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Reproductive factors and the endometrial cancer morbidity

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Summary

Introduction: Endometrial cancer is one of the most common cancers among women of highly developed countries. *Purpose:* The purpose of the study was to evaluate the selected reproductive factors increasing or decreasing the odds ratio (OR) of endometrial cancer in women. *Material and Methods:* The study involved 400 women aged 40 to 84 years of Obstetrics and Gynecology University Hospital in Poznań. It evaluated parameters such as age, anthropometric data (body weight, height). In addition, number of births and miscarriages, age of the first and last menstruation, the age at which the first child was born, duration of breastfeeding, use of hormonal contraception, and co-morbidities were analyzed. *Results:* Women menstruating over the age of 55 years are characterized with nearly eight-fold increased risk of endometrial cancer (OR = 8.8, 95% Cl 1.348–57.428). The OR of developing the cancer in women giving the first birth between 20 and 25 years of age is OR= 0.297; 95% Cl 0.307–0.969, and in women between 26 and 30 years of age OR = 0.218; 95% Cl 0.073–0.650 when compared to women giving birth to their first child below 20 years of age. *Conclusions:* Women menstruating over 55 years of age and using hormonal contraception have an increased risk of developing endometrial cancer.

Key words: Reproductive factors; Menopause; Contraception.

Introduction

Endometrial cancer is characterized by rich histopathological texture, slow progression, and good prognosis. Occurrence of clinical symptoms such as abnormal bleeding or spotting from the genital tract in about 75-80% of cases enables its diagnosis in Stage I of clinical advancement. The percentage of five-year survival is over 90% [1].

Based on histopathological and molecular classification, we can distinguish two types of endometrial cancer [2, 3]. Estrogen-dependent cancer (even 80% of cases) is characterized by atypical endometrial hyperplasia. Tumor tissue shows expression of estrogen and progesterone receptors. In addition, women are more likely to be diagnosed with obesity, diabetes, and hypertension [4, 5]. Type II, serum carcinoma, is more common among older women. Given the high rate of recurrence, dynamic course and poor prognosis, only 37–50% of cases is diagnosed in the first and second stage of clinical advancement [6].

Among the genetic disorders within endometroid cancer there are mutations in PTEN, K-ras, β-catenin, PIK3CA, and microsatellite instability, while in type II endometrial cancer mutations in p53, p16, and HER-2/neu genes are present [7].

The aim of this study is to evaluate the selected reproductive factors affecting the increase or reduction of the odds ration (OR) of endometrial cancer in women.

Materials and Methods

The analyses involved healthy women attending the annual health check (n = 332, named AC for the needs of the publication) and the women diagnosed with endometrial cancer (n = 68, named EC for the publication).

Qualification of the group of healthy women was based on the results of the physical and intravaginal ultrasound examinations, while in the EC group, the qualification was based on the results of histopathological examination of material obtained from scraping of the walls of the uterine cavity or from the surgical treatment.

The research was performed in 2017 at the Obstetrics and Gynecology University Hospital in Poznań. It involved 400 women aged 40 to 84 years. It evaluated parameters including: age, anthropometric data (body weight, height). In addition, the study analyzed number of births and miscarriages, age of the first and last menstruation, age at which the first child was born, duration of breastfeeding, use of hormonal contraception, and co-morbidities.

OR for certain risk factors were determined (Table 1). The risk of developing cancer in case when a risk factor appears, was calculated according to the following: chance yes = aa+c1-bb+d and when in does not occur: chance no = bb+d1-bb+d. As a relative risk measure, the OR and its confidence interval (CI) were calculated, using logistic regression: OR = a*dc*b.

The estimations were made with the use of the statistical package StatSoft (2011), STATISTICA (data analysis software system), version 10. The OR with 95% CIs were determined with the use of the logistic regression model. The significance of the OR was examined with a test using the following statistical hypothesis H0: ORi = 1, H1: ORi ≠ 1. The Wald test statistic was used in the research. The statistics had asymptotically χ^2 distribution with 1 degree of freedom, and based on the p-value compared with a

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Table 1. — *OR for certain risk factors were determined.*

Risk factor	Occurs	Does not occur	Total
Study group	a	b	a+b
Control group	c	d	c+d
Total	a+c	b+d	a+b+c+d

significance level $\alpha = 0.05$, the decision was made: if $p \leq \alpha$ rejected H0 accepting H1, and if $p > \alpha$, there was no reason to reject H0.

The approval of the Bioethics Committee of the University of Medical Sciences in Poznan no. 52/17 was obtained in order to conduct the research.

Results

Selected parameters have been presented which affect the increase or decrease of the risk of endometrial cancer. The first parameter was the age for specific age ranges: 50-59, 60-69, 70-79, and ≥ 80 years of age for women between 40 and 49 years of age. Women between 50 and 59 years of age show a four-fold higher increase in the risk of endometrial cancer. The remaining numerical values and percentages are shown in Table 2 and Figure 1.

Another analyzed parameter was the value of BMI. The following ranges of BMI values were analyzed: 18.9–24.9, 25–29.9, 30–34.9 and 35–39.9 kg/m^2. Obese women with BMI between 35–39.9 kg/m^2 have an increased risk of disease, OR = 4.5; 95% Cl 0.374–54.158. Figures and percentages are presented in Table 3 and Figure 2.

The OR of developing the endometrial cancer for the women giving birth to a first child at the age of 20–25 years of age is OR= 0.297; 95% Cl 0.307–0.969, and for the women in the age group of 26–30 years is OR = 0.218; 95% Cl 0.073–0.650, when compared to women who gave their first birth below 20 years of age (Table 4 and Figure 4).

The duration of breastfeeding among the surveyed women was also an object of analysis. Table 5 presents figures and percentages. The differences between the groups were not statistically significant ($p = 0.4086$).

The surveyed women were also asked about the age of the first menstruation. The mean age of first menstruation in the group of women without malignant changes was 13.51 years, whereas in the EC group age was slightly higher and amounted to 15.69 years of age. The first menstruation under 10 years of age occurred in 25% of women in the EC group (n = 4), and between 10 and 14 years of age in 16.13% (n = 45), over age of 14 years old in 18.1% (n = 19). In the group without malignant changes the first menstruation under the age of 10 occurred in 75% of women (n = 12), between 10–14 years old in 83.9% (n = 234), and 81.9% (n = 86) had their first menstruation over 14 years of age. Differences between groups were not statistically significant ($p = 0.5232$).

Late age of first menstruation causes the increase in risk of endometrial cancer. Women still menstruating over 55 years of age have over eight-fold higher increased risk of developing the disease, OR = 8.8; 95% Cl 1.348–57.428, The data is presented in Table 6 and Figure 3.

Hormonal contraception increases the risk of developing endometrial cancer. OR for this group is 2.331; 95% Cl 1.173–4.629, when compared to women who did not take contraception at all ($p = 0.01347$).

The surveyed women were also asked about the number of miscarriages. Within the respondents with endometrial cancer, 18.31% experienced miscarriage, compared to 16.72%. in the BZ group. The differences between group EC and group AC were statistically significant ($p = 0.74595$).

Other parameters, for which the OR of developing endometrial cancer were comorbidities, such as diabetes, hypertension, and obesity. Women who suffer from hypertension have over four-fold higher risk of developing the disease, OR = 4.582, 95% Cl 2.571–8.167 ($p < 0.0001$). When it comes to the respondents suffering from diabetes OR = 8.889; 95% Cl 2.571–8.167 ($p < 0.0001$), whereas for both diabetes and obesity OR = 12.000; 95% Cl 4.462 to 32.271 ($p = 0.00000$). Women with hypertension and diabetes have an 18-fold higher risk of developing endometrial cancer, OR=18.505; 95% Cl 1.067–320.87 ($p = 0.01079$).

Discussion

In the course of the physiological menstrual cycle, hormone stimulating endometrial cells for division are estrogens, particularly estradiol (E2). In the follicular phase,

Table 2. — *OR of developing the endometrial cancer depending on age.*

PARAMETER	EC n (%)	AC n (%)	M ± SD	OR	95% Cl	*p*
Age						
40–49	5 (3.1)	156 (96.9)				
50–59	18 (12.78)	123 (87.2)	62.52 ± 9.26	4.57	1.65–12.64	0.0035
60–69	32 (47.8)	35 (52.24)		28.53	10.38–78.42	0.0000
70–79	14 (53.8)	12 (46.1)		26.74	8.23–86.85	0.0000
≥ 80	4 (80.0)	4 (20.0)		7.80	0.73–83.05	0.0887

OR = odds ratio; CI = confidence interval.

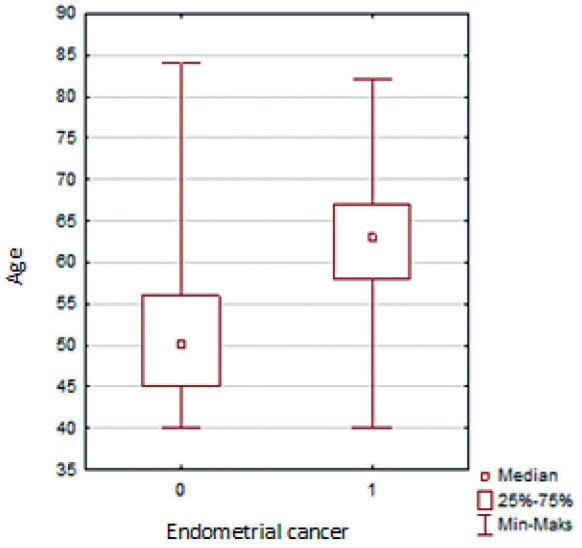

Figure 1. — Relation between endometrial cancer and the age of the respondents.

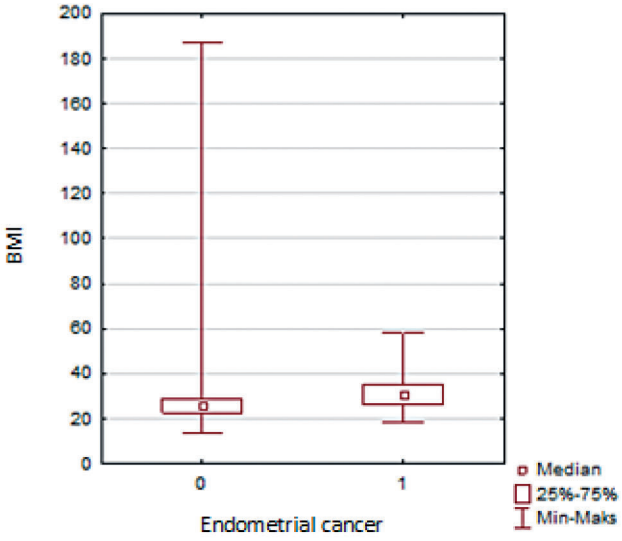

Figure 2. — Relation between endometrial cancer and the value of BMI of the respondents.

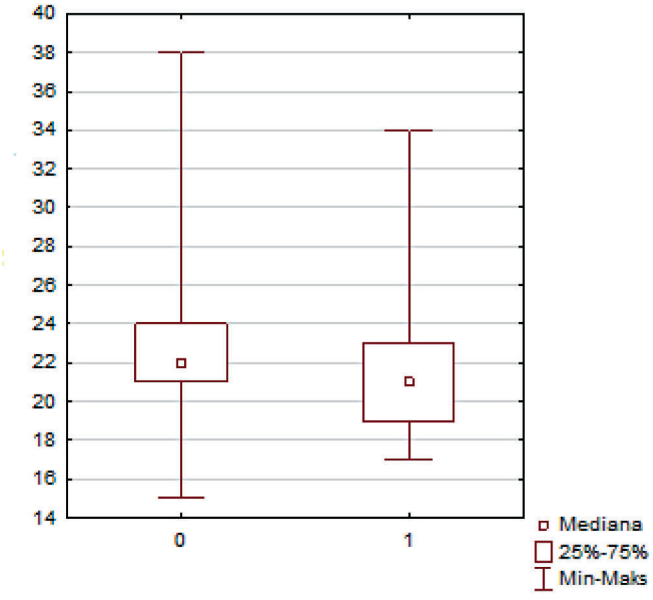

Figure 3. — Relation between endometrial cancer and the respondents' age of the first menstruation.

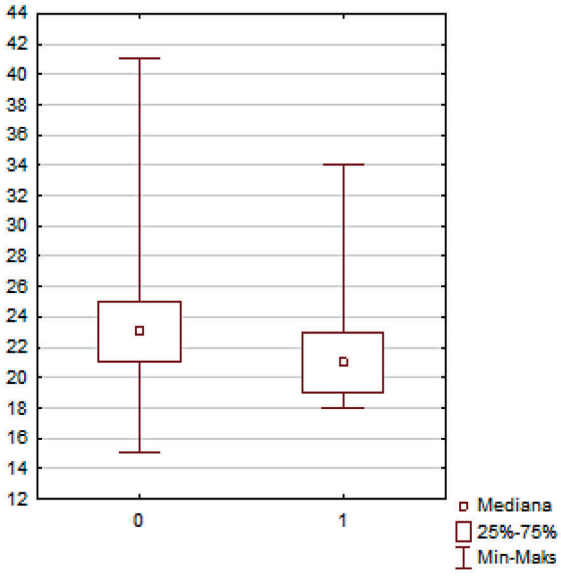

Figure 4. — Relation between endometrial cancer and the respondents' age of birth of the first child.

estrogens allow to rebuild the exfoliated uterine mucosa.

Progesterone produced by the corpus luteum inhibits the proliferation of endometrial cells by decreasing the number of estrogen receptors and promoting the conversion of E2 to less active estrone (E1) and estrogen sulfates. Furthermore, production of IGF-1 binding peptide and so called insulin-like growth factor binding protein 1 (IGFBP 1) prevents binding to the receptor and inhibits cell division. In the case of estrogens, insulin-like growth factor (IGF-1) and IGF-1-receptor are stimulated.

Increased amount of estrogen contributes to chronic stimulation of cell divisions in endometrial cells that may result in development of DNA replication errors and mutations in suppressor genes or proto-oncogenes responsible for cell division regulation and apoptosis [7].

Basing on the unopposed estrogen hypothesis, it can be

Table 3. — *OR of developing the endometrial cancer depending on BMI.*

Parameter	EC n (%)	AC n (%)	M ± SD	OR	95% Cl	*p*
BMI						
< 18.9	3 (75.0)	1 (25.0)				
18.9–24.9	156 (93.4)	11 (6.6)	31.24 ± 6.9	0.212	0.020–2.206	0.3414
25–29.9	112 (84.2)	21 (15.8)		0.6255	0.056–5.671	0.563
30–34.9	55 (67.9)	26 (32.1)		1.418	0.141–14.299	0.767
35–39.9	6 (40.0)	9 (60.0)		4.500	0.374–54.158	0.236

OR = odds ratio; CI = confidence interval.

Table 4. — *OR of developing the endometrial cancer depending on the age of first birth.*

Paramenter	EC n (%)	AC n (%)	M ± SD	OR	95% Cl	*p*
First pregnancy (in years)						
< 20	18 (35.3)	33 (64.7)				
20–25	35 (13.9)	216 (86.1)	21.0 ± 3.6	0.297	0.307–0.969	0.0004
26–30	5 (10.6)	42 (89.4)		0.218	0.073–0.650	0.0062
31–35	3 (15.0)	17 (85.0)		0.324	0.083–1.254	0.1026
> 35	0 (0.0)	3 (100.0)		0.000	0.000–0.000	0.9969

OR = odds ratio; CI = confidence interval.

Table 5. — *Duration of breastfeeding in the survey.*

PARAMETER	EC n (%)	AC n (%)	M ± SD	*p*
Duration of breastfeeding (in months)				
0	17 (18.0)	80 (82.0)		
1– 5	27 (20.0)	107 (80.0)	21.0±3.6	0.4086
6–10	13 (18.0)	59 (82.0)		
11–15	6 (16.0)	32 (84.0)		
16–20	0 (0.0)	15 (100.0)		
> 20	5 (11.0)	9 (89.0)		

Table 6. — *OR for development of endometrial cancer depending on the age of the last menstruation.*

Parameter	EC n(%)	AC n(%)	M ± SD	OR	95% Cl	*p*
Last menstruation (in years)						
40–45	9 (28.1)	23 (78.9)	48.9 ± 10.2	1.565	0.277–8.834	0.6119
46–50	22 (20.0)	88 (80.0)		1.000	0.198–5.045	1.000
51–55	20 (27.8)	52 (72.2)		1.538	0.301–7.876	0.6051
55–60	11 (68.8)	5 (31.3)		8.800	1.348–57.428	0.0231

OR = odds ratio; CI = confidence interval.

stated that the pregnancy is a physiological time in woman's life where progesterone, produced at the beginning by corpus luteum and then by placenta, can prevent the negative influence of estrogens on cells of endometrium. Moreover, each subsequent pregnancy reduces the risk of developing endometrial cancer as it decreases the time of exposure to the excess of the estrogens. The study by Amankwah *et al.* [8] indicated that in women who gave birth to three or four children, the risk of development of endometrial cancer is reduced and the OR = 0.56; 95% Cl 0.36–0.89, and for women who gave birth to five and more children OR = 0.28; 95% Cl 0.15–0.52. Also the age of mother at the time of her first child's birth is significant. The research conducted by Setiawan *et al.* [9] indicated that the age of a mother while giving a first birth between 25–29 years of age reduces the risk of the disease (OR = 0.83; 95% Cl 0.69–0.98), when compared to women giving birth to their first child below 25 years of age. The present study showed that the women giving their first birth to a child between 20–25 years of age also have lower risk of developing the disease. The OR= 0.297; 95% Cl 0.307–0.969, and for women between 26–30 years of age, OR = 0.218; 95% Cl 0.073–0.650.

A meta-analysis conducted by Zhan *et al.* [10] based on 13 cohort-clinical trials and three cohort studies indicated that breastfeeding is associated with lower risk of development of endometrial cancer, where OR = 0.74; 95% Cl 0.58–0.95. In addition, the authors indicated that the risk is reduced by 1.2% with each month of breastfeeding.

There were 13 cases of endometrial cancer conformed

within women who attended 11 years of observation in The Ohsaki Cohort Study conducted by Sugawara *et al.* [11]. The study involved 26,680 women between 40 and 79 years of age. Women who fed their child with breast had a lower risk of developing the disease (OR = 0.31; 95% Cl 0.12–0.81) when compared to women had never fed their children this way. Most probably the protective influence of lactation on mucus membrane of endometrium is associated with reduced level of estrogens in blood.

Early menarche and late menopause are universally recognized factors of risk of endometrial cancer as they prolong the influence of estrogens on mucus membrane of endometrium. According to the results obtained by Amankwah *et al.* [8] the occurrence of the first menstruation before 11 year of age is associated with am almost two-fold higher risk of disease when compared to women who experienced menarche when they were over 13-years-old. In this group OR = 1.79; 95 Cl 1.06–3.03. Studies conducted by Xu *et al.* [12] indicated that women whose menstruation periods ended between 50 and 55 years of age are at a two-fold higher risk of developing the disease (OR = 2.2; 95% Cl 1.42–3.63) and almost at a six-fold higher risk when menopause takes place above 55 year of age (OR = 5.80; 95% Cl 2.96–11.75). This was also confirmed with present study, in which the women still menstruating above 55 years of age presented an eight-fold higher increase in risk of developing endometrial cancer (OR = 8.8; 95% Cl 1.348–57.428). Late menopause is associated with excessive estrogen stimulation in perimenopausal period, dominated by anovulatory cycles resulting in progesterone deficiencies.

The relation between hormonal contraception and the risk of developing endometrial cancer was a subject of many previous studies [13, 14]. The use of hormone replacement therapy (HRT) based on estrogens unbalanced with gestagens is associated with the increased risk of endometrial cancer (OR = 2.3; 95% Cl 2.1–2.5), when compared with women not using HRT [13]. Furthermore, it was found that the risk increases together with the duration of use of HRT. Women using HRT for one year the OR for developing the disease is 1.4; 95% CI 1.0–1.8, and for those who use it up to five years OR = 2.8 95% CI 2.3–3.5. The use of HRT for over ten years results in almost a nine-fold increase of risk (OR = 9.5 95% CI 4.7–12.3). While investigating 205 women with endometrial cancer and 590 healthy respondents between 29 and 70 years of age, Andarieh *et al.* [14] observed almost a two-fold increase of risk (OR = 1.9; 95% Cl 1.4–2.6) when compared to women not using HRT at all.

Beral *et al.* In Million Women Study [15], analyzed 716,738 women between 50 and 64 years of age. The authors found that from 320,953 women using HRT 22% were using continuous combined HRT, 45% cyclical HRT, 9% were using tibolone, and 4% estrogens. About 20% of surveyed women could not tell the type of HRT they were using. The use of continuous HRT in perimenopause and postmenopausal period was associated with lower risk of endometrial cancer, OR = 0.71; 95% CI 0.56–0.90. Estrogen or tibolone therapy caused higher risk of disease. OR for both mentioned therapies is as follows:1.45 95% Cl 1.02–2.06 and 1.79; 95% Cl 1.43–2.25. Continuous use of gestagens causes atrophy of the endometrium by reduction of estrogen and progesterone receptors and promotion of the conversion of E2 to less active estrone. The use of combined oral contraceptives (COC) reduces the risk of endometrial cancer and is directly proportional to the time of use. Iversen *et al.* [16] proved that COC reduces the risk of disease COC (OR = 0.66; 95% CI 0.48–0.89). In this study, the use of hormonal contraception increased the risk of developing the disease. The OR was 2,331; 95% Cl 1,.173–4.629, for women who did not take contraception at all.

A risk factor for endometrial cancer is obesity. Excess body mass is found in about 80% of women with this cancer. The predictive effect of obesity on endometrial cells is associated with an increase in estrogen levels through aromatization of androgens within adipose tissue. In addition, type 2 diabetes with hyperinsulinemia, and increased IGF growth contribute to a decrease in SHBG production, leading to an increase in the pool of unbound active estrogens [2, 17, 18].

According to Andarieh *et al.* [14] the risk of endometrial cancer for women with BMI ≥ 25 is OR = 1.71; 95% CI 1.16–2.52. Similar results were obtained by Shaw *et al.* [19], where the women with BMI >30 and < 35 had almost a three-fold increase in risk of endometrial cancer, whereas the women with BMI > 35 had almost a five-fold greater risk when compared to the women with BMI < 25. It was also confirmed with present study in which the women with BMI 30–34.9 had greater risk of endometrial cancer OR = 1.418 95% Cl 0.141–14.299, and the women with BMI 35–39.9 OR = 4.500; 95% Cl 0.374–54.158, when compared to the women with correct body mas.

An important factor that increases the risk of developing endometrial cancer is diabetes. Pathomechanism is not fully understood, but it is believed that the elevated E2 and hyperinsulinemia levels may play a role by the growth of androgens, and their aromatization leads to increase in estrogens. Under the influence of insulin sex hormone binding globulin (SHBG) synthesis is also reduced, which results in increase of unbound estrogens [19, 20].

While investigating a group of 121,230 women older than 40 years of age, Sun *et al.* [20] found that the women with diabetes have almost a 1.5-fold higher risk of endometrial cancer, OR = 1,47; 95% CI 1.02–2.12. A retrospective cohort study of 916 women, Wise *et al.* [21] observed an increased risk of disease, OR = 1.78; 95% Cl 0.76–4.15. Furthermore, for obese women with BMI ≥ 30 the risk increases and the OR was 3.76; 95% CI 1.31–10.80, when compared to the women with normal weight. In the present study the women with diagnosed diabetes

had an almost nine-fold increased risk of endometrial cancer (OR = 8.889; 95% Cl 2.571–8.167. In addition, for diabetic women with obesity OR = 12.000; 95% Cl 4.462–32.271.

The effect of hypertension on the risk of endometrial cancer is also important. However, it seems that this is not an independent factor, but coexists with diabetes and obesity, enhancing the carcinogenic effect on endometrial cells. Sponholtz *et al.* [22] investigated the effect of hypertension on the risk of developing endometrial cancer and they came to conclusion that there was nearly a 1.5-fold increase of the risk (OR = 1.29; 95% Cl 0.99–1.67). It was also confirmed in the present our study (OR = 4.582, 95% Cl 2.571–8.167). Furthermore, when hypertension, diabetes, and obesity coexist the OR = 12.000; 95% Cl 4.462–32.271. It is probably related to disorders of apoptosis and cell renewal in the mucus membrane of endometrium.

Conclusions

The conducted study and analysis of collected materials lead to the following conclusions: the highest risk of endometrial cancer is in women over 60 years of age, presence of menstruation in women over 55 years of age and the use of hormonal contraception increase the risk of disease, and co-existence of diabetes, hypertension, and obesity are associated with reduced risk of endometrial cancer.

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