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

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ABSTRACT

The aim of this study was to investigate risk factors for cervical cancer in Turkish women. In a hospital-based case-control study in İstanbul, 209 patients with histologically confirmed cervical cancer were compared with 1050 controls, who were admitted to the different departments of the same hospital. Odds ratios (OR) and 95% confidence intervals (CI) were obtained from multivariate logistic regression analysis, fitted by the method of maximum likelihood.

Risk factors for cervical cancer were found to be early age at first sexual intercourse (OR = 58.07, 95% CI: 27.88-120.95) and history of genital infection (OR = 5.17, 95% CI: 3.51-7.60). However, compared with controls, it was found that cases including higher education (OR = 0.18, 95% CI: 0.10-0.30), non-married (OR = 0.07, 95% CI: 0.04-0.12)   and non-use of alcohol (OR = 0.30, 95% CI: 0.14-0.65)   had a decreased risk for cervical cancer.

Our results are supportive of the hypothesis that early age at first sexual intercourse and history of genital infection is related with the risk factors for cervical cancer. Therefore, monogamy, late commencement of sexual activity, personal hygiene and use of barrier contraceptive methods help towards primary prevention.

Keywords: Cervical cancer, Risk factors

ABSTRACT

Servikal Kanser İçin Risk Faktörleri: Hastane Temelli Vaka-Kontrol Çalışmasının Sonuçları

Bu araştırmanın amacı, Türk kadınları'ndaki servikal kanser risk faktörlerini belirlemektir. İstanbul'da yürütülen hastane temelli vaka-kontrol çalışmasında, histolojik olarak servikal kanser tanısı konulmuş 209 hasta, aynı hastanenin farklı bölümlerine başvuran 1050 kontrol grubuyla karşılaştırıldı. Göreli risk oranları (ORs) ve %95 güven aralığı (CI), maksimum benzerlik metoduyla uygunluğu sağlanan, çok değişkenli lojistik regression analizinden elde edildi. Servikal kanser için risk faktörleri, erken yaşlarda ilk cinsel ilişki (OR = 58.07, 95% CI: 27.88-120.95) ve genital infeksiyon öyküsü (OR = 5.17, 95% CI: 3.51-7.60) olarak bulundu. Buna ragmen kontrol grubuyla karşılaştırıldığında, yüksek eğitim (OR = 0.18, 95% CI: 0.10-0.30), evli olmama (OR = 0.07, 95% CI: 0.04-0.12) ve sigara kullanmama (OR = 0.30, 95% CI: 0.14-0.65), servikal kanser için azaltıcı risk faktörü olarak belirlendi.

Araştırma sonucu, erken yaşta ilk cinsel ilişkinin ve genital infeksiyon öyküsünün servikal kanser için risk faktörü olduğunu göstermektedir. Bu nedenle primer korunmada tek eşlilik, seksüel aktivitenin uygun yaşta başlatılması ve bariyerli kontraseptif yöntem kullanımı önemlidir.

Anahtar Kelimeler: Serviks kanseri, Risk faktörleri

INTRODUCTION

Cervical cancer is second only to breast cancer as the most common female malignancy in both incidence and mortality worldwide.[1] More than 200,000 deaths due to it are registered each year, predominantly among economically disadvantaged women in both developing and industrialized nations.[2] Some of the world's highest rates are from sub-Saharan Africa, including South Africa (40/100.000). In Africa, most patients with cervical carcinoma present with late stage disease (59.3% stage III vs. 5.2 % stage 1B). While a decline in incidence and mortality from cervical cancer has been documented in first world countries such as the United States, Canada, and Scandinavia, this trend is not apparent for most developing countries due to lack of or inefficient screening programs.[3] It is hardly possible to present proper and updated data concerning Turkey due to the insufficiency of the statistical records. According to the data of the year 2008, the incidence in Turkey is 4.2 per 100.000.[4]

Various agents have been reported either as an association or cause of cervical cancer. These include ethnic factors, number of partners, and age at first sexual intercourse, age at first birth, steroid contraception, and infectious agents such as human papillomavirus (HPV), herpes simplex virus type 2 and Chlamydia trachomatis, among others.[3,5] As HPV infection is considered a sexually transmitted disease, investigations to reveal sexual behavioral risk factors have been conducted.[6,7] Overall, women who had first sexual intercourse at an early age or who have had many sexual partners have an increased risk of developing cervical cancer. Apart from sexual behavior, smoking, nutrition, parity and oral contraceptive use have been reported as major environmental risk factors for cervical cancer.[5,8] However, to date, there has been no clear-cut proven evidence of a biologic basis for these agents and the incidence of cervical cancer varies greatly from one population to another, depending on the prevalent risk factors mostly influenced by lifestyle.[2,5,9] These factors are well established in many countries.

Awareness of the risk factors believed and known to lead to cervical cancer is quite significant for preventing the illness, for detecting the groups with risk and for the early diagnosis.[10,11] Although our literature review has shown there are a lot of epidemiological studies and publications in other countries, we are not aware of any earlier investigation into risk factors for cervical cancer carried out in our country. Therefore, the present study was carried out in order to determine the risk factors leading to cervical cancer in Turkish women.

MATERIAL AND METHODS

Between September 2002 and October 2003, we conducted a case-control study of cervical cancer. Cases included 209 women with a histologically confirmed diagnosis of cervical cancer, who were admitted to the Breast and Gynecologic Policlinic of Oncological Institute of Istanbul University in Istanbul. Between these dates, we visited the outpatient clinic of the hospital every two days of the week (Monday and Wednesday), and interviewed with 209 women who applied to the clinic and agreed to participate in the study.

Controls were women residing in the same geographical regions, and they were admitted to the wards or outpatient clinics of the different departments of the same university's hospital during the same interval. In between these dates, we visited the ward and outpatient clinics every two day of the week (Thursday and Friday) and a total of 1050 women were interviewed. Half of the controls had no disease (%50) and they were the relatives of the patients accompanying them during their stay at hospital. The others had an orthopedic disease, surgical (eye disease) or miscellaneous illnesses, such as disorders of the ear, nose and throat. Women who had a malignant, endocrine, or gynecologic disease were not included in control group. In addition, none of the relatives of the patients applying to the oncology department were admitted to the control group.

Ethics: After Institutional Review Board approval had been obtained, data were collected. All the participant patients gave their informed consent, and if they preferred not to continue, they could withdraw from the study any time they wish. Also, the cases and controls were told that their decision of whether to participate in the research would not affect the healthcare services given to them and their patients, and none of the participants (cases and controls) refused the interview.

Data Collection: Trained study staff interviewed both case patients and control subjects, and all interviews were conducted in hospitals and interviewed the subjects who agreed to take part in the study were interviewed. Interviews with the case group were made at the oncology clinics where they come for their routine medical check-ups and at a suitable room after the control. The cases were given enough time for each interview. Similarly, the interviews of the control group were made at a suitable place and in an adequate period.

Data were collected through questionnaire. The questionnaire consisted of questions related to demographic characteristics (age, education, marital status, body mass index, chronic diseases, smoking and alcohol), menstrual and reproductive history (parity, age at first birth, breast-feeding, age at menarche, oral contraceptive and hormone replacement therapy (HRT) use, and sexual history (age at first sexual intercourse, sexual partner, genital infection). Body mass index (BMI) was calculated as weight (kg) / height (m^2), according to Quatelet's formula. Parity was the number of full-term pregnancies, which were defined as pregnancies longer than 6 months regardless of the outcome. HRT use was categorized as follows: never users (none or less than 6 months of cumulative use), and current users (at least 6 months of use within previous 12 months before the reference date). Analysis according to the type of therapy (estrogen alone or estrogen combined with progesterone) was not presented due to small sample size. Hypertension or diabetes was registered if a woman reported treatment for the condition or said that it had been diagnosed by a physician. A woman was considered a 'smoker' if she had smoked at least one cigarette/day for at least one year. In the group of cases, four women knew that they were infected with HPV, HSV. However, why the others did not know and were not sure that the similar infections were diagnosed in themselves, they did not insert in statistical analyzes.

Statistical Analysis: Data about all the risk factors were entered into an SPSS 10.0 for Windows' computer program. We modeled the probability of disease by means of the following logistic regression model.[12] The statistical analysis of the study was evaluated with regard to 16 variables in age, education, marital status, body mass index, chronic diseases, smoking and alcohol, parity, age at first birth, breast-feeding, age at menarche, oral contraceptive and HRT use, age at first sexual intercourse, sexual partner, genital infection to find their associated with cervical cancer. This analysis was used Chi-square. Later these variables that are related with cervical cancer were examined to figure out which variables increase or reduce the risk factor for cervical cancer.

RESULTS

Table 1 presents the distribution of 209 cervical cancer cases and 1050 controls according to age and selected general characteristic variables. Table 2 gives the distribution of cervical cancer cases and controls according to reproductive history and menstrual factors. As for the distribution of cases and controls according to sexual history, it is presented in Table 3. Table 4 presents also the results of multivariate logistic regression analyses.

Compared with the age at first sexual intercourse of above 21 years, age at 16 or less increased the risk (OR = 58.07, 95% CI: 27.88-120.95). Overall, women who ever had sexually transmitted tract reproductive infection (neisseria gonorrhoeae, chlamydia trachomatis, etc) had an OR of cervical cancer of 5.17 (95% CI: 3.51-7.60) compared with non-reproductive infection. However, However, compared with controls, it was found that cases including higher education (OR = 0.18, 95% CI: 0.10-0.30), non-married (OR = 0.07, 95% CI: 0.04-0.12) and non-use of alcohol (OR = 0.30, 95% CI: 0.14-0.65) had a decreased risk for cervical cancer.

DISCUSSION

Most women who develop cervical cancer tend to have one or more identifiable factors that increase their risk for the disease. These include ethnic factors, number of partners, and age at first sexual intercourse, age at first birth, steroid, contraception, and infectious agents such as human papillomavirus (HPV), herpes simplex virus type 2 and Chlamydia trachomatis, among others.[3,5] Apart from these, smoking, nutrition, parity and oral contraceptive use have been reported as major environmental risk factors for cervical cancer.[5,8] However, there has been no clear-cut proven evidence of a biologic basis for these agents and the incidence of cervical cancer varies greatly from one population to another.[2,5,9] In this study; edu-

Table 1. Distribution of cases and controls according to age and selected general characteristics

Factor	Cases (n=209)		Controls (n=1050)		X²	p
Age						
≤49	91	(48.5)	560	(53.3)		
50-59	51	(24.4)	260	(24.8)	10.858	0.004
60 ≤	67	(32.1)	230	(21.9)		
Education						
Illiterate	52	(24.9)	168	(16.0)	30.822	0.001
Literate+Primary school	104	(49.8)	730	(69.5)		
Secondary school+Higher education	53	(25.3)	152	(14.5)		
Marital status						
Ever married	153	(73.2)	989	(94.2)	91.058	0.001
Never married	56	(2.8)	61	(5.8)		
Body mass index						
Normal (18.5-24.99)	77	(36.8)	291	(27.8)	6.976	0.008
Obese (25.0 ≤)	132	(63.2)	758	(72.2)		
Chronic illnesses						
No	148	(70.8)	821	(78.2)	5.351	0.020
Diabetes+Hypertension	61	(29.2)	229	(21.8)		
Smoking						
Never	149	(71.3)	841	(80.1)	8.040	0.004
Ever	60	(28.7)	209	(19.9)		
Alcohol						
Never	187	(89.5)	1004	(95.6)	12.884	0.001
Ever	22	(10.5)	46	(4.4)		

cation, marital status, use of alcohol, age at the first sexual intercourse and history of genital infection were found to be associated with cervical cancer.

In population-based case-control studies, Parikh et al.[9] and Gawande et al.[13], found illiteracy as a factor associated with cervical cancer. Similarly, In our study, It was found that higher education had a decreased risk for cervical cancer; the OR being 0.18. Presumably, decreased educational level causes an increase in intercourse at an early age, sexual partner and poor genital hygiene.

We found that non-married had a decreased risk for cervical cancer; the OR being 0.07. Therefore, our study confirmed that reproductive history of woman is associated with risk factors for cervical cancer. Atalah et al.[14], Bjorge and Kravdal[15],Yoo et al.[16] reported that early age at first full term pregnant was associated with risk factors. However, there is a study that could not find such a relationship.[17] These

studies showed that cervical cancer increased in women who gave birth to their first child at an earlier age.

In epidemiological research it was reported that cigarette smoking and use of alcohol are an increased risk of developing cervical cancer.[14,18] According to our study results, non-use of alcohol had a decreased risk for cervical cancer, the OR being 0.30, which was parallel with other study results.[19,20,21] Sikstrom et al.[22] reported that smoking, alcohol and drug abuse are risk markers for cervical human papillomavirus infection. However, there are some studies that could not find such a relationship.[8,23] Today, the life style of Turkish women is changing. They predispose to use of alcohol and cigarette and these changes are striking for the finding that ''use of alcohol and cigarette smoking are risk factor for cervical cancer''.

The association between sexual history and cervical cancer is well established. Coitus-related behaviors,

Table 2. Distribution of cases and controls according to reproductive history and menstrual factors

Factor	Cases (n=209)	Controls (n=1050)	X²	p
Parity				
≤ 2	81 (38.8)	527 (50.2)	9.127	0.002
≥ 3	128 (61.2)	523 (49.8)		
Age at first birth				
≤ 20	147 (70.3)	502 (47.8)	28.575	0.001
21-29	54 (25.9)	446 (42.5)		
≥ 30	8 (3.8)	102 (9.7)		
Breast-feeding				
(At least 1 year)				
Yes	177 (84.7)	883 (84.1)	0.046	0.829
Never	32 (15.3)	167 (15.9)		
Age at menarche				
≤ 12	58 (27.8)	176 (16.8)	14.600	0.001
13-14	117 (56.0)	648 (61.7)		
≥ 15 -	34 (16.2)	226 (21.5)		
Oral contraceptive use				
Ever	58 (27.8)	154 (14.7)	25.951	0.001
Never	117 (56.0)	896 (85.3)		
HRT use				
Ever	61 (29.2)	58 (5.5)	6.066	0.014
Never	148 (70.8)	992 (94.5)		

such as early age at first intercourse and multiple sexual partners have been found to be associated with cervical cancer.[11,19,20,24-26] In our study, compared with women in late age at first intercourse, women in the early age had a higher risk for cervical cancer. Sierra-Torres[2], Turkistanli[11], Yoo et al.[16], Liu et al.[19], Pettifor et al.[24], Biswas et al.[25], have also determined results in conformity with those of ours. Therefore, our results and other studies support the common idea that early age at first intercourse increases the risk.

In our study, multiple sexual partners were not found to be associated with cervical cancer. But most other studies[2,11,20,24], the increased number of sexual partners increased cervical cancer risk compared with fewer number of sexual partners. One other study[19] also found that the mean cervical cancer age of the Chinese was significantly lower than the Australians (44 versus 53 years), because of multiple sexual partners and history of sexually transmitted diseases. The results support the hypothesis that multiple sexual partners play a role in cervical carcinogenesis. According to results of the study, late commencement of

sexual activity is an important prevention in our country that has married and the first sexual intercourse at early age.

Case-control studies have generally reported positive associations between history of genital infection such as neisseria gonorrhoeae, chlamydia trachomatis and cervical cancer.[7,9,19,22,25] Our study confirmed that history of genital infection is an increased risk of developing cervical cancer. In parallel to our study's results, there are some case-control studies that reported positive associations between history of genital infection and cervical cancer. Predisposition to such history of genital infection puts Turkish women in a high-risk group for cervical cancer. Therefore, women are emphasized that personal hygiene and use of barrier contraceptive methods help towards primary prevention in our country.

The results from the current study must be considered in light of certain limitations. Firstly, the study was carried out in a small group of 209 subjects for a year. Another limitation of the study is that all data

Table 3. Distribution of cases and controls according to sexual history

Factor	Cases (n=209)	Controls (n=1050)	X^2	p
Age at first sexual intercourse				
≤ 16	80 (38.3)	91 (8.7)	167.243	0.001
17-20	105 (50.2)	466 (44.3)		
≥ 21	24 (11.5)	493 (47.0)		
Sexual partner				
1-2	192 (91.9)	1035 (98.6)	31.639	0.001
≥ 3	17 (8.1)	15 (1.4)		
Genital infection				
Yes	136 (65.1)	264 (25.1)	128.199	0.001
No	73 (34.9)	786 (74.9)		

were obtained from the women's self-reports. All these data may not be true. For some of the questions were too difficult for them to remember: i.e. pregnancy cases resulting in dead births, the age of menarche, age at the first sexual intercourse and story of HPV and HSV. However, the findings and limitations of the study are quite useful in that they illuminate the progressive research in this field.

In conclusion, our results are supportive of the hypothesis that history of early age at first sexual activity and genital infection are risk factors for cervical cancer. Therefore, monogamy, late commencement of sexual activity, personal hygiene and use of barrier contraceptive methods help towards primary prevention.

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Table 4. The results of multivariate logistic regression analyses

Factor	p	OR (95% CI)		
Education				
Illiterate (reference)		1		
Literate+Primary school	0.001	0.13	0.07	0.24
Secondary school+Higher education	0.001	0.18	0.10	0.30
Marital status		1		
Ever married (ref: no)	0.001	0.07	0.04	0.12
Never married				
Alcohol		1		
Ever (ref: no)	0.002	0.30	0.14	0.65
Never				
Age at first sexual intercourse		1		
≥ 21 (ref: no)	0.001	17.69	9.22	33.93
17-20	0.001	58.07	27.88	120.95
≤ 16				
Genital infection		1		
No	0.001	5.17	3.51	7.60
Yes				

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