Risk Factors Associated with Uterine Cervical Cancer in Korea: A Case-Control Study with Special Reference to Sexual Behavior

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Objective. A hospital-based case-control study was conducted to identify characteristics of women at high risk of developing cervical cancer with special reference to sexual behavior in Korea.

Methods. Histologically confirmed cases of invasive cervical cancer were selected from the Department of Gynecology, Seoul National University Hospital between September 1992 to May 1995 (n = 203). Women with normal pap smear tests and women free of past history of any malignancies were regarded as controls (n = 827). Information on risk factors were collected by both a self-administered questionnaire and a direct interview.

Results. Uterine cervical cancer risk was higher in women with a less educated spouse (Ptrend=0.0003), women with a family history of cervical cancer (adjusted odds ratio [OR]=2.20, 95% confidence interval [CI] 1.21-4.01), women of shorter height (Ptrend=0.02), women with early age at first full term pregnancy (Ptrend=0.0005), and women who have had multiple full term pregnancies (Ptrend=0.006) by the multiple linear logistic analysis. Particularly noteworthy was a significant decreasing trend in the adjusted OR with the age at first sexual intercourse increasing (Ptrend=0.002) after adjusting the number of sexual partners. The husband’s indecent sexual history showed a borderline significance (Ptrend=0.07).

Conclusions. This study confirmed that the risk factors of cervical cancer in Korea are similar with those found in other countries. J Epidemiol, 1997; 7 :117-123.

case-control study, cervix neoplasms, Korea, reproductive factor, risk factor, sex behavior
countries. Third, although earlier studies identified cervical cancer risk factors including early age at first sexual intercourse, multiple sexual partners, and histories of sexually transmitted diseases in the 1950's and 1960's, there has been limited investigation on the etiology of the cancer in Korea.

It might be asked whether cervical cancer in recent years resembles that described earlier since these exposure pattern may have been changed over time.

To identify characteristics of women at high risk of developing cervical cancer, a case-control study was conducted in Seoul, Korea. Particular concern lies in the possibility of the sexual hypothesis raised by previous investigations in the etiology of uterine cervical cancer, adjusting for other confounders, e.g., demographic, anthropometric, behavioral, and reproductive factors that have been known to be related with the risk of cancer.

MATERIALS AND METHODS

Study Subjects

Of the first-visit outpatients for the detection or the diagnosis of uterine cervical cancer at the Department of Obstetrics and Gynecology in Seoul National University Hospital between September 1992 and May 1995, women under the age of 60, who had intact uterus, who had undertaken both the pap smear test and a direct interview were eligible (n = 1,101). Histological confirmation of invasive cervical cancer was carried out for those who had 'class II or more' in the pap smear test. The number of invasive cervical cancer cases were 219. Included were 882 women who had visited the Department during the same period and had a normal pap smear as controls. Women with self-reported history of any malignancies (10 cases; 21 controls), women who had undertaken oophorectomy (5 cases; 27 controls), and women with missing information on sexual behavior (1 case; 7 controls) were deleted from the study population (203 cases; 827 controls).

Data Collection

Information on the risk factors of uterine cervical cancer was collected through both a self-administered questionnaire and a subsequent face-to-face interview by a well-trained nurse epidemiologist. The risk factors encompassed 1) general demographic characteristics (age, educational attainments of the interviewee, educational attainments of the spouse, marital status, religion, family history of cervical cancer among the first degree relatives, etc.), 2) anthropometric measures (current height, current weight, weight at age around 20, etc.), 3) life style (alcohol drinking, cigarette smoking, etc.), 4) reproductive factor (age at menarche, menstrual regularity, parity, age at first full term pregnancy, number of full term pregnancy, age at menopause, etc.), 5) sexual behavior (history of sexually transmitted disease, age at first sexual intercourse, number of sexual partners, history of sexual intercourse during menstruation, husband's indecent sexual history, husband's circumcision status, etc.). The interview was conducted in a separate room in order to ensure the validity of the answers, especially on the sensitive and private questions. The information was obtained before either the study subjects or the interviewer were aware of the final diagnosis.

Data analysis

To identify the potential risk factor that might interfere in the relationship between a sexual factor and a cancer risk, correlation analysis, t-test and X²-test were used. All the continuous variables were categorized into two or more subgroups. Crude odds ratios (OR) were calculated based on the coefficients and 95% confidence intervals (CI) of the linear logistic regression model with adjustment for the age at interview.

As a multivariate analysis, unconditional linear logistic regression model was used to obtain maximum likelihood estimates of adjusted OR with their 95% CI. Odds ratio was estimated as antilogarithm of the partial logistic regression coefficient. Likelihood ratio test for trend was applied to the ordinal variable, assigning the score j to the jth exposure level of the categorical variable, and treating the scored variable as a continuous variable.

The multivariate logistic model was constructed based on both the statistical significance and the biological plausibility. Three separate models were used to estimate the adjusted OR. The first model included demographic characteristics and life style factors as independent variables, and the second model added reproductive factors to the first model to estimate the adjusted ORs on reproductive factors after adjusting the variables used in the first model. Because of a convergency error due to zero cell, age at first full term pregnancy and the number of full term pregnancies were separately incorporated into the second model. In the final model, the ORs for the sexual factors and 95% CI were estimated after adjusting for all the previous variables. In the multivariate analysis, missing values for the continuous variables were replaced with age-stratum specific median values. Subjects with missing values for smoking habits were assigned as ‘never-smokers’.

RESULTS

Uterine cervical cancer risk was significantly increased in women with a less educated spouse (Pₓₓ=0.0003), women with family history of cervical cancer among the first-degree relatives (adjusted OR=2.20, 95% CI 1.21-4.01), and women of shorter height (Pₓₓ=0.02). Current weight were not significantly associated with the cancer risk (Table 1).

Smokers increased the risk of cervical cancer (adjusted OR=1.40, 95% CI 0.72-2.70), although this factor was not significantly associated. Alcohol drinking was not related to the
Table 1. Adjusted odds ratios and 95% confidence intervals of risk factors related to the carcinoma of uterine cervix among 203 cases and 827 hospital controls interviewed at Seoul National University Hospital, 1992-1995, Korea.

| Risk factors                      | No. of cases | No. of controls | aOR^ 95% CI^ |
|-----------------------------------|--------------|-----------------|--------------|
| Age at interview (years)          |              |                 |              |
| 20-29                             | 2            | 28              | 1.0          |
| 30-39                             | 67           | 275             | 3.98 0.89-17.8 |
| 40-49                             | 73           | 330             | 3.17 0.70-14.4 |
| 50-59                             | 61           | 194             | 4.28 0.92-20.0 |
|                                   |              |                 | P\text{\textit{test}}=0.42^ |

| Educational attainments           |              |                 |              |
|-----------------------------------|--------------|-----------------|--------------|
| primary school                    | 46           | 169             | 1.0          |
| middle school                     | 56           | 165             | 2.06 1.21-3.48 |
| high school                       | 65           | 332             | 1.52 0.84-2.75 |
| college +                         | 26           | 153             | 1.79 0.83-3.84 |
|                                   |              |                 | P\text{\textit{test}}=0.25^ |

| Husband’s educational attainments |              |                 |              |
|-----------------------------------|--------------|-----------------|--------------|
| primary school                    | 23           | 38              | 1.0          |
| middle school                     | 30           | 104             | 0.38 0.18-0.78 |
| high school                       | 80           | 301             | 0.36 0.18-0.72 |
| college +                         | 64           | 381             | 0.20 0.09-0.45 |
|                                   |              |                 | P\text{\textit{test}}=0.0003^ |

| Family history of cervix cancer among the first-degree relatives |              |                 |              |
|------------------------------------------------------------------|--------------|-----------------|--------------|
| no                                                               | 185          | 783             | 1.0          |
| yes                                                              | 18           | 44              | 2.20 1.21-4.01 |

| Height, current (cm)                                               |              |                 |              |
|------------------------------------------------------------------|--------------|-----------------|--------------|
| -154                                                             | 59           | 160             | 1.0          |
| 155-159                                                          | 78           | 325             | 0.81 0.53-1.23 |
| 160 +                                                            | 62           | 339             | 0.59 0.37-0.94 |
|                                   |              |                 | P\text{\textit{test}}=0.02^ |

| Weight, current (kg)                                               |              |                 |              |
|------------------------------------------------------------------|--------------|-----------------|--------------|
| -49                                                              | 44           | 123             | 1.0          |
| 50-59                                                            | 98           | 437             | 0.73 0.46-1.13 |
| 60 +                                                             | 61           | 267             | 0.81 0.48-1.35 |
|                                   |              |                 | P\text{\textit{test}}=0.55^ |

| Smoking history                                                   |              |                 |              |
|------------------------------------------------------------------|--------------|-----------------|--------------|
| never                                                            | 188          | 787             | 1.0          |
| ever                                                             | 15           | 40              | 1.40 0.72-2.70 |

| Alcohol drinking history                                          |              |                 |              |
|------------------------------------------------------------------|--------------|-----------------|--------------|
| never                                                            | 131          | 517             | 1.0          |
| ever                                                             | 72           | 302             | 0.82 0.57-1.16 |

| Number of marriages                                              |              |                 |              |
|------------------------------------------------------------------|--------------|-----------------|--------------|
| single                                                           | 198          | 808             | 1.0          |
| multiple                                                         | 5            | 11              | 1.69 0.55-5.13 |

| Age at first full term pregnancy                                 |              |                 |              |
|------------------------------------------------------------------|--------------|-----------------|--------------|
| <19                                                              | 7            | 12              | 1.0          |
| 20-24                                                            | 110          | 312             | 0.62 0.23-1.70 |
| 25+                                                              | 84           | 461             | 0.33 0.12-0.73 |
|                                   |              |                 | P\text{\textit{test}}=0.0005^ |

| Number of full term pregnancies                                  |              |                 |              |
|------------------------------------------------------------------|--------------|-----------------|--------------|
| 0                                                                | 1            | 34              | 1.0          |
| 1-2                                                              | 102          | 470             | 9.27 1.18-72.5 |
| 3+                                                               | 100          | 323             | 12.98 1.64-102.8 |
|                                   |              |                 | P\text{\textit{test}}=0.006^ |

\(^a\) Adjusted odds ratio and 95% confidence intervals of each risk factor was based on the regression coefficient and its standard error of the multiple linear logistic regression model. Adjustment for age at interview, educational attainments, husband’s educational attainments, family history of cervix cancer, height, weight, smoking history, alcohol drinking history, number of marriages, and age at first full term pregnancy or the number of full term pregnancies was done.

\(^b\) P-value of likelihood ratio test for trend to assess the linear increase in the logit risk with exposure to the risk factor.

\(^c\) Women who have ever married and living with husband or divorced or bereaved were regarded as single, whereas remarried were included as multiple.

\(^d\) Among parous women.
Table 2. Multivariate analysis on the risk of the carcinoma of uterine cervix with special reference to the sexual factors among 203 cases
and 827 hospital controls interviewed at Seoul National University Hospital, 1992-1995, Korea.

| Risk factors                                      | No. of cases | No. of controls | cOR* 95% CI | aOR* 95% CI |
|--------------------------------------------------|--------------|-----------------|-------------|-------------|
| Age at first sexual intercourse                  |              |                 |             |             |
| -19                                              | 43           | 83              | 1.0         | 1.0         |
| 20-24                                            | 120          | 470             | 0.49 0.32-0.74 | 0.56 0.34-0.90 |
| 24 +                                             | 40           | 268             | 0.29 0.17-0.47 | 0.37 0.20-0.68 |
| Number of sexual partners                        |              |                 |             |             |
| one                                              | 159          | 691             | 1.0         | 1.0         |
| two or more                                      | 44           | 130             | 1.58 1.07-2.34 | 0.95 0.59-1.53 |
| Husband’s indecent sexual history                |              |                 |             |             |
| yes                                              | 101          | 329             | 1.0         | 1.0         |
| equivocal                                        | 47           | 198             | 0.60 0.42-0.87 | 0.94 0.46-1.03 |
| no                                               | 54           | 297             | 0.79 0.53-1.18 | 0.69 0.62-1.44 |
| Husband’s circumcision                           |              |                 |             |             |
| not circumcised                                   | 54           | 152             | 1.0         | 1.0         |
| circumcised                                       | 138          | 632             | 0.64 0.44-0.92 | 0.99 0.68-1.45 |

*Crude odds ratio and 95% confidence intervals of each risk factor was based on the regression coefficient and its standard error of the linear logistic regression model with adjustment for age at interview.

Adjusted odds ratio and 95% confidence intervals of each risk factor was based on the regression coefficient and its standard error of the multiple linear logistic regression model. Age at interview, educational attainments, husband’s educational attainments, family history of cervix cancer, height, weight, smoking history, marital status, number of full term pregnancies, and all the sexual factors were simultaneously included in the multiple linear logistic model.

P-value of likelihood ratio test for trend to assess the linear increase in the logit risk with exposure to the risk factor.

A strong trend of increased risk with decreasing age at first full term pregnancy was found ($P_{\text{trend}}=0.0005$), and there was also a significant trend of increased risk with the number of full term pregnancies ($P_{\text{trend}}=0.006$). Because factors related with menstruation (age at menarche, age at menopause, menstrual regularity) and abortion history were not significantly associated with the risk of cervical cancer at all, the results are not listed in the Table 1.

Table 2 shows the results of multivariate analysis on the independent association of each sexual factor with the risk of the uterine cervix cancer in Korea. Univariate analysis revealed that women with a history of first sexual intercourse at an early age were at a significantly elevated risk of uterine cervical cancer; compared to those having first sexual intercourse under 19, with the '20-24 group' having a 0.49-fold risk (95% CI 0.32-0.74), and the 'above 24 group' having a 0.29-fold risk (95% CI 0.17-0.47). These associations remained statistically significant even after adjusting other risk factors, including the number of sexual partners ($P_{\text{trend}}=0.002$). In the univariate analysis, risk of cervical cancer was associated with the number of sexual partners (crude OR = 1.58, 95% CI 1.07-2.34). However, this association disappeared after adjusting for potential confounders, including age at first sexual intercourse.

Women with a self-reported history of their husband's indecent sexual behavior were at increased the risk of cervical cancer with borderline significance even after adjusting other variables ($P_{\text{trend}}=0.07$). Husband's circumcision was a significant risk factor in the univariate analysis, but this association also disappeared after controlling for other covariates.

DISCUSSION

This study suggests that cervical cancer is related to both reproductive factors and sexual behavior in Korea. Particularly noteworthy was the strong association of the age at first sexual intercourse to the risk of cervical cancer independent of the number of sexual partners. Inversely, the association of the number of sexual partners with the cancer risk was confounded by the age at first sexual intercourse. Shorter height, having less educated spouse, multiple marriage, multiple delivery, and family history of cervical cancer also showed independent effects on cervical cancer risk.

These results seemed to be less affected by recall bias since information on the risk factors was obtained before either the study subjects or the interviewer were aware of the cytologic test results. It is less likely that there was misclassification bias of outcomes since diagnoses of cervical cancer patients...
were made by the histo-pathological examination at the Hospital. Moreover, all the controls were also confirmed as cancer-free at the same Hospital. Inter-interviewer bias was largely avoided since the data collection was done by only one interviewer. Finally, there must be no temporal ambiguity between the exposure to the sexual behaviors and the outcome not only due to recruitment of incident study population, but also to the fact that most of the study population were married.

The major limitation of this study is that there was no community control groups. However, it is unlikely that this study was affected by selection bias since both the case and the control group was prospectively and incidently selected during the study period. During the pretest for the validity and reliability of the questionnaire, validity of the interview by the interviewer about the questions on past history of sexual behaviors of both her and her husband had been thoroughly assessed with the gold standard of a separate interview by the coauthors, which showed an excellent agreement. The data has been collected through an intensive application of a self-administered questionnaire followed by a subsequent direct interview conducted in a separate room to avoid information bias which may occur when critical or sensitive questions are asked. There is no definite evidence of information bias in this study.

The relationship between age at interview and the cancer risk was not so prominent in this study. It has been demonstrated that cervical cancer predominantly affects women of lower social class. This study showed similar results of the inverse relationship between socio-economic status indexed by husband's educational attainments and the cervical cancer risk. There was no apparent relationship between religion and the cancer risk.

It is an interesting finding that women with a family history of cervical cancer were at 2.2-fold elevated risk. Although it is possible to be affected by recall bias that cases have better remembrance of familial history of cervical cancer than controls in case-control design, the possibility of such a recall bias might not be very high in this study because all information were collected before making a diagnosis on study subjects.

The increasing trend in the risk of uterine cervical cancer with current height was statistically significant, which implies the possibility of confounding effect by socio-economic status in her adolescent stage; shorter height may have been caused by poor nutrition or lower economic status.

Although the results from several epidemiologic studies support the relationship between smoking habits and the risk of cervical cancer, the result of this study did not show a significant association. This may have resulted from the nondifferential misclassification of smoking history due to the cultural trait that women's smoking is not generally accepted in Korean society. This kind of misclassification may reduce the observed odds ratios toward the null. The prevalence of current smokers among females is 7.6% in 1989, and 6.1% in 1992, which is much lower than that of other countries. This may be another reason of non-significant result in the odds ratio for smoking.

Early studies revealed that cervical cancer risks are high among women marrying at younger ages. Our finding that women with multiple marriages have 2.78-fold excess risk compared to those with single marriage is consistent with the results of other investigations that multiple marriages or marital instability increase the risk of cervical cancer by 2-fold or more. Findings on the increased risk with decreasing age at first full term pregnancy, and with increasing the number of full term pregnancies in this study are also consistent with previous findings in the western countries. Parity has been consistently shown to be associated with an increased risk for invasive cervical cancer. But it is not yet clear how pregnancy affects the risk of uterine cervical cancer, and the question of whether pregnancy itself is the independent risk factor of cervical cancer or not is still controversial.

Some investigators report that the types of delivery, hygiene at delivery or increased chance of infection of agents suspected in the origins of cervical cancer such as human papilloma virus (HPV) infection or direct physical trauma may be the risk factors of cancer. However, unequivocal evidences were not presented yet. Kjaer et al. in their large case-control study found that multiple pregnancies elevate the risk for HPV infection. Hildesheim et al. however, could not find any association between the detection rate of HPV DNA and the number of pregnancies.

Later investigations have indicated the importance of sexual activity than parity, especially early age at first sexual intercourse. This study apparently indicated a strong relationship of age at first sexual intercourse with the cervical cancer risk. Although multiple sexual partners have previously been recognized as important risk factors of cervical cancer, we failed to detect an association between cervical cancer risk and the number of sexual partners. Despite the recognition that age at first intercourse and number of sexual partners are closely correlated, independence of these two effects are still controversial. However, there was a strong association of the age at first sexual intercourse to the risk of cervical cancer independent of the number of sexual partners. Moreover, the association of the number of sexual partners with the cancer risk seems to be confounded by the age at first sexual intercourse. This finding supports earlier suggestions that age at first intercourse might be the more important of the two factors because of increased susceptibility of the cervix during adolescence.

Although not many studies showed increased risk in sexual behavior of women's partners, the result of this study that there are increased risks of women with husband's indecent sexual history support the concept of an infectious agent as an etiologic factor for cervical cancer. It may be due to the increased chance of infection from both earlier age of first sex-
ual intercourse and indecent sexual history of the spouse. Further study that focuses on the elevated risk in relation to infectious agent should be pursued.

In summary, this hospital-based case-control study confirms several risk factors associated with cervical cancer in Korea. Most factors identified in this study have been previously recognized as risk factors for cervical cancer. Particularly noteworthy was a strong association of the age at first sexual intercourse independent of the number of sexual partners. These results indicate that the risk factors of cervical cancer in Korea are not so much different from those found in previously conducted studies from other countries and confirm the importance of reproductive and sexual factors in cervical cancer etiology.

The reason why the incidence of cervical cancer is still high in Korea is unclear. There is an evidence that the incidence of cervical cancer is decreasing by 1989 in Korea, and the authors believe that such a decreasing trend will be accelerated furthermore. At this point, it can be speculated that the delay in introduction of effective screening program by the National Government might be the most crucial point for the high incidence.

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