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Cancer in First Degree Relatives of Latin American Women with Cervical Cancer. A Pilot Study

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Abstract. *Background: Cervical cancer is the most frequent cancer of women in Latin America, being strongly associated with infection by certain human papillomavirus (HPV) types. Familial cancer clustering can be due to interactions between infectious agents and host genes. Materials and Methods: A cancer-related family history of first degree relatives was elicited in 335 women with invasive cervical cancer (probands) and in 335 women without cancer (controls) in Honduras, Peru and Uruguay, and the frequency of reported familial cancers among the relatives was compared between proband and control relatives. Results: The mean age at the time of interview was 49.8 years for the probands and 50.1 years for the controls (NS). 3852 proband relatives had 114 primary cancers of the following major localisations: 22 uterus, 16 lung, 12 stomach and 64 others. 3333 control relatives had 101 primary cancers of the following major localizations: 18 uterus, 13 stomach, 12 breast, 11 intestinal, 10 lung and 37 others. The frequency of all cancer diagnosis among proband relatives was similar to the frequency among control relatives (odds ratio=1.01; 95% confidence interval: 0.69-1.47). Nine haemolymphatic malignancies were reported among proband relatives versus 2 in control relatives (odds ratio=3.46; 95% confidence interval: 0.74-16.29). Conclusion: All cancer combined did not appear to be more frequent in first degree relatives of women with cervical cancer diagnosis, but haemolymphatic malignancies, a minor part of the cancer burden, may be overrepresented in relatives of women with cervical cancer, pointing to a pathogenic role of familial e.g. hereditary, immunosuppression.*

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Cancer of the cervix is the second most common cancer in women worldwide (1). The highest rates are reported from Latin American countries (2). The association of cervical carcinoma with human papillomavirus (HPV) is very strong (3,4). Vaccination studies have been initiated by IARC (International Agency for Research on Cancer).

Every human trait clusters in families. This is also true for cancer. Family cancer clustering can be caused by: 1. chance, 2. shared environmental influences, 3. common habits, 4. shared genes, 5. interactions between 1 to 4. Eliciting the family medical history represents a "genomic tool" that can capture the interactions of genetic susceptibility, shared environment and common behaviors in relation to disease risk (http://www.cdc.gov/genomics/info/conference/famhist.htm).

Strong evidence for a genetic link to cervical cancer comes from a large population- based study in Sweden (5). For biological mothers to cases, the relative risk (RR) for cervical tumors was 1.83 (95% confidence interval: 1.77-1.88), for biological full sisters to cases the RR was 1.93 (1.85 – 2.01). For half-sisters to cases, the RR was 1.45 (1.31 – 1.60). Women with HLA-DQw3 are at high risk of squamous cell cervix cancer. Defense by the immune system against tumors induced by viruses is known to be important in experimental animals (6). Specific HLA class II haplotypes may influence the immune response to specific HPV-encoded epitopes and affect the risk of cervical neoplasia (7). The Swedish data also suggest a role of familial immunosuppression (8).

Eliciting the family history can be used to identify persons at high cancer risk and to target appropriate preventive and therapeutic measures (9). Most frequently there is an

Figure 1a.

UICC FAMILY HISTORY QUESTIONNAIRE
Cervical Cancer Study

Family code: 11=father, 12=mother, 21= brother, 22=sister, 31=son, 32=daughter — Survival

First name, middle — Malignancies — 1=alive, 2=dead, 3=unknown

□□ ________ ________ (ICD-10) □□□.□ Age (YR) □□ □

Birthdate M □□ D □□ Y □□ ________ □□□.□ □□

□□ ________ ________ (ICD-10) □□□.□ Age (YR) □□ □

M □□ D □□ Y □□ ________ □□□.□ □□

□□ ________ ________ (ICD-10) □□□.□ Age (YR) □□ □

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M □□ D □□ Y □□ ________ □□□.□ □□

□□ ________ ________ (ICD-10) □□□.□ Age (YR) □□ □

M □□ D □□ Y □□ ________ □□□.□ □□

Patient's name ________ ________ ________ (________)

Family name — First name — Middle name — Married name

Birthdate Malignancy________ □□□.□ Date of Diagnosis M □□ D □□ Y □□

M □□ D □□ Y □□ Prior Malignancies________ □□□.□ ________ □□□.□

Survival □ (1=alive, 2=death,3 = unknown)

Total number of sisters and brothers □□ Total number of children □□ Age at first intercourse (YR) □□

Comments:

Figure 1b.

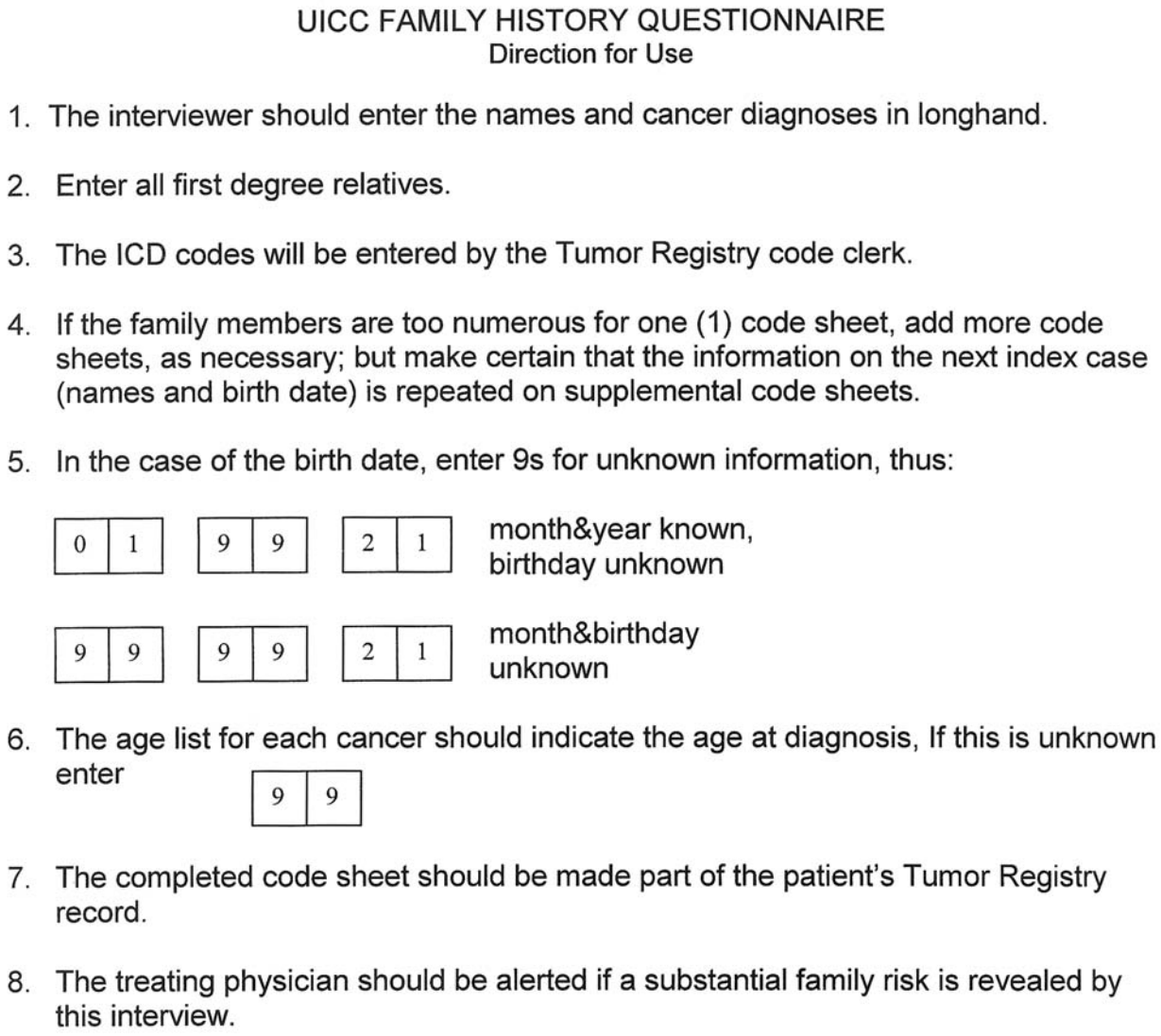

Figure 1.

over-representation of malignancies of the same localization in cancer patients and their first degree relatives. The family history method is a low technology approach which can be used in every part of the world.

It is surprising that few studies have addressed the familial aggregation of cervix cancer (10-12). In an ongoing study in Costa Rica, women with cervical neoplasia have twice as many first degree relatives with gynecological malignancies than women with squamous intraepithelial lesions or women with a normal cervix (13).

The following question was addressed in this study: What malignancies occur in first degree relatives of women with cervical cancer in Latin America ? This first collection of family data will serve future family studies.

Materials and Methods

A cancer-related family history of first degree relatives was elicited in 335 women with invasive cervical cancer (probands) and in 335 women without cancer (controls) in Honduras, Peru and Uruguay, in the years 2000 to 2002. The interviews were performed by social workers or nurses. The interview lasted from 30 minutes to one hour. The controls were non-cancer patients originating from the same region and socio-economic strata as the probands. A one page questionnaire was used for our project (Figure 1a and b) that has been validated for comparative geographical family studies (14).

To compare continuous variables, like age at diagnosis or at first sexual intercourse, one-way analysis of variance was performed or the Kruskal-Wallis test was used, where appropriate. We calculated the Chi-square test statistics (15) and odds ratios with 95 percent

Table I. *Malignancies in the first degree relatives of index cases (CA) and of index controls (CO).*

Primary site	All relatives		Fathers		Mothers		Brothers		Sisters		Children	
	CA	CO	CA	CO	CA	CO	CA	CO	CA	CO	CA	CO
Uterus	22	18			13	11			8	6	1	1
Lung	16	10	10	6	1	1	3	2	2	1	0	0
Stomach	12	13	6	6	1	5	2	1	3	1	0	0
Haemolymphatic	9	2	0	1	3	0	2	1	4	0	0	0
Liver	9	6	2	2	3	1	2	2	1	1	1	0
Breast	7	12	0	0	2	5	0	0	4	6	1	1
Intestine	5	11	3	3	2	5	0	1	0	2	0	0
Skin	5	1	2	1	1	0	0	0	2	0	0	0
Prostate	5	5	4	3			1	2			0	0
Oropharynx	4	4	1	2	1	0	0	2	2	0	0	0
Bone	4	0	2	0	1	0	1	0	0	0	0	0
Unknown	4	3	1	1	1	1	0	1	2	0	0	0
Oesophagus	3	1	2	1	0	0	1	0	0	0	0	0
Brain	3	7	1	2	0	3	2	0	0	1	0	1
Bladder	2	3	2	1	0	1	0	1	0	0	0	0
Pancreas	1	5	1	4	0	1	0	0	0	0	0	0
Kidney	1	0	0	0	1	0	0	0	0	0	0	0
Thyroid	1	0	0	0	0	0	0	0	1	0	0	0
Eye	1	0	0	0	0	0	1	0	0	0	0	0
Total	114	101	37	33	30	34	15	13	29	18	3	3

confidence intervals (15) to compare the proportion of cancer diagnosis (all cancer combined or for specific cancer sites) among proband first degree relatives with the proportion among control first degree relatives. The analyses were performed with the statistical package Epi Info (16).

Results

Index cases and controls. Information on first primary neoplasms diagnosed in first degree relatives (parents, siblings and offspring) were collected in Honduras, Peru and Uruguay by interviewing 335 index cases (women with invasive cancer of the uterine cervix) and 335 index controls (women without cancer of the same population from which index cases were drawn). The mean age at diagnosis of cervical cancer of the index cases was 49.8 years. The mean age at the time of interview was 49.8 years among index cases and 50.1 years among index controls (no significant difference). The mean age at first sexual intercourse was 17.9 years among the index cases and 18.9 years among index controls ($p<0.01$).

First degree relatives. Index cases reported 114 first primary cancers among their 3852 first degree relatives (Table I). The 114 cases belonged to 84 families. Index controls reported 101 first primary cancers among their 3333 first degree relatives (Table I). The 101 cases belonged to 53 families. Among case relatives, the most frequent malignancies originated from the following primary sites: uterus (22), lung (16), stomach (12), haemolymphatic (9) and liver (9). Among control relatives, the most frequent malignancies originated from the following primary sites: uterus (18), stomach (13), breast (12), intestine (11) and lung (10).

The proportion of all cancer diagnosis among the relatives of the cervical cancer patients was not increased compared to the proportion in the relatives of the controls (odds ratio [OR]=1.01; 95% confidence interval [CI]= 0.69-1.47), and neither was the uterine cancer proportion (OR=1.05; 95% CI=0.53 – 2.08).

The highest excess cancer risks were those of developing liver cancer among index cases' mothers (OR=3.05; 95% CI=0.24-160.72), of developing skin cancer among parents (OR= 2.99; 95% CI=0.24-157.00), of developing stomach cancer among siblings (OR=2.24; 95% CI=0.37-23.51) and of developing lung cancer among fathers (OR=1.65; 95% CI=0.54-5.59).

An interesting finding is the observation that only 2 malignancies of the heamolymphatic system were reported among control relatives while 9 malignancies were reported among case relatives (OR=3.46; 95% CI=0.74-16.29).
None of the differences between the families of cervical cancer patients and the control families of non-cancer patients reached statistical significance at $p<0.05$.

Discussion

This pilot study showed that the simple one-page UICC family history questionnaire (Figure 1) is applicable for eliciting a cancer-related family history in first degree relatives of cancer and non-cancer patients in different Latin American countries. The questionnaire may be used for future comparative epidemiological familial cancer studies.

We have to acknowledge a main limitation of this questionnaire in that the attribution of sites of cancers diagnosed in relatives relies on the information obtained in the interview. Corroboration of the specific cancer by more objective means would certainly improve the reliability of this information. Undoubtedly, the conduct of the interview needs to be standardized regarding how information on the cancer site is obtained. We expect the information on the diagnosis of cancer of unknown localization to be more robust than that on cancer of a specific site.

Despite the lack of statistical significance, there was a trend toward elevated odds ratios of malignancies of the haemolymphatic system, liver , skin, stomach and lung in first degree relatives of women with cervical cancers. The risk of all these malignancies is increased by infections and/or lifestyle: viruses in malignancies of the haemolymphatic system (EBV, HIV), liver (hepatitis viruses), skin (papilloma viruses), bacteria in stomach cancer (*Helicobacter pylori*) and smoking in lung cancer. Familial (*e.g.* hereditary) disturbances of the immune system could facilitate infections and carcinogenesis (7,8).

The clustering of cancer sites found in this study was similar in a large population- based familial cancer risk study in offspring from discordant parental cancers, where cervical cancer is associated with cancers of the liver, skin, lung and GI-tract (rectum) (17). Larger studies should address this observation.

There was no increase in uterine cancer in first degree relatives of women with cervical cancer as compared to first degree relatives of women without malignancies in these Latin American countries with high cervical cancer incidence and mortality. A positive association has been found in Sweden, a low incidence and mortality country. In such a country, possible familial (hereditary) clustering is less diluted by pathogenic environmental factors such as infections and/or lifestyle and is, therefore, easier to detect.

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