Dietary patterns and risk of cervical cancer: a case-control study in Uruguay

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ABSTRACT

In the time period 1996-2004, a case-control study on diet and cervical cancer was conducted at the National Cancer Institute in Uruguay. The study included 268 cases and 536 controls with non-neoplastic diseases. The foods and beverages in the food-frequency questionnaire were included in a factor analytic model. This method retained three factors which were labeled as the *drinker, red meat*, and *prudent* patterns. The model explained 60% of the variance. Whereas the *red meat* and *drinker* patterns were directly associated with the risk of cervical cancer (OR for red meat pattern 1.79, 95% CI 1.12-2.86), on the other hand, the *prudent* pattern was inversely associated with cervical cancer (OR 0.60, 95% CI 0.38-0.93). To our knowledge, this study was the first one using factor analysis in order to elucidate the role of the diet in relation with cervical cancer.

Keywords: Dietary Patterns; Cervical Cancer

1. INTRODUCTION

Cervical cancer is the third cancer site in frequency in Uruguay, following breast cancer and colorectal cancer. This malignancy shows an age-standardized incidence rate of 17.5 per 100,000 Uruguayan women [1]. A previous study conducted in Uruguay showed that cancer of the uterine cervix presented a steady decline in mortality from the early fifties until the late eighties [2]. More precisely, in the time period 1953-1957, this decline reached mortality rates of 4.4 per 100,000 women, which implies a relative risk of 0.56.

The main risk factors for cervical cancer are related to the infection caused by human papilloma virus (HPV) and related sexual activities. Smoking and other environmental risks have been studied in detail [3,4] and tobacco smoke has been considered a potential carcinogen in cervical cancer.

The role of the diet has been examined in a rather small number of studies and the consistency of the findings is limited [3,5]. In a monograph by the World Cancer Research Fund [5] carrots have been suggested as a possible protective vegetable, but aside from this finding, little else is known about the role that diet plays in cervical cancer.

Since traditional approaches to research into cervical cancer have been considered limited due to the high collinearity of individual foods or nutrients, we decided to use factor analysis in this study, in the view that it could offer a new approach in the etiology of cervical carcinoma. This analytical method consists of reducing a large number of foods to a smaller number of factors [6], and has been employed to date in the study of numerous cancer sites [6-10]. We considered that this approach could offer new information regarding the role of diet in the etiology of cervical carcinoma.

2. SUBJECTS AND METHODS

2.1. Selection of Cases

In the time period 1990-2000 all newly diagnosed and microscopically confirmed patients with carcinoma of the cervix were considered eligible for the study. A total of 274 patients were approached and only 5 refused the interview, leaving a final total of 268 patients (response rate 97.8%). Two hundred and sixty (260) patients presented squamous cell carcinoma of the cervix (97.3%) and 8 patients showed undifferentiated carcinoma (2.7%). All the cases were diagnosed by biopsy and were admitted to the National Institute of Cancer, Uruguay.

2.2. Selection of Controls

In the same time period and in the same Institute, all female patients with non neoplastic diseases which were

not related to tobacco smoking or alcohol drinking and without recent changes in their diets were considered eligible for the study. A total of 2,136 patients were asked for voluntary participation in the study, and 2074 accepted the interview. Only 62 women refused the interview (response rate 97.1%).

From this pool of controls, 536 patients were included in the study. These controls were randomly selected following a control/case ratio of 2:1 and were frequency matched to cases on age and residence. These patients presented the following conditions: sebaceous cyst (140, 26.1%), seborrheic keratosis (130, 24.2%), breast abscess (109, 20.3%), osteomielitis (55, 10.3%), lipoma (41, 7.6%), injuries (26, 4.9%), varicose veins (16, 3.0%), diseases of the genital tract (11, 2.1%), and hydatid cyst (8, 1.5%). All the cases and controls were of Hispanic White ancestry.

2.3. Inteviews and Questionnaire

All the participants (cases and controls) were interviewed after admission to the Institute by two trained social workers. Proxy interviews were not accepted. The patients were administered a structured questionnaire which included the following sections: sociodemographics (age, residence, education, income), a complete occupational history based on the last four jobs, self reported height and weight 5 years prior to the interview, a complete history of cancer among first-degree relatives, a complete history of smoking (age at start, age at quit, number of cigarettes smoked per day, type of tobacco, type of cigarette), a complete history of alcohol drinking (age at start, age at quit, number of glasses per day or week, type of alcoholic beverage), a complete history of mate consumption (age at start, age at quit, number of litres of the beverage, mate temperature), menstrual and reproductive events (age at menarche, age at menopause, number of livebirths, abortion, age at first pregnancy, age at last pregnancy, breastfeeding, age at first intercourse, number of sexual partners), and a food-frequency questionnaire (FFQ) focused on meat consumption, dairy foods, total vegetables and total fruits.

2.4. Statistical Analysis

The food groups were categorized using a Likert-type scale and were introduced in a factor analysis among controls. The factor analysis retained three factors [6,11] after running the scree plot. The factorability was measured through Cronbach alpha and sampling adequacy was tested through the Kaiser-Meyer-Olkin statistic. The factors were then rotated using the orthogonal varimax method and normalized by the Kaiser procedure. The factors were scored through the Thompson regression method [12] and the scores were applied to cases and controls. The scored patterns were correlated by selected variables using Spearman rank correlations.

The relative risks of cervical carcinoma was approximated by the odds ratios, using unconditional multiple logistic regression [13]. In short, we fitted a model which included as independent variables the following terms: age (continuous), residence (categorical), urban/rural status (categorical), education (categorical), smoking index (categorical), number of partners (categorical), age at first intercourse (categorical), total energy intake (continuous), and all three scored dietary patterns. The reason for including all four score patterns is the fact that dietary patterns are conditional on one another. All the calculations were performed using STATA [14].

3. RESULTS

The distribution of cases and controls by sociodemographics and tobacco variables is shown in **Table 1**. As expected from the matched design, age and residence were similar among cases and controls. Also, education and income were similar for both groups of participants. On the contrary, current smokers showed an odds ratio of 1.7 (95% CI 1.1-2.7) when compared with never smokers. Also, an early age at first intercourse and a high number of sexual partners were directly associated with risk of cervical cancer (OR for high number of partners 2.7, 95% CI 1.6-4.4).

The factor loadings matrix for controls is shown in **Table 2**. Factor 1 presented high loadings for salted meat, beer, and hard liquor and was labeled as the *drinker* pattern. The pattern showed a high negative loading for wine consumption and the pattern explained 31.8 % of the variance. Factor 2 displayed high loadings for red meat, and barbecued meat and high negative loading for whole milk and was labeled as the *red meat* pattern. This pattern explained 16.2% of the variance. Factor 3 showed high loadings for total vegetables and total fruits and was called the *prudent* pattern, explaining 12.0% of the variance. The total variance was 60%, a high value indeed.

Spearman rank correlations between dietary patterns and the selected variables are shown in **Table 3**. The *drinker* pattern was inversely associated with age and directly associated with smoking intensity, years smoked, and number of sexual partners. The *red meat* pattern was inversely associated with age, and directly associated with parity, and early age at first intercourse. Finally, the *prudent* pattern was highly correlated with education.

Patient characteristics among factor quartiles for controls are shown in **Table 4**. The *drinker* pattern displayed a positive gradient for smoking intensity and number of sexual partners and an inverse gradient for red meat in-

take. The *red meat* pattern was negatively associated with years of education and a clear increased gradient for means of meat intake. Finally, the *prudent* pattern displayed a positive gradient for education, raw vegetables consumption and an inverse association with red meat intake.

Table 1. Distribution of cases and controls for sociodemographics, tobacco use, and sexual events.

Variable	Category	Cases		Controls		Global p-value
		Nº	%	Nº	%	
Age (years)	20 - 29	10	3.7	20	3.7	
	30 - 39	55	20.5	110	20.5	
	40 - 49	74	27.6	148	27.6	
	50 - 59	56	20.9	112	20.9	
	60 - 69	51	19.0	102	19.0	
	70 - 79	16	6.0	32	6.0	
	80 - 89	6	2.2	12	2.2	1.00
Residence	Montevideo	138	51.5	276	51.5	
	Other counties	130	48.5	260	48.5	1.00
Percentage of rural patients	Urban	246	91.8	491	91.6	
	Rural	22	8.2	45	8.4	0.93
Education (yrs)	0 - 3	60	22.4	125	23.3	
	4 - 6	138	31.5	264	49.3	
	7 +	70	26.1	147	27.4	0.84
Income (U$D)	< = 67	76	28.4	162	30.2	
	68 +	101	37.7	200	37.3	
	Unknown	91	33.9	174	32.5	0.85
Smoking	Never smokers	151	56.3	324	62.3	
	Former	25	9.3	66	12.3	
	Current 1 - 14	43	16.1	70	13.1	
	Current 15 +	49	18.3	66	12.3	0.04
Age at first intercourse	30 +	4	1.5	41	7.6	
	20 - 29	62	22.1	215	40.1	
	15 - 19	179	66.8	261	48.7	
	< = 14	23	8.6	19	3.5	<0.0001
Nº partners	0 - 1	102	38.1	281	53.5	
	2	88	32.8	152	28.4	
	3	37	13.8	54	10.1	
	4 +	41	15.3	43	8.0	<0.0001
Nº patients		268	100.0	536	100.0	

Table 2. Factor loadings matrix among controls[1].

Food groups	Drinker	Red meat	Prudent
	Factor 1	Factor 2	Factor 3
Red meat	0.02	**0.52**	−0.36
Salted meat	**0.50**	0.03	−0.02
Barbecued meat	−0.00	**0.41**	−0.03
Processed meat	−0.03	0.31	0.11
Whole milk	−0.02	**−0.57**	−0.39
Total vegetables	−0.02	0.04	**0.61**
Total fruits	0.04	−0.08	**0.56**
Beer	**0.51**	0.02	0.02
Wine	**−0.46**	0.08	−0.00
Hard liquor	**0.52**	0.01	0.00
Mate	−0.02	0.34	−0.11
Variance (%)	31.8	16.2	12.0
Cumulative variance	31.8	48.0	60.0

[1]Loadings higher than 0.39 are typed in bold.

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Table 3. Spearman rank correlations between dietary patterns and selected variables.

Variables	Dietary patterns		
	Drinker	*Red meat*	*Prudent*
Age	**−0.13**	**−0.19**	0.03
Education	0.09	−0.05	**0.22**
Smoking intensity	**0.21**	0.09	−0.00
Smoking duration	**0.20**	0.08	0.00
Nº of livebirths	0.02	**0.18**	−0.07
Age of intercourse	0.04	**0.14**	−0.01
Nº of partners	**0.11**	−0.04	0.04

Table 4. Participant characteristics for controls by factor quartile.

Variable	Category	*Drinker*	*Red meat*	*Prudent*
Age (years)	1	52.4	54.0	49.4
	2	51.8	49.9	50.5
	3	50.3	50.6	52.1
	4	47.4	47.1	49.8
Education	1	6.3	7.4	6.3
(years)	2	7.0	7.1	6.2
	3	6.7	6.6	7.3
	4	7.7	6.5	7.9
Smoking	1	3.9	4.8	5.6
(cigarettes/day)	2	5.1	5.5	4.8
	3	6.1	4.3	5.8
	4	6.4	6.9	5.4
Meat	1	7.8	2.5	7.7
(servings/week)	2	5.3	4.2	6.1
	3	5.1	6.4	5.1
	4	3.8	8.9	3.0
Vegetables	1	3.9	2.8	1.3
(servings/week)	2	3.4	3.2	2.5
	3	2.9	3.4	3.6
	4	2.0	2.8	4.9
Age of first intercourse	1	19.5	19.5	20.3
	2	20.0	19.1	19.5
	3	18.9	20.4	18.8
	4	19.2	19.7	19.1
Nº partners	1	1.7	1.9	1.6
	2	1.8	2.3	2.1
	3	1.8	2.6	1.8
	4	2.1	2.9	1.8

[1] Numbers in each cell corresponds to mean values of the variable.

Odds ratios of cervical cancer for dietary patterns are shown in **Table 5**. Cancer of the cervix was positively associated with *red meat* and *drinker* patterns (OR for highest category versus the lowest one for *red meat* pat- tern 1.79, 95% CI 1.12-2.86, p-value for linear trend = 0.02). On the other hand, cervical cancer was inversely associated with the *prudent* pattern (OR 0.60, 95% CI 0.38-0.93).

Table 5. Odds ratios of carcinoma of the cervix for dietary patterns[1].

Dietary pattern	Category	Cases/Controls	OR	95 % CI
Drinker	Low	60/134	1.0	reference
	2	54/134	1.07	0.66 - 1.71
	3	68/134	1.23	0.78 - 1.94
	High	86/134	1.49	0.95 - 2.31
	p-value for trend		0.053	
	Continuous	1.08	0.99 - 1.18	
Red meat	Low	47/134	1.0	reference
	2	65/134	1.31	0.81 - 2.12
	3	61/134	1.30	0.81 - 2.10
	High	95/134	1.79	1.12 - 2.86
	p-value for trend		0.02	
	Continuous	1.13	1.00 - 1.28	
Prudent	Low	87/134	1.0	reference
	2	71/134	0.87	0.57 - 1.33
	3	57/134	0.67	0.43 - 1.04
	High	53/134	0.60	0.38 - 0.93
	p-value for trend		0.01	
	Continuous	0.83	0.73 - 0.95	

[1]Adjusted for age, residence, education, income, age at first intercourse, number of partners, smoking, total energy intake and all scores for dietary patterns.

4. DISCUSSION

To our knowledge, the present study is the first one on factor analysis and risk of cervical cancer. The principal components approach has some limitations related to the FFQ and the management of the data. The inclusion of foods and beverages should be validated previously to the factor analysis being run. In fact, principal components analysis should be conducted in order to obtain the simple structure following Thurstone's criteria [15,16]. In our model, this simple structure was obtained through the rotated principal components analysis.

In our study, an early age at first intercourse, a high number of sexual partners, and a high number of live-births were directly associated with cervical cancer risk, replicating previous reports [3,17-19]. It has been suggested that the male factor could be related to the etiology of cervical cancer through venereal diseases, which could foster the infection of their spouses with HPV [17-21]. The *drinker* pattern displayed a clear gradient associated with the number of partners, and so did the *red meat* pattern.

In the present study, cigarette smoking did not signify an important risk in cancer of the cervix. It should be noted that in general, the intensity of smoking and the duration of this habit are not particularly high among women of low socioeconomic status in Uruguay [22]. Furthermore, when cigarette smoking was controlled by the above sexual and reproductive variables, the risk was close to null. Nevertheless, smoking intensity displayed a positive gradient for the *drinker* pattern. It is worth noting that Gunnell *et al.* [23] also found a synergy between HPV infection and smoking duration.

The role of red meat was positively associated with cervical cancer in our study. This could be explained by the presence of heterocyclic amines in red meat, which are powerful carcinogens in animals [24]. Moreover, red meat is an important source of fat and cholesterol and it has been suggested that whereas heterocyclic amines act as initiators, fat plays a role of promoter [25]. Further studies on the role of red meat in cervical cancer are warranted.

Finally the effect of total vegetables and total fruits was particularly protective in the etiology of cervical cancer [26]. This applies mainly to the strata of women with a high number of sexual partners. In fact, vegetables and fruits were the main components of the *prudent* pattern.

Like other case-control studies, this study has its limitations and strengths. The major limitations are selections bias, recall bias, and the possibility of error due to multiple comparisons (that is, chance findings). Perhaps, the lack of information about HPV status is a major limitation. Therefore, in the place of HPV we attempted to use the age at first intercourse and number of partners as proxy indicators of this infection. Another limitation is the rather small amount of foods used as a routine in the

FFQ administered by the Cancer Institute. Among the strengths, in the first place, is the power of the study, measured by the sampling adequacy, which allowed the estimation of small ORs as significant. Secondly, all the cases were validated by expert pathologists, and finally, the high response rate among cases and controls suggests that participants were drawn from the same population base.

In summary, we conducted a factor analysis on the relationship between foods and beverages and risk of cervical cancer. Whereas the *red meat* pattern was directly associated with this malignancy, the *prudent* pattern was inversely associated with cancer of the cervix. In short, the main novelty of this study is the use of factor analysis in cervical cancer to evaluate the role of diet in this malignancy.

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