RESEARCH ARTICLE

Risk of Cancer with Combined Oral Contraceptive Use among Iranian Women

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Abstract

Oral contraceptive use is the most common type of contraception. More than 300 million women worldwide take oral contraceptives every day. However, there is a concern about the relationship with the incidence of cancer. This analytical retrospective study aimed to investigate the relationship between the incidence of cervical and breast cancers and oral contraceptive use in 128 Iranian patients with cervical cancer, 235 with breast cancer and equal numbers of controls. Data were collected through interviews with an organized set of questions. Details were also extracted from patient files. Data were analyzed using Student's t-test, chi-square and Fisher's exact tests, and Pearson's correlation analysis. The result revealed correlations between both cervical and breast cancers and history of contraceptive pills use. While cervical cancer significantly correlated with duration of use of pills, breast cancer had significant correlations with the type of oral contraceptive and age at first use. No significant relationships were found between the two types of cancer and age at discontinuation of oral contraceptives, patterns of use, and intervals from the last use. The use of oral contraceptives may triple the incidence of cervical cancer and doubles the incidence of breast cancer. Therefore, performing Pap smears every six months and breast cancer screening are warranted for long-term oral contraceptive users.

Keywords: Cancer risk - cervical cancer - breast cancer - oral contraceptive use - Iran

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Introduction

In 1999, the world population reached 6 billion, an increase of approximately 4.4 billion since 1900. Contraceptive technology has been a medical success, and for the majority of users, contraception enhances the quality of life, allowing couples to choose whether and when they have children. Oral contraceptives have been studied since 1960; they are used every day around the world for the prevention of unintended pregnancies. Also oral contraceptives are the most effective and reversible method of contraception, and is one of the main methods used to time the spacing between children (Farajzadegan et al., 2000). Oral contraceptive pills are among the most popular contraceptive methods (Ehsanpour et al., 2013). Since the introduction of OC in the early 1960s more than 300 million women are thought to have used it (Zhou et al., 2014). Despite OCP benefit Many studies have examined the potential association between OC use and cancer. (Wei et al., 2014). Oral contraceptives may influence the risk of certain cancers (Gierisch et al., 2013). As other parts of the world, cancers are major public health problems in Iran. According to reports of the Iranian Ministry of Health and Medical Education (MOHME), cancer is the third cause of death in following coronary heart disease and accidents (Taheri et al., 2012).

The relationship between oral contraceptive and cancer incidence is controversial. However, researchers, physicians, and patients are concerned about the possible increased incidence of breast and cervical cancers and due to the reports regarding the elevated rates of these cancers in recent decades (Arbyn et al., 2011). The increased incidence of these two cancers in the U.S. and many other parts of the world in the past 50 years has coincided with the wide use of contraceptive pills which started in 1960. In Iran, the pills were introduced in 1973 and according to the country's family planning statistics, 2,105,000 women were using this contraception method in 2010 [Health Ministry of Iran 2009). Worldwide 31% of cancers in women are in the breast or uterine cervix. Cancer of the uterine cervix is one of the leading causes of cancer death among women. (Zechariah et al., 2014). Various studies in 187 countries during 1980-2010 have highlighted cervical cancer as an important cause of mortality in women aged 15 years and older. Moreover, the incidence rate of this cancer has been found to have dramatically increased from 378,000 cases in 1980 to 465,000 cases in 2010 (Foreman et al., 2011). Alston and researchers of Manchester University have indicated a 40% increase in the incidence of cervical cancer among young women

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in recent decades (Foley et al., 2011) An evaluation of statistics in Eastern Europe suggested the augmented incidence of cervical cancer in the Baltic states (Estonia and Latvia), Romania, and Bulgaria, especially among women born during 1940-60 (Antoine et al., 2011). Of the 503 thousand registered new cases of cervical cancer in 2008, 85% belonged to developing countries. In fact, there is a significant difference in incidence of this disease between developed and developing countries (Arbyn et al., 2011). Statistics has also revealed a similar trend in Asia, particularly since 1970. The increased incidence has even been seen in countries like India, Japan, and Korea that used to have the lowest rates of breast cancer (Beiki et al., 2012). In Turkey, breast cancer ranks first with an incidence of 41.6% and cervical cancer is the tenth most common cancer with an incidence of 4.4%. (Karadag et al., 2014). Likewise, the rates in Australia in 1982 (530 cases) were more than doubled by 2009. Actually, 37 new cases of the disease are registered in the country every day [Australian Institute of Health and Welfare., 2012]. The incidence of breast cancer is rapidly growing in China, Latin America, and Africa and has been doubled or even tripled in Malaysia and Singapore during the recent decades (Bhoo-Pathy et al., 2012). Breast cancer is one of the most common cancers of women in India with high fatality rate. (Das et al., 2012). Breast cancer has been increased in South East Asia countries (Matalqah et al., 2012). Breast cancer is one of the most common cancers and the first-leading cause of cancer deaths among women in the world. Indeed, breast cancer is ranked as the first malignancy among Iranian women cancer [Ahmadinejad et al., 2013) Increments in the incidence of cervical and breast cancers have also been proved in Iran [Center for Disease Control & Prevention. Iran]. The country has recently witnessed a 150% increase in mortality rate due to breast cancer, especially among women under 50 years of age (Taghavi et al., 2012) However, the relation between the increased incidence of breast and cervical cancers and use of oral contraceptives, as a health issue, is still vague for both the physicians and patients. The results of research on this subject can thus help early prevention and timely treatment and diagnosis in high-risk individuals.

Materials and Methods

This analytical case-control study assessed the effects of contraceptive pills on the incidence of cervical and breast cancers.

Cervical cancer

Overall, 128 patients with cervical cancer and 128 healthy controls were studied.

Case group

The case group included women who referred to Gorgani Radiotherapy Center and Cancer Institute (both affiliated to Imam Khomeini Hospital, Urmia, Iran) where their cancer had been diagnosed. They were all receiving treatment and had no contraindications to contraceptive pills.

Control group

The control group included women without cervical cancer who referred to obstetrics and gynecology clinics of Imam Khomeini and Imam Hussein Hospitals (Urmia, Iran). They did not have a history of malignancy or contraindications to oral contraceptives. The subjects were all Iranian, Muslim, married, and 20-65 years old.

After obtaining informed consent, 20-minute interviews were performed with all participants. Data about marital status, age, sexual activity, age at first marriage and first pregnancy, number of pregnancies, deliveries, and miscarriages, history of abortion or induced abortion, history of cervical lesions and cryotherapy and cauterization, history of Pap smears, number of marriages, age at menarche, menstrual cycle regularity, menopause, use of contraceptive methods, family history of cancer, and history of diseases were collected from both groups. Besides, the case and control groups were matched for age, socioeconomic status, number of children, age at first marriage and first pregnancy, history of miscarriage and abortion, and history of sexually transmitted diseases.

Breast cancer

A total of 235 patients with breast cancer (the case group) and 235 healthy controls were selected.

Case group

Convenience sampling was used to select subjects from women who referred to chemotherapy and radiotherapy departments of Imam Khomeini and Omid Hospitals (Urmia, Iran) for examination or follow-up.

Control group

The control group was selected through a public notice and also from daily referrals to obstetrics and gynecology clinics of the mentioned hospitals. After breast examinations by a trained general surgeon, only the healthy subjects were included and those with suspected breast cancer were referred to relevant specialists for further examinations.

Both groups were interviewed and data about age, marital status, education, socioeconomic status, history of breast feeding, family history of cancer, history of benign breast masses, number of children, age at menarche, menopause, menstrual cycle, use of contraceptive methods, and history of diseases, alcohol use, hormone-therapy for menopausal complications, infertility, smoking, and chest radiography were collected.

The case and control groups were matched for age, economic status, weight, and number of children. In both groups, single women and those with history of first pregnancy after 25 years of age, history of chest radiography, family history of breast cancer, weighing over 80 kg, lack of breast feeding, history of hormonal infertility treatment, and alcohol and cigarette use were excluded. Finally, more women were excluded to make both groups equal size.

The collected data were analyzed using Student's t-test, Fisher's exact and chi-squared test, and Pearson's correlation analysis in SPSS for Windows XP (SPSS Inc.,

Chicago, IL, USAP values less than 0.05 were considered significant.

Results

The mean ages of patients with cervical cancer and their controls were 49.05 and 47.75 years, respectively. The mean age of patients with breast cancer and their controls were 47.63 and 46.45 years, respectively. Therefore, the case and control groups in both cancer types were matched in terms of age.

History of oral contraceptives use

i) Cervical cancer: Overall, 63.3% of the case group and 35.9% of the control group had used contraceptive pills. Chi-squared test revealed significant difference between the two groups (p<0.001). The odds ratio (OR) and 95% confidence interval (CI) for cervical cancer was estimated at 3.072 and 1.84-5.11, respectively (Table 1).

ii) Breast cancer: The majority of the case and control groups (70.2% and 52.8%, respectively) had used oral contraceptives. Chi-squared test results suggested a significant difference between the two groups (p=0.001; OR=2.110; 95%CI: 1.44-3.08) (Table 1).

Duration of oral contraceptives use

i) Cervical cancer: Most subjects in the case group (40.7%) had used contraceptive pills for more than 97 months. In the control group, however, the highest relative frequency belonged to 13-60 months use (p<0.05; OR=3.072). The odds increased to 5.2 times when the duration of use was more than 97 months (Table 2).

ii) Breast cancer: The case and control groups had used oral contraceptives for 94.5 and 100.2 months, respectively (p>0.05) (Table 2).

Age at first use of contraceptive pills

i) Cervical cancer: The relationship between cervical cancer and age at first use of contraceptive pills was not significant.

ii) Breast cancer: In the case group, there was a significant difference between the initiation of oral contraceptives before and after the age of 25 years. The odds of developing the disease increased by starting the pills at an age older than 25 years. The OR of suffering from breast cancer was 1.99 (95%CI: 1.2-3.3) in those who had started oral contraceptives after the age of 25 years and increased to 6.47 (95%CI: 2.46-17.04) in subjects who had started the pills after 30 years of age.

Type of contraceptive pills

i) Cervical cancer: There was no significant relationship between the incidence of cervical cancer and type of pills used.

ii) Breast cancer: The case and control groups had a significant difference in terms of the type of oral contraceptives (p=0.002), i.e. the patients had more frequently used high-dose birth control pills or high-dose estrogen. While individuals who had used low-dose contraceptive pills had an OR of 1.18 for developing the disease, the odds increased to 2.83 in those who had used high-dose pills.

Table 1. Absolute and Relative Frequency Distribution of Contraceptive Methods and Breast Cancer

Group Contraceptive method		Case		Control		Total		Result
		Number	Percent	Number	Percent	Number	Percent	
Cervical cancer	OCP	81	63.3	46	35.9	127	99.2	χ^2=31.03
	Other	24	18.7	65	50.8	89	69.5	p=0.0001
	None	23	18	17	13.3	40	31.3	df=2
Brest cancer	OCP	165	70.2	124	52.8	289	61.5	χ^2=33.69
	Other	63	26.8	92	39.1	155	32.95	p=0.001
	None	7	3	19	8.1	26	5.55	df=2

Table 2. Risk of Cervical And Brest Cancer Acording to the use of Combination Oral Contraceptives

Variable		Cervical cancer			Brest cancer		
		Case 128	Control 128	OR (%95 CI)	Case 235	Control235	OR (%95 CI)
No use		47	82	3.72 (1.84-5.11)	63	92	
Any use		81	46		165	124	2.11 (0.46-3.33)
Duration of use	<12 month	11	7	1.6 (0.46-3.33)	29	12	2.06 (1.31-3.01)
	13-60	23	25	0.9 (0.51-1.78)	52	44	1.23 (0.78-1.93)
	61- 96	14	6	2.4 (0.54-3.9)	17	11	1.58 (0.72-3.46)
	>97	33	8	5.2 (2.28-11.8)	67	57	1.33 (0.88-2.02)
Age at first use	13-18 Year	11	8	1.41 (0.54-3.63)	20	22	0.88 (0.44-1.61)
	19-24	38	20	2.28 (1.23-4.19)	64	69	0.9 (0.61-1.34)
	25-30	19	10	2.05 (0.91-4.61)	50	28	1.99 (1.20-3.30)
	>30	13	8	1.69 (0.84-4.24)	29	5	6.47 (2.46-17.4)
Time since last use	>12 month	5	2	2.56 (0.48-13.44)	25	11	2.42 (1.63-5.04)
	12-36	19	12	1.68 (0.78-3.63)	17	7	2.54 (1.03-6.24)
	37-96	41	23	2.15 (1.19-3.85)	37	25	1.56 (0.91-2.70)
	>97	16	9	1.88 (0.8-4.4)	86	81	1.09 (0.75-1.60)
Type of OCP	HD	28	14	2.28 (1.13-4.57)	49	20	2.83 (1.62-4.93)
	LD	51	32	1.98 (1.16-3.38)	116	106	1.18 (0.82-1.70)

Age at discontinuation of oral contraceptives

We did not find any significant relationship between cervical and breast cancers and age at discontinuation of oral contraceptives.

Pill usage pattern

There was no significant relationship between cervical and breast cancers and the pattern of contraceptive pills use (regular or intermittent use).

Discussion

Our findings indicated that oral contraceptives use tripled the incidence of cervical cancer and doubled the incidence of breast cancer. The mean age of patients with cervical and breast cancer was 49.05 and 47.63 years, respectively. Thomas reported the age of affliction with cervical squamous cell carcinoma and adenocarcinoma as 46 and 42 years, respectively(David et al., 1996). The mean age of breast cancer prevalence was calculated as 49.1 years by Shamsaldini (Shamseddine et al., 2002) 49.18 years by Najafzar (Najf Zare et al., 2013) and 51.3 years by Mosavi (Mousavi et al., 2006) Although we excluded patients who aged over 65 years, the mean age of the subjects was still higher compared to other studies. This difference can be justified by late diagnosis of cancer due to the absence of screening programs for Iranian women.

The OR of developing cervical cancer following the use of Oral contraceptive (OR=3.072; 95%CI: 1.84-5.11) in the present study was similar to the results obtained by Zondravan (OR=3.34) (Zondervan et al., 1996). Henderson(Henderson et al., 1994)argued that the risk of Cervical adenocarcinoma increases with Oral contraceptive use (OR=2.1). While Mcfarlin (Mc Farlane et al., 2008) confirmed such results, Becker (Becker et al., 1994) concluded that Oral contraceptive have a protective effect against dysplasia. Likewise, in a study on the effects of oral contraceptives on abnormal changes in Pap smears, Nowzadi (Sayednozadi et al., 2005) found the pills to have a protective effect against dysplasia. Among all contraceptive methods, OCP are the most common. Moreover, since some other methods and devices such as diaphragms are not available in Iran, their effects cannot be evaluated.

In the current study, use of contraceptive pills doubled the odds for affliction with breast cancer (OR=2.11; 95%CI: 1.44-3.08). A similar level of risk (OR=2.20) has also been reported in Isfahan, Iran [28]. In the study by Shobairy (Shobeiri et al., 2010)] and Paul (Paul et al., 2011) calculated the as 2.83 and 3.02, respectively. Studies in Italy suggested an OR of 1.30 (La Vecchiaet al., 1995) In addition, Wang (Wang et al., 1992) Stanford (Stanford et al., 1995), Fassall (Fasal et al., 1975) and Comal (Kumle et al., 2002) affirmed the relationship between history of Oral contraceptive use and breast cancer. Marshi examined 4575 cancer cases and 4682 controls aged 35-65 years in Atlanta. In contrast to the mentioned studies, they did not find Oral contraceptive to increase the incidence of cancer as the difference between the two groups was not significant (March et al., 2002). In the same way, a study on 373 patients and a control group (age <40 years) by Tavoani could not establish a relationship between useOral of contraceptive and the incidence of cancer (Tavani et al., 1993) Whiteman not only rejected oral contraceptive use as a risk factor, but suggested it as a protective factor (Whiteman et al., 2007)

We did not categorize the participants in different age groups in the present study. Furthermore, our findings were not indicative of increased risk of cervical or breast cancer due to longer use of oral contraceptives. The findings of Ehsanpour regarding breast cancer were consistent with ours (Ehsanpour et al., 2013) Nevert heless, Kelsey believed long-term use of Oral contraceptive to increase the risk of the disease (Kelsey et al., 1993). Stanford also fo und the relative risk in women who used Oral contraceptive for more than 10 years to be 2.2 (Stanford et al., 1995).

The current study did not show any significant relation between age at first use of oral contraceptives and incidence of cervical cancer. However, according to Thomas, the risk of developing adenocarcinoma was higher in women that had started the pill before 20 years or after 35 years of age (David et al., 1996) In 2002, the World Health Organization announced that the incidence of cancer would increase in women who start oral contraceptives before the age of 20 (OR=2.9) (WHO 2002).Since it is common for Iranian women to give birth at younger ages, Oral contraceptive are rarely used before 20 years of age. Differences in age at first delivery and use of contraceptive methods before 20 years of age between Iran and other countries might have influenced the above-mentioned results.

The findings of the present research pinpointed the significant relation between age at first oral contraceptive use and the incidence of breast cancer. In other words, using pills before the age of 25 years was associated with higher odds of developing the disease. Faramni found higher odds of affliction with breast cancer in women who started these pill after 40 years of age (FRAUMENI et al., 1982). Battis et al. deduced that starting oral contraceptives before 18 years of age would decrease the age at the onset of cancer by four years (Bates et al., 2012). On the contrary, Whiteman did not find any relationship between age at first use of pills and the incidence of cancer (Whiteman et al., 2007).

The current study failed to establish a significant relationship between the incidence of cervical cancer and type of Oral contraceptive. Although Henderson reported similar findings (Henderson et al., 1993). WHO concluded that cervical cancer was more prevalent in women who used pills with high doses of progesterone (David B Thomas and WHO., 1996) Conversely, Becker did not find any relationship between dysplasia and type of Oral contraceptive used (Becker et al., 1994).

We found a significant relationship between breast cancer and type of oral contraceptives, i.e. high-dose birth control OCP were more common among women with breast cancer and the odds of developing the disease was higher in those who had received higher doses of estrogen. Likewise, Eliassen detected higher levels of estrogen in women with breast cancer (Eliassen et al.,

2006). A number of studies have also investigated the role of progesterone in breast cancer. Alsakar discovered a relationship between the incidence of cancer and use of progesterone (Alsaker et al., 2003). It is noteworthy that our participants had used a variety of OCP with equal dose of progesterone but different levels of estrogen.

Finally, age at discontinuation of Oral contraceptive had no insignificant effect on either types of cancer assessed in the present study. Moreover, the two groups were not significantly different in terms of regular daily use and constant/intermittent use of OCP.

We found the use of Oral contraceptive to triple the incidence of cervical cancer and double the incidence of breast cancer. Our findings along with those of previous research emphasize the necessity of performing Pap smears every six months and paying particular attention to screening for breast cancer in long-term users of oral contraceptives also breast cancer screening programs are necessary in Iran. Results of this study indicate that women that use Oral contraceptive have greater needs for preventive and screening programs.

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