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Co-existence of a second primary malignancy in patients with either ovarian or endometrial cancer

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Objective. The aim of publication was the retrospectively analysis patients with ovarian and endometrial cancers at which occurrence second primary malignancies were affirmed.
Material and methods. From 1989-1999 117 ovarian and 144 endometrial carcinomas have been evaluated and 33 multiple primary malignant neoplasms were detected. All double neoplasms have been histological recorded, doubtful cases have been excluded. Coexistence of ovarian and endometrial carcinoma with second primary malignant neoplasm was evaluated and controlled for age, parity, menarche age, last menstruation age, length of reproductive period, hypertension, diabetes, body mass index, pelvic inflammatory disease (PID), grading, staging.
Results. Two primary cancers coexistence was found in 17 patients with ovarian tumour (14.3%) and in 16 patients with endometrial tumour (11.2%). The most often prevalent neoplasm in both groups was breast cancer (5.1%) and (6.4%). In the patients with ovarian cancer, breast cancer was found at much younger age than in patients with endometrial malignancy ($p=0.02$). It was also observed that breast cancer diagnosis preceded that of ovarian cancer about 11.2 year average and about 3.2 year in women group with endometrial cancer.
Stomach cancer however, was diagnosed earlier at the group with endometrial cancer, than at the group with ovarian cancer, and difference was statistically significant ($p<0.001$). At the group with endometrial cancer morbid obesity was observed statistically significant more often ($p=0.03$) than at the group with ovarian cancer.
Conclusion. Patients with ovarian and endometrial carcinoma should be carefully and regularly followed up by monitoring et every anatomic site, especially the breast, uterus, stomach, and bowel, in order that the development of a second primary carcinoma can be detected as early as possible, and not be overlooked in examinations.

Analiza 33 przypadków wspólnego występowania drugiego pierwotnego nowotworu złośliwego u chorych na raka jajnika i raka endometrium

Cel. Celem pracy była retrospektywna analiza pacjentek z rakiem jajnika oraz rakiem błony śluzowej macicy, u których stwierdzono ponadto występowanie drugiego pierwotnego nowotworu złośliwego.
Materiał i metoda. Poddano analizie grupę 117 chorych na raka jajnika oraz 144 pacjentek z rakiem endometrium, leczonych w latach 1989-1999. U 33 pacjentek stwierdzono występowanie drugiego pierwotnego nowotworu złośliwego. Wspólne występowania raka jajnika oraz raka endometrium z drugim pierwotnym nowotworem złośliwym oceniono pod względem takich czynników jak: wiek, rodność, wiek pierwszej i ostatniej miesiączki, występowanie nadciśnienia tętniczego, cukrzycy, nadwagi, chorób zapalnych miednicy mniejszej, stopień zróżnicowania histologicznego i zaawansowania klinicznego nowotworu.
Wyniki. Wspólne występowanie dwóch pierwotnych nowotworów złośliwych stwierdzono u 17 pacjentek z rakiem jajnika (14,3%) oraz u 16 kobiet z rakiem endometrium (11,2%). Najczęstszym drugim nowotworem złośliwym w obu badanych grupach chorych był rak sutka (5,1%) i (6,4%). U pacjentek z rakiem jajnika nowotwór gruczołu piersiowego stwierdzano znamiennie w młodszym wieku aniżeli u chorych na raka endometrium ($p=0,02$). Zaobserwowano ponadto, że rozpoznanie raka sutka poprzedzało średnio o około 11,2 lat wykrycie raka jajnika oraz o 3,2 lat w grupie kobiet leczonych z powodu raka endometrium. Natomiast występowanie raka żołądka wcześniej stwierdzano u chorych na raka endometrium aniżeli u pacjentek z rakiem jajnika i była to zależność znamienna statystycznie ($p<0,001$). Stwierdzono ponadto, że statystycznie znamiennie częściej ($p=0,03$) obserwowano olbrzymią otyłość u chorych na raka endometrium ze współistnieniem drugiego nowotworu, aniżeli w analogicznej grupie kobiet chorych na raka jajnika.

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Wnioski. Pacjentki chore na raka jajnika i raka błony śluzowej macicy powinny być szczególnie uważnie badane pod kątem występowania drugiego pierwotnego nowotworu złośliwego. Dotyczy to szczególnie takich narządów jak sutek, żołądek i jelito, tak, by rozwój drugiego nowotworu mógł zostać jak najwcześniej rozpoznany.

Key words: ovarian cancer, endometrial cancer, breast cancer, coexistence second primary malignant neoplasm
Słowa kluczowe: rak jajnika, rak endometrium, rak sutka, współistnienie drugiego pierwotnego nowotworu złośliwego

Introduction

Multiple primary malignancies have been divided into two sub-groups. The term metachronic tumours is used for primary malignancies which appear within six months or more of one another. Synchronic tumours appear simultaneously or are recognized within a period shorter than six months [1]. Among the reasons for multiple malignancies those recognized as the most common include genetic defects, disturbancies of the immunological system, exposure to environmental carcinogens and the effects of previous oncolytic treatment [1, 2]. In women with either ovarian or endometrial cancer metachronic or synchronic cancers of the breast, the stomach and the colon are significantly more common. One may also observe a reversal of this situation – i.e. in women with breast cancer or colorectal cancer the likelihood of developing endometrial cancer, ovarian cancer or breast cancer is increased [3]. The best documented genetic defect associated with endometrial cancer is the Lynch II syndrome. The Lynch II syndrome is a subgroup of Hereditary Non Polyposis Colorectal Cancer in which colorectal cancer, endometrial cancer and breast cancer are inherited acc. to the autosomal, dominant pattern [4-7]. Among the multiple malignancy syndromes associated with ovarian cancer arising from genetic defects the most common is the breast cancer/ovarian cancer syndrome [8, 9]. Therefore, every female patient reporting with one of the listed malignancies must undergo careful scrutiny for possible associated tumours, both during initial diagnosis and in the follow-up period. Before the treatment course is decided these patients should also undergo additional examination – abdominal ultrasound, mammography, colonoscopy, computed tomography and contrast X-Ray of the gastrointestinal tract.

Material

We have analyzed 261 women undergoing surgical treatment at the Dept. of Gynaecology and Obstetrics of the Regional Specialist Hospital in Słupsk. 117 of these patients were treated for ovarian cancer and 144 for endometrial cancer. Altogether in 33 patients we observed the co-existence of two primary neoplasms – 17/117 with ovarian cancer (OC) and 16/144 with endometrial cancer (EC). The pathological specimens were examined by the same doctor at the pathology Dept. of the Regional Specialist Hospital in Słupsk. In those cases when a second primary tumour was diagnosed the samples were reexamined in order to rule out metastases or recurrence of the initial malignancy. In every case the second primary tumour was found before the diagnosis of ovarian or endometrial cancer or during the surgical treatment for these two malignancies. No patient developed a second malignancy during follow-up.

For the purpose of further analysis the patients with two co-existing primary tumours were divided into two groups: (1) 16 patients with ovarian cancer and a co-existing second malignancy and (2) 17 patients with ovarian cancer and a co-existing second malignancy. We analyzed the following parameters: mean age, number of births/miscarriages; mean age of second primary cancer diagnosis; the time of the first and last menstruation; duration of the reproductive period; obesity, arterial hypertension; diabetes; presence of uterine myomas, endometriosis; diagnosis of malignancy among first degree relatives; the grade of histological differentiation; degree of clinical advancement acc. to FIGO.

Method

Throughout the statistical analysis we applied the following methods: group (1) estimation – estimators of mean probability, standard deviation; in group (2) hypothesis verification – chi-square test, Student's T-test. Differences were assumed to be statistically significant when $p=0.05$.

Results

The analysis of the co-existence of a second primary malignancy was performed on 117 women with ovarian cancer (OC) and 144 women with endometrial cancer (EC). In the OC group a second primary malignancy was found in 17 pts. (14.45), while in the EC group it was found in 16 pts. (11.2%). Altogether we observed 33 cases of co-existent second primary malignancy – all of them synchronous. In the OC group the most common second malignancy was breast cancer – diagnosed in 6 pts. (5.1%). Breast cancer was also the most common second malignancy in the EC group, where it was found in 9 cases (6.4%). A detailed presentation of the frequency of different types of second primary malignancies appears in Table I.

The mean age of ovarian cancer diagnosis in the OC group was 59.4 yrs, while for endometrial cancer diagnosis in the EC group it was 60.2 yrs and did not show a statistically significant difference ($p=0.81$). Table II presents the mean age of the patients at the time of diagnosis of the second primary malignancy. We found that breast cancer as the second primary malignancy affected ($p=0.02$) younger patients ($p=0.02$) in the OC group (48.2 yrs) than in the EC group (57.0 yrs). On the contrary, gastric cancer appeared in younger patients from the EC group as compared to the OC group, reaching statistical significance ($p<0.001$).

Table I. Secondary primary malignancy in patients with ovarian cancer and endometrial cancer

	number	%	number	%	number
Breast cancer	9	6.4	6	5.1	15
Colorectal cancer	2	1.4	2	1.7	4
Cervical cancer	1	0.7	2	1.7	3
Gastric cancer	1	0.7	1	0.8	2
Gallbladder cancer	0	0	2	1.7	2
Endometrial cancer	0	0	2	1.7	2
Ovarian cancer	2	1.4	0	0	2
Cancer in endometriosis	1	0.7	0	0	1
Melanoma of the mandible	0	0	1	0.8	1
Lymphogranulomatosis maligna	0	0	1	0.8	1
Total	16	11.3	17	14.3	33

Table II. Mean age at diagnosis of second primary malignancy in patients with ovarian cancer and endometrial cancer

	Mean age [yrs.]	Mean age [yrs.]
Breast cancer	57.0	48.2
Colorectal cancer	51.5	55.5
Cervical cancer	47.0	50.5
Gastric cancer	55.0	81.0
Gall bladder cancer	(-)	55.0

Arterial hypertension was observed in 38% of patients in the EC group and in 24% of patients in the OC group (p=0.38); while diabetes – in 12% and 6% of patients, respectively (p=0.51).

For the body mass analysis the patients were further divided into three subgroups depending on the calculated body mass index (BMI) – group 1 with correct body mass (BMI 19-24); group 2 – obese patients (BMI 25-32) and group 3 – with extreme obesity (BMI>32). After calculations we assigned 25% of patients with EC and 47% of patients with OC to group I; group II encompassed 13% of patients with EC and 35% of patients with OC; group III consisted of 62% of patients from the EC group and of 18% of patients from the OC group. Among patients from the EC group who developed a second primary carcinoma extreme obesity was statistically significantly more common than in the analogous group of patients from the OC group.

The mean number of childbirths was the same in the OC and the EC group – 2.5 per woman. In the EC group non-parturients accounted for 19% of pts; women who gave birth 1-2 times – 44%, and women who had over 2 childbirths – 37%. In the OC group the same figures were 12%; 35% and 53%, respectively. The differences between the number of childbirths did not reach statistical significance (p=0.65). The mean number of miscarriages was 0.7 in the EC group and 0.8 in the OC group and failed to reach statistical significance (p=0.75). The mean age of first menstruation was 13.8 in the EC group and 14.4 in the OC group and also failed to reach statistical significance (p=0.21). The mean age of the last menstruation was 50.7 yrs. in the EC group and 49.1 yrs. in the OC group and failed to reach statistical significance (p=0.27). We discerned no statistically significant difference between the entire duration of the reproductive period (36.9 in the EC group; 34.7 in the OC group; p=0.11). Detailed family history revealed malignancies in first degree relatives of 17% of women from the EC group and in 6% of women in the OC group.

Pelvic inflammatory diseases (PID) were reported by 6% of women from the OC group and by no women from the EC group (p=0.32). Myomas of the uterus were found in 25% of patients with EC and in no patients with OC, the difference reaching statistical significance (p=0.003). Endometriosis was present in 12% of patients with EC and in no patients with OC (p=0.13).

An analysis of EC patients who had developed a second malignancy revealed stage I of clinical advancement in 62% of patients, stage II in 19% of patients, stage III in 19% of patients; there were no patients in stage IV.

In an analogous analysis of the OC patients we found stage I of clinical advancement in 6% of patients, stage II in 18% of patients, stage III in 36% of patients; there also were no patients in stage IV.

More advanced stages of advancement were statistically significantly more common in patients with ovarian cancer (p=0.001).

In EC patients histopathological stage G1 was found in 88% of patients, G2 in 6% and G3 in 6% of patients while in OC patients histopathological stage G1 was found in 59% of patients, G2 in 24% and G3 in 17% of patients, failing to reach statistical significance (p=0.18).

Discussion

Many authors report that patients with ovarian cancer and endometrial cancer are at a higher risk of developing cancer of the breast and cancer of the colon, and vice versa [10-12]. Shinohara et al [13], having analyzed 316 patients with primary malignancies of the female genitary system have found 17 cases of concomitant second malignancy. The most common of these was colorectal cancer (5 cases) and breast cancer (4 cases). Having examined 25 605 women Delin et al [14] have reported that EC was present in 5% of cases while the concomitant appearance of numerous malignancies was in 9% of cases associated with EC. In 44% of women with more than one malignancy associated with EC they discerned a familial trait of cancer. Schunemann [15] observed 163 cases of a secondary malignancy (11%) among 1503 women with EC; in 60% of cases this secondary malignancy was breast cancer while in 1% of cases the patients developed two secondary malignancies. Similar observations have been made by Bucy et al [16] – among 266 patients with EC they discerned 12% of cases of a secondary malignancy, mostly breast cancer.

Bokhman et al [17], having retrospectively analyzed the cases of 5450 women with primary breast cancer have pronounced the risk of concomitant EC to be 13.9 times higher than in the general population. In a group of 1400 women with EC the risk of developing breast cancer as a secondary malignancy was 9 times higher than in the general population. Prospective studies performed on 481 patients with EC have shown 1.9% of concomitant breast cancer (19 times more common than in the control group). In a similar study of 318 women with breast cancer EC was found in 2.4% of women (6 times more often than in the control group) and OC in 1.3% of women. Ayhan et al [18] have analyzed the cases of 29 patients who presented with concomitant malignancies of the female genitary system. The most common co-existence of malignancies was that of OC and EC – 51.7% of patients, with a 5-year survival of 73.3%. Auranen et al [10] evaluated women with concomitant OC and breast cancer and found, that if the first diagnosed malignancy was breast cancer the mean age at diagnosis was statistically significantly lower (50 yrs.) than in patients in whom breast cancer was the only diagnosed malignancy (61.1 yrs.). Such relations were not observed when the primary malignancy was OC. Women who developed ovarian cancer and then breast cancer were of the same age at initial diagnosis (62.2 yrs.) as women with ovarian cancer only (61.1 yrs.). In our study material breast cancer was diagnosed at a significantly younger age than ovarian cancer (approx. 11.2 years earlier) and some 3.2 yrs earlier than endometrial cancer; achieving statistical significance ($p=0.02$). Suris-Swartz et al [19] report that women who developed breast cancer at an age of below 50 yrs have a 4.3 higher risk of developing ovarian cancer, as compared to women who developed breast cancer at an age of over 50 yrs. On the other hand in women with ovarian cancer who had developed the malignancy at an age of less than 50 yrs the risk of developing breast cancer as a second malignancy is 0.6, as compared to women who had developed ovarian cancer at an age of more than 50 yrs. Falkenberry et al [20] have performed an analysis of 22 women with concomitant OC and EC and report that these patients are generally younger than women who develop either EC or OC as a sole malignancy. These results have found no confirmation in previously published papers on EC [3, 4] nor in our present material. Franceschi et al [21] have found that late menopausal age is a risk factor of the development of OC. The relative risk ratio for women who became menopausal before 44 yrs of age, between 45 and 52 yrs and over 52 yrs is 1.4, 1.6 and 1.9, respectively. An analysis of our data has shown that later menopause increases the risk of developing a secondary malignancy, especially breast cancer, EC and cancer of the colon [12]. In our study BMI was pronounced as an important risk factor for developing concomitant EC and breast cancer. We have also found that women with EC had a significantly higher BMI than women with OC. Our earlier analysis [12] concerning the co-existence of EC with a second primary malignancy has shown that women with BMI > 32 were at en extensive risk of such a clinical situation.

Conclusions

1. The co-existence of a second primary malignancy is similar among patients with ovarian cancer and endometrial cancer.
2. In women with ovarian cancer and endometrial cancer the most common second malignancy was breast cancer.
3. Patients with co-existent ovarian cancer and breast cancer developed breast cancer at a significantly earlier age than patients with co-existent endometrial cancer and breast cancer.

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