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Past obstetric history and risk of ovarian cancer

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Abstract

Introduction: Early age at menarche and late age at last menstrual period, as well as other reproductive factors, may be the cause of development of some types of cancer concerning the female reproductive organs. It has been estimated that late menopause may be responsible for the occurrence of even 16% of cases of ovarian cancer in the population. The incidence of ovarian cancer is also higher among nulliparous women, and among those who rarely become pregnant.

Objective: The objective of the study was analysis of the effect of reproductive factors on the risk of ovarian cancer.

Methodology: The study covered healthy women, without the diagnosis of focal lesions in the ovaries, and women with the diagnosis of ovarian cancer. The study was conducted during the period from September 2007 – November 2011, and covered a total number of 1,346 women. Odds ratio was calculated for individual risk factors. Statistical analysis was performed by means of the statistical packages STATISTICA v8, GrafPad Instat v 3.00, Analyse-it v. 2.2, and Cytel Studio StatXact-8. Statistical hypothesis were verified on the level of significance $p \leq 0.05$.

Results: Among females who began menstruating by the age of 11, the risk of ovarian cancer was 1.6 higher than among those in whom the first period occurred at the age of over 13. Similarly, among women who menstruated at the age of over 55 the risk of development of ovarian cancer was 1.4 times higher. The age at which a woman delivered her first live baby is also of importance. In the group of women who gave birth at the age of over 35, the risk was elevated and remained on the level of OR=1.7; 95%CI 0.66-4.5, compared to those who bore the first baby under the age of 25. If the pregnancy was terminated with miscarriage, the risk of contracting ovarian cancer decreases, and was on the level of OR=0.8; 95%CI 0.53-1.28, compared to the women who have never been pregnant. Among patients who did not breastfeed their babies, ovarian cancer risk was 1.7 times higher, compared to those breastfeeding.

Conclusion: Reproductive factors exert a significant effect of the risk of development of ovarian cancer.

Key words

ovarian cancer, risk factors, reproductive factors

INTRODUCTION

The style of sexual life exerts an effect on the development of reproductive system cancers. Some behaviours may enhance the probability of exposure to sexually-transmitted carcinogenic factors. Ovarian cancer risk increases in women who started sexual life early, while it rarely occurs in virgins. A positive correlation has also been observed between this risk and the number of sexual partners, it increased with the number of partners of women, as well as the number of sexual partners of the husband or partner. This clearly indicates an important role of males in transmitting agents which may increase cancer risk, in this case, HPV virus [1, 2, 3, 4].

Based on the patters of behaviours of members of an individual community, morbidity due to ovarian cancer may be foreseen. A high level of morbidity is observed in Latin America, where the percentage of legal prostitution is the highest. In this population, the risk increases not only for the prostitutes, but also for monogamous wives whose husbands show high extramarital activity [2, 3, 5, 6].

The effect of high sexual activity on the occurrence of carcinomas other than uterine cancer, has also been confirmed, e.g. penile, vaginal and vulvar cancer.

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Early age at occurrence of the first menstruation and late age at last menstrual period may be the cause of the development of some reproductive system carcinomas in women.

In women who had been sexually-active for a period of over 40 years, the risk of breast cancer was twice as high as among those who had menstruated for 30 years. Women who started menstruating at the age of about 12 were at a 3.7-fold higher risk of the development of breast cancer, compared to those in whom the first period occurred at the age of over 13 [7].

Early age at menarche and late age at menopause are also ovarian cancer risk factors. It has been estimated that late menopause may be responsible for the occurrence of even 16% of cases of ovarian cancer in the population [8, 9, 10, 11, 12, 13].

In nulliparous women, and those who rarely became pregnant, the incidence of ovarian cancer was higher. The relative risk for women who had never given birth was 1.3, and it has been estimated that this factor is responsible for 5% of cases of ovarian cancer. Four or more childbirths probably decrease ovarian cancer risk [5, 9, 14, 15].

It is also noteworthy that each subsequent pregnancy decreases the risk of ovarian cancer by 10-15%, on average [10].

Low fertility, which is frequently the result of the lack of ovulation, is also related with an increased risk of ovarian cancer. Therefore, the conclusion can be drawn that, on the one hand, the lack of ovulation is associated with an increased risk; but on the other hand, an inhibition of ovulation as a

result of pregnancy, lactation, or hormonal contraception, is a factor reducing this risk [9, 13, 16].

There are also reports which indicate that ovulation itself may be a mutagenic factor. During ovulation, the epithelium adjacent to the site of the graafian follicle breaks open, and the damage caused is repaired by the proliferation of epithelial cells. In this process, inclusive cysts are formed containing epithelial cells, in which the process of carcinogenesis may be initiated [9, 13, 16].

While analyzing the effect of breastfeeding on the development of ovarian and breast cancer it should be stated that breastfeeding protects against the development of both carcinomas, and its protective value increases with the prolongation of lactation [9, 14, 15, 16, 17, 18].

OBJECTIVE

The objective of the study was analysis of the effect of reproductive factors on the risk of ovarian cancer.

MATERIAL AND METHOD

The study covered healthy women, with no focal changes diagnosed in the ovaries, and women with the diagnosis of ovarian cancer. The study was conducted from September 2007 – November 2011 among patients of the Gynaecological-Obstetric Clinical Hospital, on Polna Street in Poznań, and patients in the Transfiguration Clinical Hospital in the Oncologic Surgery Ward. A total number of 1,346 women were examined.

The criterion for qualification of women into the group who were healthy (n=1,144) with a normal result (without changes) in physical examination and medical history taking performed by a medical specialist, and no deviations from the normal state revealed in vaginal ultrasound. The subsequent criterion was family history taking, excluding the genetic risk factors. The basis for qualification into the group of women with ovarian cancer (n=202) was an histopathologic test result obtained after surgery.

One of the research instruments was a questionnaire consisting of 40 items designed for the purpose of the study. The questionnaire contained questions concerning socioeconomic data, menstrual and obstetric history, breastfeeding, and the course of postpartum period.

Variables, such as age, age at menarche, age at first pregnancy, age at first childbirth, were described with the use of arithmetic mean and standard deviation, minimum and maximum values in the groups analyzed. Goodness of fit of the distribution of the above-mentioned variables with normal distribution was tested with the use of Shapiro-Wilk test for normality. The significance of differences between two independent groups for normally distributed variables were assessed by means of t-Student test (for equal variances) or Welch test (for unequal variances). In other cases, non-parametric Mann-Whitney test was applied.

Nominal variables, such as miscarriages, therapeutic interventions during the postpartum period, were presented in counts and respective percentages. The relationship between the above-mentioned variables and affiliation to an individual groups was investigated by means of chi-square test, Fisher's exact test or Fisher-Freeman-Halton exact test.

Odds ratio was determined for individual risk factors.

Risk factor	Present	Absent	Total
Study group	a	b	a+b
Control group	c	d	c+d
Total	a+c	b+d	a+b+c+d

Odds ratio of developing breast and ovarian cancer was calculated when the risk factor was present.

$$\text{Ratio}_{\text{Yes}} = \frac{\frac{a}{a+c}}{1-\frac{a}{a+c}}$$

and when it was absent

$$\text{Ratio}_{\text{No}} = \frac{\frac{b}{b+d}}{1-\frac{b}{b+d}}$$

Odds ratio (OR) was also calculated with 95% confidence interval

$$\text{OR} = \frac{a*d}{c*b}$$

Calculations were performed by means of statistical packages: STATISTICA v8, GrafPad Instat v 3.00, Analyse-it v. 2.2 and Cytel Studio StatXact-8. Statistical hypotheses were verified on the level of significance of $p \leq 0.05$.

Consent for the study (No. 574/11) was obtained from the Bioethical Commission at the Karol Marcinkowski Medical University in Poznań,.

RESULTS

Early age at menarche and late age at last menstrual period are associated with increased risk of ovarian cancer. Among women who began menstruating by the age of 11 the risk of ovarian cancer is 1.6 higher than among those in whom the first period occurred at the age of over 13, OR= 1.66; 95% CI 0.9-3.3. In women who menstruated at the age of over 55, the risk was 1.4 higher; OR for this group of women was 1.42; 95% CI 0.48-4.18.

Ovarian cancer risk increased 2.7 times among woman who became pregnant for the first time at the age of over 35, compared to those who were pregnant before the age of 25; OR for this group of women was 2.72; 95% CI 1.05-7.05.

The effect of the number of pregnancies on increased odds ratio was also analyzed. These calculations covered patients aged over 45, irrespective of whether it was terminated with miscarriage or full term delivery of a live baby. For women who had never been pregnant, ovarian cancer risk was slightly elevated and odds ratio was OR 1.1; 95% CI 0.5-2.5, compared to the women who conceived once, twice and three times. Nevertheless, compared to women who conceived more than three times, the risk for women who had never been pregnant increased, and the odds ratio was on the level of OR=1.4; 95% CI 0.6-3.3.

If the pregnancy was terminated with miscarriage, ovarian cancer risk decreased and was on the level of OR=0.8; 95% CI 0.53-1.28, compared to women who had never been pregnant.

The age at which a woman delivered the first live baby was also important. In the group of women who gave birth at the age of over 35, the risk was elevated and remained on the level of OR=1.7; 95% CI 0.66-4.5, compared to women who delivered their first baby at the age of under 25. Among women who gave birth at the age 26-34, the risk of ovarian cancer was not significantly elevated.

Among patients who did not breastfeed their babies, ovarian cancer risk was 1.7-fold higher, compared to those breastfeeding; in the group of patients who did not breastfeed OR was 1.73; 95% CI 1.22-2.45.

In women who breastfed, the effect of the duration of lactation on odds ratio was analyzed.

Among women who breastfed for a period shorter than one month, the risk of ovarian cancer was slightly elevated OR=1.11; 95% CI 0.13-1.42, compared to the women who breastfed for 6 months and longer.

DISCUSSION

Age at menarche, as a risk factor of the development of ovarian cancer, was the object of studies in the United Kingdom, Greece and Italy. No relationship was found between the age at occurrence of the first menstruation and risk of contracting the disease. However, analysis of a total number of 1,400 women suffering from ovarian cancer demonstrated that the first menstruation occurred at a younger age, and with subsequent menstrual periods being painful [9, 10, 19].

The greatest majority of researchers [9, 10, 19, 20] assumed that late age at menopause is the factor favouring the occurrence of ovarian cancer. In their studies, Franceschi et al. [21] estimated ovarian cancer risk for women in whom menopause occurred at the age of under 44, between 45 – 52, and over 52. Although the values obtained were statistically insignificant, a tendency was observed that this risk increased with later age at menopause. In individual groups, the level of risk was 1.4: 1.6: 1.9, respectively.

The presented study showed that both early age at menarche and late age at menopause increase ovarian cancer risk. Among women who began menstruating at the age of under 11, the risk was nearly twice as high as among those who had their first menstruation at the age of over 13. For women who menstruated beyond the age of 55, the risk was 1.4 times higher, compared to women in whom menopause occurred early, at the age of under 45.

According to Parazzini et al. [22], if menopause occurred at the age between 50-53 and the woman have never given birth, the relative risk of contracting ovarian cancer remained on the level of 1.3. However, if in these nulliparous woman menopause would occur at the age of over 54, the risk of falling ill would increase up to 1.4.

A protective effect of pregnancy and lactation was noted, with relation to the number of past pregnancies and duration of lactation. Lactation is the factor decreasing the risk of ovarian cancer as a result of the inhibition of ovulation. This relationship was also confirmed in the presented study. Among women who did not breastfed their children the risk of ovarian cancer was 1.7 times higher.

Possessing numerous offspring and bearing the first baby at the age of under 25 decreased the risk of ovarian cancer even by 40-60%, compared to nulliparous women and those who delivered their first baby at the age of over 35 [13, 23, 24]. This was also confirmed by the presented study. For the group of women who gave birth at the age of over 35, the risk of the development of ovarian cancer increased 1.7 times, compared to those who conceived and bore their first baby at the age of under 25. Parazzini et al. [22] reported that the relative risk for nulliparous women was 1.3, and this factor may be responsible for 5% of cases of ovarian cancer. Similar results were obtained in the presented study – the risk calculated for nulliparous women was 1.4, compared to those who gave birth. In the literature [19], an unfavourable effect of earlier past miscarriages on ovarian cancer risk was reported. In the presented study an opposite relationship was noted – if the pregnancy was terminated with miscarriage the risk of contracting the disease decreased and remained on the level of OR=0.8, compared to women who have never been pregnant. The discrepancies between literature reports and the results of the presented study may result from the fact that in this study, odds ratio for contracting ovarian cancer was calculated in relation to women who have never been pregnant. The authors of the above-mentioned reports could have considered miscarriage with respect to pregnancies terminated with full term delivery. Each inhibition of ovulation decreases risk; therefore, it seems that pregnancy which terminated with miscarriage should also exert a protective effect.

Some researchers [19, 25, 26] are of the opinion that physiological ovulation may be a mutagenic factor. During ovulation, the ovarian epithelium is disrupted, at the site of disruption repair processes are initiated, associated with proliferation of epithelial cells. Proliferation processes may increase the risk of development of cancer by the occurrence of spontaneous mutations of tumour suppressor gene *p53*, as well as through the formation of inclusive cysts, which are considered as precursors of the carcinogenic processes. Based on the metaanalysis conducted, Ness and Cottreau [27] did not confirm the relationship between ovulation and *p53* mutation.

In the light of the latest studies, stimulation of ovarian function also exerts an effect on ovarian cancer risk. Similar to physiological stimulation, this process is associated with a high proliferation of the ovarian epithelium. Nevertheless, during therapy the level of gonadotropine is considerably elevated, which, according to the latest clinical observations, may increase the risk of contracting ovarian cancer. The risk of ovarian cancer increases 2.8 times in women using ovulation stimulating drugs. An increase risk was also observed in women with polycystic ovarian syndrome, which is characterized by hypersecretion of LH [9, 10, 26, 28].

CONCLUSIONS

1. Early age at menarche and late age at menopause increase the risk of ovarian cancer.
2. Lactation and its duration, as a result of inhibition of ovulation, is the factor reducing the risk of contracting ovarian cancer.
3. Possession of numerous offspring and bearing the first infant at the age of under 25 reduces the risk of ovarian cancer, compared to nulliparous women and those who gave birth at the age of over 35.
4. Pregnancy which terminated with miscarriage is associated with the reduction of ovarian cancer risk, compared to women who have never been pregnant.

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