1.2-fold. The risk for non-smoking females is 2.5-fold higher than for smokers, similarly to alcoholic beverages (two-fold increase).

Hormonal, genetic, and environmental interactions have been shown to increase the risk for OC.

Age at first menarche as a possible risk factor for OC has been the topic of research in Great Britain, Greece, and Italy, but no correlation has been found. Nevertheless, after studying a total of 1,400 OC patients, early menarche and later painful menstrual cycles were detected [16].

A vast majority of authors [16, 17] assume late age at menopause to be a factor promoting OC. Franceschi *et al.*, calculated the OC risk factor for the following ages of menopause: < 44, between 45-52, and > 52 years of age [18]. Despite the lack of statistical significance, a tendency was observed: the later the age of menopause, the greater the risk for OC. The risk level in the studied age groups was 1.4: 1.6: 1.9, respectively.

The present study demonstrated that early menarche and late menopause increase the risk for OC. Women who were < 11 years old at their first menarche have a two-fold higher chance of ovarian malignancy when compared to women who were 13 years old at first menarche. Women who menstruate over the age of 55 are at a 1.4-fold elevated risk of disease compared to peers who were menopausal before the age of 45.

According to Parazzini *et al.*, [19], if menopause occurred between 50-53 years of age in a nullipara, the relative risk for OC is at the level of 1.3, but increases to 1.4 if the same nullipara underwent menopause after the age of 54.

A protective effect of parity and lactation, depending on the number of pregnancies and time to weaning, has been reported as well. Lactation, due to the fact that it inhibits ovulation, is a factor that lowers the risk for OC. The present study has confirmed that dependency. Women who do not breastfeed their children are at a 1.7-fold greater risk of disease.

Early age at first birth (< 25) and multiparity reduce the risk of OC even by 40-60% when compared to nulliparas and women who gave birth after the age of 35 [8, 20, 21], what was also confirmed by the present results. The risk of disease increases 1.7-fold for primiparas > 35 years of age when compared to women who gave birth before the age of 25. Parazzini *et al.*, [19] calculated the relative risk for OC to be 1.3 for nulliparas and that factor might be responsible for 5% of OC cancer cases. The present investigation brought similar results (OR=1.4). Contrary to the present findings, the literature [16] reports detrimental effect of previous miscarriages on the OC risk. The authors observed that if a pregnancy was miscarried, the risk decreased (OR=0.8) in comparison to women who never conceived. The discrepancy between the present results and other authors may stem from the fact that the authors calculated the OR in relation to nulliparas, whereas authors of the above mentioned publications may have juxtaposed miscarriage and term pregnancies. Inhibited ovulation decreases the risk so it seems a miscarried pregnancy should also have a protective effect.

Oral contraceptives are believed to reduce the risk for OC. According to the present study, women who never used contraceptives are at a 13.6-fold higher risk of disease. Protective effect of contraceptives begin after a few months and lowers the risk of malignancy, even by 50% after five or more years. After four yo six years of contraceptive use, the risk reaches the level of OR=0.04. Schlesselman [22] demonstrated that the use of contraceptives for four, eight, and 12 years reduced the risk by 40%, 53%, and 60%, respectively. Vassey [23] also showed a decline in OC risk, and the relative risk was RR = 0.4. The protective effect continues for at least ten years after a woman stopped using contraceptives [8, 17]. The studies on the dependency between contraceptives and OC found no increased risk due to estrogen use. Oral contraceptives are the strongest protective factor for OC. Inhibited ovulation for the course of one year has the same protective effect as pregnancy and term delivery. Carriers of *BRCA1* and *BRCA2* gene mutations are recommended to use contraceptives.

Hormonal replacement therapy (HRT) and its effect on the risk for developing OC has been the source of much debate and controversy. Neither protective nor predictive influence has been unequivocally proven. Some studies [24] show a time connection between estrogen use for over ten years and slightly elevated risk of disease. Rodriguez *et al.*, [24] calculated the risk for women using HRT to be OR=1.15, growing to OR=1.40 after six to ten years and OR=1.71 after 11 years. Patients who start estrogen therapy ought to be aware of the fact that it may significantly lower the concentration of Ca125 – the best known marker for OC [16, 17].

The present research revealed a protective effect of HRT. Women who never used HRT have a 1.9-fold higher risk for OC. Nevertheless, it is not recommended to use HRT for less than one year because in such case the RR reaches the level of 2.5 when compared to women who use HRT for one to six years.

Preventive measures and early diagnosis are the most effective methods of fighting cancer. Detection in the non-symptomatic phase has the best outcome and the greatest economic and social benefits. Screening test is an essential element of secondary prevention. It is performed in people without visible symptoms of the disease. Each screening test is connected with appropriate direction, selection, and program design [25].

Growing knowledge about risk factors and behaviors for malignant neoplasms increases the probability of cancer elimination and avoidance in everyday life. Awareness of the problem, combined with knowledge of cancer symptoms, may also contribute to more timely treatment in early stages of the disease. Unfortunately, the relevant Polish lit-

erature lacks reports on the number of women at higher risk of malignancy, especially OC.

Undoubtedly, what was confirmed by various studies and investigations, carriers of *BRCA1* and *BRCA2* gene mutations have an elevated life-long risk for ovarian and breast cancers. It is important to know which non-genetic factors, and in what configurations and intensity, might increase the risk for the malignant disease. That knowledge is essential to design a prevention strategy.

To the best of the present authors' knowledge, no attempts to evaluate the level of OC risk have been made so far. The literature, apart from well-known genetic factors, lacks reports on the scale of the problem and the risk assessment level. Also, no model or tool to calculate the risk has been created, unlike in the case of breast cancer.

The RAFOCC might select high-risk women in need of further monitoring and/or diagnostic tools, from the population of healthy females. If a patient scores > 31.5 points on the scale from 0-72, with 72% sensitivity and 75% specificity of the test, it seems safe to conclude the risk for OC is elevated. The management algorithm should also include the test of HE4, CEA, VCAM, and Ca125 markers, that are indicators of cancer progression and biomarkers for detection of OC. A gynecological exam with transvaginal ultrasound should constitute the next phase of the diagnostic process [26, 27].

Hopefully, the possibility to assess the risk and detect cancer with highly sensitive and specific tests in early stages of the disease will allow to change OC from 'the silent killer' to a highly detectable and curable neoplasm.

Conclusions

RAFOCC is a useful screening tool for identifying women with increased risk for OC. Women who scored > 31.5 according to RAFOCC face a statistically significantly increased risk for OC. High-risk patients according to RAFOCC should be offered timely medical care and undergo further diagnostic testing.

References:

[1] Nowak-Markwitz E., Spaczyński M.: "Ovarian cancer – modern approach to its origin and histogenesis". *Gin. Pol.* 2012, *83*, 454.

[2] Bray F., Loos AH., Tognazzo S., La Vecchia C.: "Ovarian cancer in Europe: cross-sectional trends in incidence and mortality in 28 countries, 1953-2000". *Int. J. Cancer,* 2005, *113*, 997

[3] Pięta B., Grodecka-Gazdecka S., Chmaj-Wierzchowska K., Kramer L., Opala T.: "Analysis of the odds ratio for developing breast cancer in women". *Gin. Pol*., 2011, *82*, 755.

[4] Gromadzka A., Kubiczak M., Jankowska A.: "Gene therapy applications in gynecologic malinances management". *Ginekol. Pol.,* 2010, *81*, 50-54

[5] Smoleń A., Stachowicz N., Czekierowski A., Kotarski J.: "The estimation of the probability of tumor malignacy on the basis of test combination in the primary diagnosis of adnexal tumors". *Ginekol. Pol.,* 2010, *81*, 254.

[6] Bednarek W., Mazurek M., Ćwiklińska A., Barczyński B.: "Expression of select angiogenesis markers and modulators in pre-, peri-, and postmenopausal women with ovarian cancer". *Ginekol. Pol.*, 2009, *80*, 88.

[7] Pięta B., Chmaj-Wierzchowska K., Opala T.: "Life style and risc of development of breast and ovarian cancer". *AAEM.,* 2012, *19*, 379.

[8] Pięta B., Chmaj-Wierzchowska K., Opala T.: "Past obstetric history and risc of ovarian cancer". *AAEM.,* 2012, *19*, 385.

[9] Beehler G.P., Sekhon M., Baker J.A., Teter B.E., McCann S.E., Rodabaugh K.J., Moysich K.B.: 'Risk of ovarian cancer associated with BMI varies by menopausal status". *J. Nutr.* 2006, *136*, 2881.

[10] Zatoński W.: "European Code of Fight against cancer". 2003

[11] Kaleta-Stasiołek D., Szmigielska K., Jegier A.: "Physical activity in selected cancers prevention". *Pol. Arch. Med. Wewn.* 2003, *6*, 661.

[12] Pukkala E., Poskiparta M., Apter D., Vihko V.: "Life-long physical activity and cancer risk among Finnish female teachers". *Eur. J. Cancer. Prev.*, 1993, *2*, 369.

[13] Dorgan J.F., Brown C., Barrett M, Splansky G.L., Kreger B.E., D'Agostino R.B., *et al.*: "Physical activity and risk of breast cancer in the Framingham heart study". *Am. J. Epidemiol.*, 1994, *139*, 662.

[14] Verloop J., Rookus M.A., van der Kooy K., Van Leeuwen F.E.: "Physical activity and breast cancer risk in women aged 20-54 years". *J. Natl. Cancer Inst.*, 2000, *92*, 128.

[15] Zadrożny M.: "Treatment of malignant and benign diseases of breast". *In:* Pertyński T. (ed). *Diagnostics and therapy of the age of menopause*. Wrocław: Urban&Partner, 2004.

[16] Gabryś M.St., Popiela A., Popiela M., Mazur R.: "Ovarian cancer in the aspect of oncological profilaxis". *Polska Medycyna Rodzinna*, 2004, *6*, 837.

[17] Markowska A.: "Review of theories on development of ovarian cancer. Leptin as a potential agent engaged in carcinogenesis". *J. Oncol*., 2007, *57*, 518.

[18] Franceschi S., La Vecchia C., Booth M., Tzonou A., Negri E., Parazzini F., *et al.*: "Pooled analysis of 3 European case-control studies of ovarian cancer: II. Age at menarche and menopause". *Int. J. Cancer*, 1991, *19*, 57.

[19] Parazzini F., Chatenoud L., Chiantera V. Benzi G, Surace M, La Vecchia C.: "Population attributable risk for ovarian cancer". *Eur. J. Cancer*, 2000, *36*, 520.

[20] Kutarska E.: "Ovarian cancer – ways to improve curability". *Onkologia i Radioterapia*, 2007, *1*, 26.

[21] Bulsa M., Czaja-Bulsa G.: "Ovarian cancer prevention". *Family Medicine&Primary Care Review,* 2006, *8*, 375.

[22] Schlesselman J.J.: "Net effect of oral contraceptive use on the risk of cancer in women in the United States". *Obstet. Gynecol.,* 1995, *85*, 793.

[23] Vessey M.: "Mortality in relation to oral contraceptive use and cigarette smoking". *Lancet,* 2003, *362*, 185.

[24] Rodriguez C., Callae E.E., Coates R.J.: "Estrogen replacement therapy and fatal ovarian". *Am. J. Epidemiol.*, 1995, *141*, 828.

[25] Michalak J., Godlewski D., Grodecka-Gazdecka S.: "Methodology of breast cancer screening". *Przegląd Położniczo-Ginekologiczny*, 2003, *3*, 231.

[26] Park Y., Lee J.H., Hong D.J., Lee E.Y., Kim H.S.: "Diagnostic performances of HE4 and Ca125 for the detection of ovarian cancer from patients with various gynecologic and non-gynecologic diseases". *Clin. Biochem.*, 2011, *44*, 884.

[27] Paek J., Lee S.H., Yim G.W., Lee M., Kim Y.J., Nam E.J., et al.: "Prognostic significance of human epididymis protein 4 in epithelial ovarian cancer". *Eur. J. Obstet. Gynecol. Reprod. Biol.,* 2011, *158*, 338.

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