RESEARCH ARTICLE

Risk Factors for Endometrial Cancer: Results from a Hospital-Based Case-Control Study

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Abstract

Objectives: The purpose of this investigation was to examine the association between endometrial cancer and possible etiological agents. **Methods:** A case-control study was conducted in Iran between March 2012 and May 2016. The demographic and reproductive factors of 205 women with endometrial cancer were compared, and 590 healthy cases were participated in the control group. For each endometrial cancer case, there were three controls, who were matched in terms of age and residence. The data were considered significant at $p \leq 0.05$. **Results:** After adjusting the variables, the nulliparity (OR 6.23, 95% CI 2.86-13.59), the nulligravidity (OR 5.94, 95% CI 2.51-14.06), the positive family history of reproductive cancer (OR 4.97, 95% CI 2.33-10.59), the infertility history (OR 2.38, 95%CI 1.32-4.31), the obesity (BMI ≥25) (OR 1.71, 95% CI 1.16-2.52), the early menarche age (<12 years) (OR 2.10, 95% CI 1.17-3.75), and the hormonal contraception use (OR 1.69, 95% CI 1.15-2.49) were found to be associated with an increased risk of endometrial cancer. Nevertheless, the education level, the job of women, the marital age, the leisure activities, and the breast feeding were not found to be associated with the endometrial cancer after adjusting the variables. **Conclusion:** Scheduling of the screening program is vitally indispensable to identify endometrial cancer in women with nulliparity, nulligravidity and the positive family history of cancer. In addition, women with early menarche, those with the history of infertility, the obese ones, and those who use contraception pills need to be particularly aware of the potential risks.

Keywords: Endometrial cancer- risk factors- case-control- parity- gravidity- positive family history

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Introduction

Uterine cancer is deemed to be the most common gynecologic malignancy in developed countries. Despite all the breakthroughs, the issue has received considerable critical attention as the mortality rate for uterine cancer is on the rise. This elevated incidence could be multifactorial (Siegel et al., 2012; Niyazi et al., 2016). The raised prevalence of endometrial cancer in US-born generations of Chinese and Japanese Americans when compared with their counterparts who were born in Asia demonstrated that the exposure to some environmental features or lifestyle modifications may alter the race-specific factors of this malignancy (Frumovitz et al., 2014). The association of endometrial cancer with such dominant characteristics as age, BMI, race, familial history, and polycystic ovary, diet, physical activity, smoking, parity, breastfeeding, birth rate, hormone-replacement therapy, hypertension, diabetes, histology, the socio-economic status, and the exposure to infertility treatment are still controversial in terms of incidence and mortality (Brinton et al., 1992; Salazar-Martínez et al., 2000; Soliman et al., 2005; Beral et al., 2007; Zhou et al., 2008; Furness et al., 2009; Liat et al., 2012; Liao et al., 2014; Filomeno et al., 2015). Several attempts have been made to distinguish the contributing factors behind Type I endometrial cancer from Type II. Flix et al. (2010) concluded that type 2 was associated with excess age, nonwhite race, and the history of additional primary tumors. Renehan et al. (2008) also recognized that excess adiposity played a critical role. Despite all the reported data, much uncertainty still exists about the factors associated with uterine cancers in the developing and less developed countries. The limited knowledge of the known symptoms, the late diagnosis at a higher-grade phase of the disease, the poorer quality of life, and the impaired socioeconomic status make women in developing and less developed counties more vulnerable to endometrial cancer (Soliman et al., 2008; Hirth et al., 2016). Research on the issue has been mostly limited to imperfect statistics from women who were involved with uterine malignancy prior to higher-grade stages, patients who died of cancer at home and those with misdiagnosis of metastases from organs adjacent to uterine. Accordingly, these women suffer disproportionately from adverse

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disease-specific prognosis of endometrial malignancy.

Cervical cancer has been proved to be preventable, but the statistics concerning the uterine cancer in regions adjacent to Asia that may have similar ethnicity with Iran indicate that the trend for diminishing the mortality rate due to uterine corpus cancer has not been found yet (Jemal et al., 2011; Lee et al., 2014). Uterine and cervical cancers still have the second greatest incidence among all cancers in East Asian countries despite all the efforts made for the reduction of the mortality rate in these countries (Arbyn et al., 2010; Torre et al., 2015). This study, however, strove to assess the association between endometrial cancer and the possible etiological agents.

Material and Methods

The present study was approved by the ethic committee of Babol University of Medical Sciences. Between March 2012 and May 2016, we identified all patients with the confirmed diagnosis of all types of endometrial neoplasm in the Cancer Center of Shahid Rajaee at Babolsar (North of Iran). A total number of 255 medical records were fully assessed based on which thirty-nine women were found to be dead or discharged, ten were too ill to contribute, and one declined to contribute. All these cases were excluded from the study. Finally, a total number of 205 cases were interviewed and were requested to complete the questionnaire (Contribution rate 80.4%). The inclusion criteria were based on the following conditions: (A) the diagnosis of endometrial cancer was histologically and cytologically confirmed; (B) there was no suspicion of endometrial metastases from a different tumor; (C) the patients were well enough to fill out the questionnaire and undergo an interview. We, however, entered only those patients who had received consents from their physicians. All patients with any clinical staging of the endometrial tumor classification or metastasis were included.

For each endometrial cancer case, there were three controls, who were matched in terms of age and residence. At first, we asked permission from the enrolled cases and went to their neighborhoods, up to two streets in each direction from the cases' residential areas. Then, we randomly met their neighbors and selected them based on the self-reported free-cancer history. Everything was done according to the screening checks, which relied on the clinical examinations, the test results like pap smear and breast examination, and the recent ultrasound. Having done all of that, we entered only those who agreed to participate. A total number of 590 controls were participated in this study (contribution rate: 98.8%). The women in the control group were interviewed and requested to fill out the questionnaire completely.

Having signed the informed consent forms, the researcher conducted the in-person interviews for two groups. Then, the structured questionnaires including demographic factors such as age, place of residence (urban or rural), occupation, educational level (illiterate and educated), leisure activity (mild dancing, climbing, fishing, swimming, etc.), the reproductive history comprising the menarche age, the age of marriage, parity, gravidity, breastfeeding, the use of hormonal contraceptive and the family history of reproductive cancer (first and second hand relatives), and the history of infertility were administered to the participants. The subjects' parity was nulligravid (Those who have never been knowingly pregnant), and the gravid women who had the history of at least one pregnancy. The term parity was defined as the number of births and no abortions. Women who had the history of at least one live or still birth were considered as parous women.

The cases were between 29 to 70 years of age when they were diagnosed to have endometrial cancer, and the age of women in the control group was their age at interview time. The weight of women was their weight when they were diagnosed to have endometrial cancer, and the weight of women in the control group was their weight at interview time. The BMI was calculated by the formula: weight (kg) / [height (m)]^2.

The structured questionnaire was developed and piloted among the participants in both groups, and the modifications were made according to the results obtained for ascertaining information from the both groups.

Statistical analysis

Standard statistical procedures were carried out using the Statistical Package for Social Sciences (SPSS) version 16.0. All variables were tested for normality by Kolmogorov-Smirnov test, and t-test was used to compare quantitative variables. Descriptive analyses including frequencies, ranges, and percentages of variables were conducted for each variable in each group. The characteristics of women with and without endometrial cancer were compared using $\chi 2$ statistics. To assess the associations between the endometrial cancer and the risk factors, bivariate conditional logistic regression analyses at P=0.2 were used. The potentially important risk factors were tested with stepwise multivariate conditional logistic regression analysis. Odds ratios (ORs) using maximum likelihood and corresponding 95% confidence intervals (CIs) were estimated by univariate and multivariate models. Differences were considered statistically significant when the two-sided p-value was ≤ 0.05.

Results

The mean age of the participants in both groups was 52.9±10.1 and 52.6±9, respectively. The characteristics of the participants in both groups are summarized in Table 1. There was a higher proportion of BMI ≥25 (p=0.005, menarche age<12 years (<0.001), nulliparity (P<0.0001), nulligravidity (P<0.001), the history of using hormonal contraception (P<0.0001), the history of infertility (<0.001), the positive family history of reproductive cancer (<0.001), the history of breastfeeding (0.029), and lower education (<0.001) in the case group as compared with those of the control group. There was no significant difference between the percentages of participants in the case group and those of the control group in terms of leisure activities, marriage age ≥30, and working outside.

Table 2 presents the odds ratios (ORs) of endometrial cancer risk factors using univariate and multiple logistic regression models with the likelihood of 95% CI in women

suffering from endometrial cancer and those in the control group. After adjusting the variables, the nulliparity (OR 6.2, 95% CI 2.9-13.6), the nulligravidity (OR 5.9, 95% CI 2.5-14.1), the positive family history of reproductive cancer (OR 5.0, 95% CI 2.3-10.6), the history of infertility (OR 2.4, 95%CI 1.3-4.3), the obesity (BMI≥25) (OR 1.7, 95% CI 1.2-2.5), the early menarche age (<12 years) (OR 2.1, 95% CI 1.2-3.7), and the use of hormonal contraception (OR 1.7, 95% CI 1.1-2.5) were found to be associated with an increased risk of endometrial cancer.

Discussion

Our most novel findings are the strongest associations that we found between endometrial cancer and the risk factors including the nulliparity, nulligravidity and the positive family history of endometrial cancer compared with those of the healthy participants.

These results are in accordance with some prospective studies that compared nulliparous with parous women and found a decreased risk of developing endometrial cancer in parous women (Kvåle et al., 1988; Dossus et al., 2010; Yang et al., 2015). Different case-control studies also demonstrated that there was a strong association between nulliparity and the increased risk of endometrial cancer (Parslov et al., 2000; Fujita et al., 2008; Brøns et al., 2015). Some controversies were, however, seen some studies (La Vecchia et al., 1984; Koumantaki et al., 1989; Parazzini et al., 1998; Terry et al., 1999). Soliman et al.'s study in Texas also indicated an endometrial cancer risk in nulli parous OR=1.8 ; 95% CI: 1.6-1.9 (Soliman et al., 2005). Our rate was, however, greater (IR 6.2 95% CI 2.9-13.6). It is difficult to justify this result, but it could be related to the cultures of the people in two different countries. The traditional thoughts in Iran persuade new couples to have children in a short period of time right after marriage. In addition, sub-fertile couples are encouraged to treat their infertility problem as soon as possible; therefore, they have to undergo various infertility treatments and this exposure to drugs can intensify the risk of endometrial malignancy, which is in line with our new finding. Although these thoughts are less heeded by young couples nowadays, it should be noted that the women in this study were middle-aged, and that their fertility period was at the time when these traditional thoughts were still in vogue.

Another important finding was that having a close

Table1. Characteristic of Cases and Controls

Variable		Case (n=205) N (%)	Control (n=590) N (%)	P-value
Residence	Urban	125 (61)	356 (60.3)	0.872
	Rural	80 (39)	234 (39.7)	
Marriage Age(years)	≥30	20 (9.8)	38 (6.4)	0.081
	<30	185 (90.2)	552 (93.6)	
Job	Worker	22 (10.7)	90 (15.3)	0.066
	Housewife	183 (89.3)	500 (84.7)	
BMI (kg/m^2)	≥25	128 (62.4)	428 (72.5)	0.005
	<25	77 (37.6)	162 (27.5)	
Leisure Activities	No	190 (92.7)	533 (90.3)	0.195
	Yes	15 (7.3)	57 (9.7)	
Menarche Age(years)	< 12	39 (19)	37 (6.3)	<0.001
	≥12	166 (81)	533 (93.7)	
Parity	Nulliparous	19 (9.3)	11 (1.9)	<0.001
	Parous	186 (90.7)	579 (98.1)	
Hormonal Contraception	Yes	85 (41.5)	160 (27.1)	<0.001
	No	120 (58.5)	430 (72.9)	
History of Reproductive Cancers	Yes	21 (10.2)	15 (2.5)	<0.001
	No	184 (89.8)	575 (97.5)	
Gravidity	Nulligravid	17 (8.3)	11 (1.9)	<0.001
	Gravid	188 (91.7)	579 (98.1)	
Breast feeding	No	23 (11.2)	16 (2.7)	0.029
	Yes	182 (88.8)	574 (97.3)	
History of Infertility	Yes	26 (12.7)	40 (6.8)	0.008
	No	179 (87.3)	550 (93.2)	
Education Women	Illiterate	63 (30.7)	93 (15.8)	<0.001
	Educated	142 (69.3)	497 (84.2)	

The P-value was obtained using Fisher exact Test

Table 2. Adjusted Odds Ratio (OR) for Endometrial Cancer[1] According to Risk Factors

Variable		OR (CI95%)	Adjusted OR (CI95%)	P-value
Marriage Age (years)	≥30	1.6 (0.9-2.8)	0.6 (0.3-1.2)	0.13
	<30	1.0	1.0	
Job	Worker	0.7 (0.4-1.1)	1.2 (0.7-2.1)	0.455
	Housewife	1.0	1.0	
BMI (kg/m2)	≥25	0.6 (0.4-0.9)	1.7 (1.2-2.5)	0.007
	<25	1.0	1.0	
Menarche age (years)	< 12	3.5 (2.2-5.7)	2.1 (1.2-3.7)	0.013
	≥12	1.0	1.0	
Parity	Nulliparous	5.4 (2.5-11.5)	6.2 (2.9-13.6)	<0.001
	Parous	1.0	1.0	
Hormonal Contraception	Yes	1.9 (1.4-2.6)	1.7 (1.1-2.5)	0.008
	No	1.0	1.0	
History of Reproductive Cancers	Yes	4.37 (2.2-8.7)	4.9 (2.3-10.6)	<0.001
	No	1.0	1.0	
Gravidity	Nulligravid	4.8 (2.2-10.3)	5.9 (2.5-14.1)	<0.001
	Gravid	1.0	1.0	
Breast feeding	No	4.5 (2.3-8.8)	0.7 (0.4-1.3)	0.303
	Yes	1.0	1.0	
Infertility	Yes	2.0 (1.2-3.4)	2.4 (1.3-4.3)	0.004
	No	1.0	1.0	
Education women	Illiterate	0.4 (0.3-0.6)	1.4 (0.9-2.1)	0.166
	Educated	1.0	1.0	

[1]Potential confounders used in each variables with other variables

relative suffering from cancer could prove a potent association (OR=5.0, 95% CI (2.3-10.6). This result is in line with the ideas of Win et al. who reported this risk factor association (OR =1.8 95% CI (1.6–2.0)) (Win et al., 2015). The difference may be attributed to the great sample size and the nature of Win's study. In addition, some cancers were not diagnosed in the past, and the statistics were to some extent unclear. This experiment did not find lack of evidence for the association between uterine cancer and positive familial cancer.

The present study also detected evidence for less strong relationship between BMI ≥ 25, menarche age <12 years, the history of using contraception pills, and the history of infertility.

In our study, women with BMI≥25 showed positive association (OR1.7, 95% CI 1.2-2.5. This result seems to be consistent with Rapp et al.'s, which found a strong association (OR 3.9, 95% CI: 2.3-6.6) between endometrial cancer and BMI. The observed increase in their association could be attributed to the higher classification of BMI (≥35 kg/m$^{2)}$, which they reported (Rapp et al., 2005). We did not, nonetheless, detect any evidence regarding the lack of association between BMI and uterine cancer. Some authors concluded that obesity was associated with type 1 endometrial cancers rather than type 2 (Bokhman, 1983), and others restricted the increased risk of endometrial cancer to BMI > 30 kg/m^2 (Foley and Lee, 1990). It is worth mentioning that adiposity is associated with metabolic syndrome, diabetes in particular. One of the limitations of our study was that we did not assess the effect of the confounding variables such as diabetes on endometrial cancer alone; hence, our finding should be interpreted with caution.

Another obvious finding emerging from the analyses is that 41.5 % of the users of the contraceptive pills suffered from cancer and 27.1% did not. This finding supports the result of the previous research by Urban et al. that found a reduced risk of endometrial cancer, which was associated with the use of oral contraception pills. He, nevertheless, concluded that this would be likely if women used hormonal contraception for a long duration of time, and the short time use of that could have no benefits (Urban et al., 2012). La Vecchia et al. also showed that protective effect could accelerate with continuously combined preparations, and could remain there for many years after it is discontinued, although higher amounts of oestrogen had been consumed through pills in the early years (La Vecchia et al., 1984). In addition, Weiderpass et al. demonstrated that progestin along pills could diminish the risk more than when we combine pills (OR 0.5 95 % CI): 0.3, 0.8) (Weiderpass et al., 1999). Unfortunately, another limitation of our work was the lack of evaluating the duration and the type of contraception pills used by the participants, which was due to some incomplete collected data.

In our study, the women with the history of infertility were approximately involved with endometrial cancer two times as much as those without the history of infertility (OR 2.4 95% CI 1.3-4.3). In recent years, despite all the progress in fertility treatments, there have been numerous

studies associated with the influence of infertility treatment on the incidence of endometrial cancer, and the results of most of these studies confirm our findings (Ichinose et al., 2013).Yang adjusted the infertility and nulliparity and concluded that women who reported infertility had an elevated risk of endometrial neoplasm compared with those without infertility (Yang et al., 2015). This result could be limited by the work of Brinton et al., suggesting that the primary infertility was due to severe forms of androgen excess, which could be associated with an elevated risk of endometrial malignancy risk (Brinton et al., 2005). We assume that infertility drugs, as a confounding element, may have a greater malignancy risk than the infertility itself, and can enhance the percentage of endometrial cancer.

Another important clinically relevant finding was the inverse association of menarche age (<12 years) with endometrial cancer (OR 2.1 95% CI 1.2-3.7). Although the result of Gong et al.'s study support our findings, they reported less value (OR 0.7, 95%CI 0.6–0.8) (Gong et al., 2015). It is difficult to explain this discrepancy. The difference may depend on the genetic factors interfering with the menarche age or various categories of the menarche age. To the best of our knowledge, we did not find evidence attributed to the lack of contribution of menarche age in endometrial cancer.

Actually, we also found a difference between smokers and nonsmokers in our study (42.4% vs. 4.9%) as it relates to the risk of endometrial cancer. Our finding is in line with a study by Al-Zoughool et al., which reported HR = 2.5; 95% CI, 1.5-4.4 (Al-Zoughool et al., 2007). Our work, nonetheless, differs from those of some authors, suggesting that smoking plays an anti-estrogenic role; therefore, it can reduce uterine cancer among smokers when compared with nonsmokers (Matikainen et al., 2001; Viswanathan et al., 2005; Lindemann et al., 2008). Of course, some studies assess a particular type of endometrial cancer. Although smoking was associated with an increased risk of endometrial cancer in some studies (Al-Zoughool et al., 2007), our study did not identify smoking as a risk factor. This contradictory result could be explained in part by the small size of our sample and lack of attention to the effect of smoking on different types of uterine cancer. Another reason could be due to the low number of women smoking cigarettes due to their religious beliefs.

Finally, this study, despite its overall and detailed goals, faced some limitations such as insufficient cooperation on the part of patients in providing information due to their disease conditions, high costs of treatment, and incomplete patient records. A large well-designed, multi-center, cohort study is required to investigate all the socio-demographic factors of endometrial cancer.

Elevated uterine cancer was greatly associated with nulliparity, nulligravidity and the positive family history of endometrial cancer. A less strong association was, however, found between the uterine cancer and the menarche age<12 years, BMI ≥ 25, the history of hormonal contraceptive use, and the history of infertility.

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Conflict of Interest

The authors revealed no conflict of interest.

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