Considerations for Conducting Epidemiologic Case-control Studies of Cancer in Developing Countries[1]

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The challenges involved in conducting epidemiologic studies of cancer in developing countries can be and often are unique. This article reports on our experience in performing a case-control study of invasive cervical cancer in four Latin American countries (Colombia, Costa Rica, Mexico, and Panama), the summary medical results of which have been published in a previous issue of this journal (1).

The study involved a number of principal activities—mainly selecting, conducting interviews with, and obtaining appropriate biologic specimens from 759 cervical cancer patients, 1,467 matched female controls, and 689 male sex partners of monogamous female subjects. This presentation provides an overview of the planning and methods used to select the subjects, conduct the survey work, and obtain complete and effectively unbiased data. It also points out some of the important advantages and disadvantages of working in developing areas similar to those serving as locales for this study.

Making epidemiologic studies succeed is always a challenge, especially in developing countries where unique problems may be encountered. Our own experience in performing a recently completed case-control study of invasive cervical cancer in four high-risk Latin American countries was no exception.

This study entailed a variety of different activities—including collection of detailed and sensitive information from monogamous female subjects and matched controls (*2, 3*), procurement of additional information from the women's sexual partners (to evaluate the relationship of cervical cancer risk to male partner characteristics—*4*), and collection of biologic samples (blood specimens, cervical smears, and penile swabs) to assess the role of various specific parameters, including infection by human genital papillomaviruses (HPV) (*5*).

[1]A working group that met in Panama in July 1983, under auspices of the Pan American Health Organization, provided initial impetus for this study. The actual study was supported in part by Contract N01-CP-41026 and Grant R01-CA-42042 from the United States National Cancer Institute, National Institutes of Health, and by a grant from the National Cancer Institute of Canada. This article will also be published in Spanish in the *Boletín de la Oficina Sanitaria Panamericana*, vol. 110.

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In the course of this work, we encountered a number of situations specific to developing countries or to the particular circumstances prevailing in the study countries involved that were different from the socioeconomic, educational, and cultural conditions commonly found in developed countries. This article presents a critical overview of these situations and the methods employed in response to them, because some of this information could prove worthwhile for those seeking to conduct similar studies, both in this hemisphere and in other countries throughout the developing world.

MATERIALS AND METHODS

Selection of Study Sites

In selecting study areas for this multicenter investigation, essential elements were the existence of interested collaborators with adequate research facilities and a sufficiently large population of patients with invasive cervical cancer. In addition, all areas to be covered in a given country had to be located within a reasonable distance of the coordinating center selected for the study.

The highly organized public health care systems and limited surface areas and populations of Costa Rica and Panama permitted inclusion of each country's entire population in the study. But in Colombia and Mexico, where the countries and their populations are relatively large, the study was restricted to the capital cities. The number of sites selected and the duration of case accrual (18 months) were dictated by the incidence of invasive cervical cancer in the study areas and the number of subjects needed to test specific hypotheses of interest, given the expected prevalence of exposures in the populations involved.

Cases

Since the study focused on invasive cervical cancer, which is readily diagnosed and requires specialized treatment, we could obtain accurate case data from tertiary care hospitals. These hospitals included: (1) the Panamanian National Oncology Institute, the referral center for at least 90% of all cervical cancer cases diagnosed in Panama (*6*); (2) the three major Social Security referral centers in San José, Costa Rica, to which 80% of all cervical cancer patients in the country are referred (*7*); (3) the Ministry of Health cancer center in Bogotá that treats most lower and lower middle class cancer patients in that city; and (4) the Social Security Oncology Hospital in Mexico City, which provides care for most salaried employees in that area.

To identify cases, we made arrangements with attending physicians at oncologic and gynecologic clinics and wards to notify study personnel of any patient newly diagnosed with invasive cervical cancer. Study personnel also performed a daily review of all hospital admissions. This rapid case detection system was essential because biologic samples were sought before initiation of treatment. To assess the completeness of this case detection, we screened pathology departments for relevant biopsies and reviewed monthly records from tumor registries.

Although virtually all cases were reliably identified by this monitoring system, the centers in Bogotá and Mexico City received many patients referred from distant areas. In addition, both of these metropolitan areas are subject to intensive immigration from more rural areas. In order to compensate for referral and geographic residency biases in these two areas, we restricted study patients to women who had resided in their particular capital city for at least six months. In Mexico City we further restricted cases to

those residing within an area known as "Delegación 5" near the Oncology Hospital, since the more than 1,200 Mexico City residents diagnosed with invasive cervical cancer each year far exceeded our enrollment capabilities. However, even with these study subject restrictions we found it difficult to define the population from which cases derived, a circumstance that made it a challenge to identify appropriately matched controls.

Controls

This study recruited both hospital and community controls. Although it would have been desirable to have community controls in all areas, there was no easy way of identifying random samples of the Bogotá and Mexico City populations from which cases derived. Thus, as a compromise solution we selected two hospital controls for each eligible case in Bogotá and Mexico City and one hospital and one community control for each eligible case in Panama and Costa Rica. Comparison of hospital and community control groups in these latter areas enabled us to evaluate whether any biases might have resulted from the use of hospital controls.

Since we selected our cases from cancer referral centers, the matter of defining hospitals from which to select controls representative of the case populations presented a major challenge. This required that we define health care delivery patterns in each area. In Bogotá and Mexico City we attempted to understand the nature of the case population by mapping places of residence and determining where each subject would seek primary medical care for conditions other than cancer. The result of this analysis was that in Bogotá we selected the controls in a random rotating fashion from eight geographically diverse hospitals, while in Mexico City we selected controls from two neighboring Social Security hospitals.

In Costa Rica, we initially intended to select the hospital controls from capital city hospitals. However, after reviewing the cases' areas of residence we decided it was necessary to select the hospital controls from the regional general hospitals from which cases had been referred (or to which they would have been admitted for nonspecialized treatment of conditions other than cancer). This necessitated frequent trips to these regional hospitals, many of which were located some distance from the capital city. The same procedure was followed in Panama.

To derive a control group representative of the population from which the study cases originated, one that would permit us to evaluate a number of hypotheses of interest, we defined certain diagnostic groups as ineligible for inclusion as controls (see Table 1 for exclusion conditions). In particular, since we were interested in evaluating the relationship of smoking and oral contraceptive use to cervical cancer risk, we eliminated patients admitted with related diseases—including selected diseases of the

Table 1. Unacceptable control diagnoses (ICD-9[a] codes), Latin American Cervical Cancer Study.

140–239	Neoplasms
240–279	Endocrine, nutritional, and metabolic diseases and immunity disorders
290–319	Mental disorders
401–414	Hypertensive disease and ischemic heart disease
490–496	Chronic obstructive pulmonary disease
610–611	Disorders of the breast
614–616	Inflammatory disease of female pelvic organs
617–629	Other disorders of the female genital tract
630–676	Complications of pregnancy, childbirth, and the puerperium

[a]World Health Organization, *International Classification of Diseases (Ninth Revision)*, Geneva, 1978.

circulatory system; chronic obstructive pulmonary disease; and diseases of the breast, ovary, fallopian tube, parametrium, uterus, and other female genital organs. As recommended by Lubin et al. (*8*), we eliminated only women admitted specifically for treatment of these conditions, and not those merely with a history of them. Likewise, because of concerns of a similar etiology regarding cervical cancer, we did not select controls from among women admitted with complications of pregnancy, childbirth, or the puerperium. In addition, although we would in any case have eliminated specific neoplasms because of their relationship with certain exposures of interest (e.g., smoking), we decided to eliminate all cancers because of the possibility that serologic measures of micronutrients would be affected. Finally, we excluded women admitted for mental disorders because of concerns regarding accuracy of the interview information. Table 2 shows the distribution of admission diagnoses of the selected hospital controls.

To ensure a completely random selection of hospital controls, we gave extremely specific instructions so that interviewers would not selectively decide which patients might best be approached for study. In all areas we developed specialized schemes for control selection. For example, when referral hospitals were visited in Panama, different wards were visited in a predetermined fashion and all eligible women were listed by age. After all had been listed, a random numbers table was used to select subjects from among those whose ages were appropriate.

Nearly ideal conditions existed in Panama and Costa Rica for selecting community controls. Both countries take a census every several years. The collected census information, which is stored in

Table 2. Diagnoses of the hospital control subjects, showing the diagnostic categories involved and the most common diagnosis (in parentheses) in each category.

Diagnostic category (most common diagnosis)	ICD-9[a] codes	Subjects	
		No.	%
Digestive system (abdominal hernia)	520–579	227	21
Injury and poisoning (fracture of lower limb)	800–999	158	14
Nervous system and sense organs (cataract)	320–389	154	14
Circulatory system (varicose veins)[b]	390–459	116	11
Musculoskeletal and connective tissue (disorders of the back)	710–739	99	9
Respiratory system (pneumococcal pneumonia)[c]	460–519	81	7
Infective and parasitic (gastroenteritis)	001–139	60	5
Skin and subcutaneous tissue (contact dermatitis)	680–709	53	5
Genitourinary system (kidney calculi)	580–608	52	5
Symptoms, signs, and ill-defined conditions (abdominal or pelvic symptoms)	780–799	40	4
Factors influencing health status and contact with health services (general medical examination)	V-code	20	2
Blood and blood forming organs (anemia, unspecified)	280–289	18	2
Congenital anomalies (musculoskeletal anomalies)	740–759	11	1
Other or unknown		4	0
Total		1,093	100

[a]World Health Organization, *International Classification of Diseases (Ninth Revision)*, Geneva, 1978.
[b]Excluding 401–414.
[c]Excluding 490–496.

computer files, includes each person's name, address, sex, and age. Our aim was to control for referral patterns without selecting subjects so similar to the cases that we would have no power to discriminate effects. Therefore, we identified the district or county of residence of the case and then selected a random "census segment" (an area typically containing 40 to 75 family units). We then used computer listings to select an appropriate age-matched control, as well as a list of additional controls in the event we needed a replacement.

A replacement was substituted if we discovered an error in information about the control subject's age or residence, or if we determined that she had previously had a hysterectomy and was thus not in the population at risk of developing cervical cancer. (We initially administered a short screening questionnaire to both community and hospital controls in order to determine study eligibility.) The highest rate of prior hysterectomy was found in Panama, where it was necessary to replace approximately 40% of all initially selected control subjects with other randomly selected controls.

We also took a Pap smear from all eligible controls to make sure that they were free of cervical cancer. These smears were obtained either in the hospital, at regional clinics, or in the control's home. The smears were given a standard reading by one pathologist in Panama, and the resulting reports were sent back to the study areas. When serious abnormalities were detected, women were referred to their respective gynecologists for treatment. Subjects with in situ or invasive cervical cancer were replaced with other eligible controls, and those with invasive cancer were included as additional cases, for which appropriate controls were selected. Control subjects who refused to participate were not replaced.

Sexual Partners of Cases and Controls

The sexual partners (current or former husbands) of all female participants who reported only one lifetime partner were also included in the study, regardless of whether this partner currently lived with the female subject or not. For cases and hospital controls, we attempted to contact, interview, and examine the husband at the time of the wife's hospital admission. Otherwise, messages were sent with the wives or through the mail to arrange for appointments at the appropriate hospitals or regional clinics. Partners not found in this manner were visited at their homes or workplaces, often at night or on repeated occasions. Many of the men no longer lived with the female study subjects and some had other wives and families, circumstances that required a tactful approach.

Interviews

The interviews, which took an average of 60 minutes with the female subjects and 25 minutes with their male partners, included a number of sensitive questions related to sexual and other behavior. To obtain reliable information, several important steps were taken. First, privacy was strictly enforced and interruptions were not allowed. Second, interviewers stressed the confidentiality of the information to be derived. And third, the interviewer adopted a respectful and warm approach to the respondent.

Laboratory Studies

In addition to the interviews, this study included collection of blood samples and specimens to test for the presence of human papillomaviruses (cervical swabs from female subjects and coronal sulcus and urethral swabs from male sub-

jects). This procurement of proper biologic material was a challenging matter. To facilitate collection, we developed a set of labels for each specimen required, thus reminding the field personnel to take the proper number of samples. The field personnel were made responsible for collection, processing, storage, and shipment of the samples—all of which commonly entailed major logistical difficulties, especially during work in the more rural areas.

To help overcome these problems, the interviewers carried "wet" (H_2O) ice chests with them to ensure that the materials would remain cold after collection. Also, since the protocol for the study required that blood be centrifuged within 24 hours of collection, the teams often made arrangements to use laboratories at local health facilities. After processing, blood specimens were to be frozen immediately; and since the interviews often took place a considerable distance away from the national study center, it was desirable for field personnel to have access to either liquid nitrogen or dry ice in order for the collected specimens to remain frozen after the initial freeze. The samples were then shipped to the coordinating center and to the U.S. repository, following complex shipment procedures requiring a variety of special permits (export/import) and appropriate packing and transportation measures carefully designed to prevent premature thawing of the samples.

Overall Study Organization

In each of the four study areas we had a co-principal investigator, a field supervisor, and three or more interviewers, two of the latter being medically qualified to conduct physical examinations and collect samples.

The co-principal investigators were all oncologists whose status gave them ready access to the desired patients. Their clinical expertise was essential for making decisions regarding subject eligibility, and they were actively involved in referring newly diagnosed cases to our study. In addition, they were responsible for all administrative aspects of the study, including personnel hiring and the control of vehicles, travel vouchers, supplies, etc.

Despite this integral involvement of the co-principal investigators, it was the field supervisors who provided day-to-day direction and oversaw all aspects of the study. Their work included case and control identification, medical record abstraction, interviewing, biologic sample collection and processing, and overall maintenance of quality control.

One of the four national study centers, the Gorgas Memorial Laboratory in Panama, also served as the study coordinating center. From there a principal investigator and study supervisor maintained rigorous control over activities in the four study areas.

A large part of the success of this study is attributed to the fact that the coordinating center personnel were aware of important cultural restraints and were bilingual, facilitating communication between local investigators and those in the United States. A further ingredient essential to successful completion of the study was constant communication between personnel at the coordinating center and local collaborators, either by telephone or through visits. Weekly telephone calls were made to the local areas, as well as frequent personal visits (usually one visit every three months over the eighteen-month course of data collection). Problems or questions arising during the study that could not be solved locally were cleared over the telephone with the study supervisor at the coordinating center. If specific situations could not be resolved, personnel from

the coordinating center would travel to the specific site involved.

In addition to establishing the coordinating center in Latin America, we also employed the assistance of Westat, a survey research firm in the U.S. that helped develop data collection forms and manuals, train abstractors and interviewers, monitor field activities, and computerize data. A bilingual study manager oversaw all of these activities and worked closely with personnel at the coordinating center.

Study Planning and Initiation

The first step toward implementing this study was a two-day planning meeting attended by the co-investigators from each of the countries, the principal investigator and study supervisor from the coordinating center, the study manager from Westat, and the study's U.S. project officer.[9] Since the study involved four different cultural settings, an extensive biochemical component, and interviews with cancer patients, controls, and selected male partners, review of the proposed procedures was quite involved.

The discussions focused on a detailed written protocol that was extensively revised as a result of the meeting. The role played by this preliminary document was essential, since the concept of such an epidemiologic study was relatively unfamiliar to the collaborators. Conversely, the input of the collaborators from the four study sites was also vital, as many tactics successfully used in U.S. studies were deemed impractical for a Latin American setting.

For instance, although it had been suggested that subjects should receive financial remuneration for participation, it was decided that such compensation was unnecessary and would set a poor precedent for future studies. On the other hand, we were informed by our Latin American collaborators that the subjects' sensitivity to a variety of interview questions on sexual behavior would not be as great as we had envisioned, and we were actually encouraged to expand our proposed questions to address additional specific hypotheses.

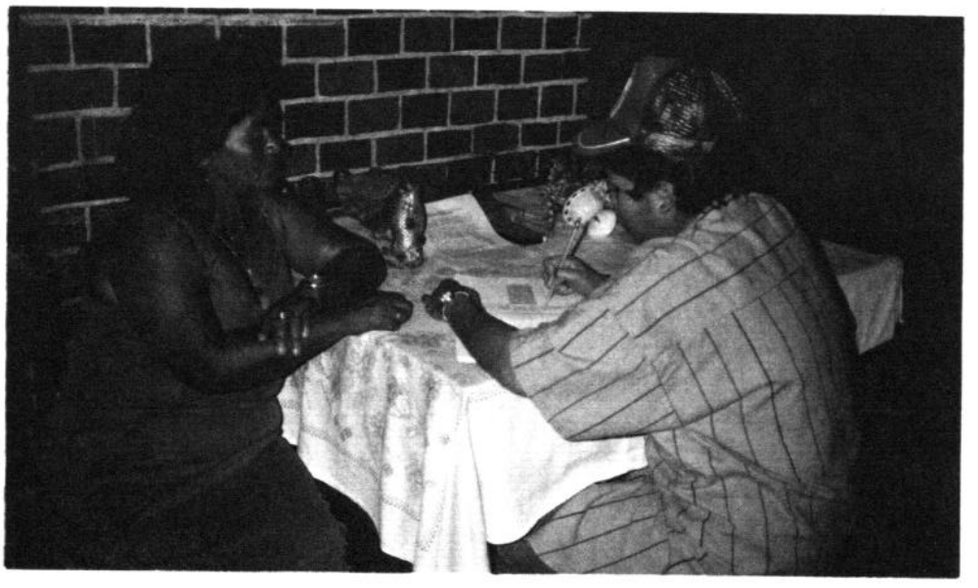
The questions, originally composed in English, were translated into Spanish and then back-translated to ensure that their original substantive content was maintained. Although we originally had some concerns that the terminology used would not be clearly comprehended in all four study areas, this did not emerge as a problem, probably because the wording of the questions was kept extremely simple to prevent misunderstanding.

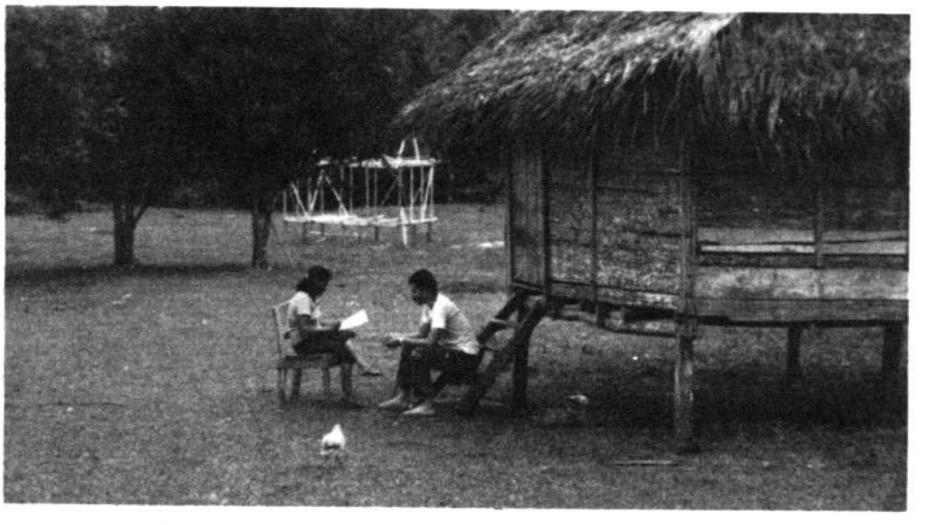
Pilot Study

Before starting the full-scale study, we launched a pilot program to test the study procedures. This pilot study, conducted over a three-month period, enrolled 46 cases and 51 matched controls (*9*). Procedures planned for the full-scale study were employed at all four study sites.

This undertaking proved an extremely useful tool for assessing the practicality of proposed methods. In some instances, modifications were made based on information gained during the pilot study. For instance, control selection procedures were changed at several sites because it appeared that the control population would not be fully representative of that from which cases derived. The pilot study was also pivotal in determining whether changes should be made in the data collection forms. (Some questions were eliminated due to low exposure rates, while others were modified to

[9]Responsible for administration of the contract for the study and for overall coordination of all study efforts.





Interviews being conducted with community controls.

make the wording more consistent with the hypotheses of interest.)

Training and Quality Control

Standardization received strong emphasis throughout the study. Standardized forms for recording information included a female subject and male subject questionnaire, a physical examination form (for males), a clinical abstract form (for cases and hospital controls), and a biologic specimen collection form. Detailed manuals were prepared for required procedures. These included a field office manual, an interviewer manual, a biologic specimen collection manual, and coding manuals for every document. In addition, special forms were devised to document all activities and decisions, including those related to coding.

All record abstractors and interviewers received uniform training in sessions lasting approximately five days before they began working on the study. Training was conducted by the study supervisor from the coordinating center and the bilingual study manager from Westat. During training sessions, the general approach to interviewing was discussed, specific role-playing occurred, and instructions were given as to how to

maintain quality control of the activities involved. Unbiased interviewing techniques were stressed, including use of neutral probes to elicit hard-to-obtain information. Practice interviews were conducted with patients similar to those intended for study, and the trainees' techniques were observed and critiqued in detail. When new personnel were hired, new training sessions were conducted and experienced personnel were retrained.

In addition, instructions were given on documenting all activities. Such documentation was absolutely essential, considering that many different individuals were involved with the study. Each interview was edited by the field supervisor and checked for inconsistencies. In the rare event that extensive information was missing or inconsistent, repeat interviews were sought.

Completed data collection forms were initially submitted to the coordinating center in Panama, where the responses to open-ended questions, recorded in Spanish, were coded by a team of trained personnel. A 10% sample of abstract forms and questionnaires was then recoded by a separate coder, and any differences were resolved by the study supervisor. After all coding had been completed and resolved, the forms were sent to Westat, where the information was keyed into a computer and eventually formatted into analysis files.

Personnel

Because the conduct of a case-control interview study was new in many of the areas involved, we sought individuals who had interviewing experience of some sort (e.g., clinical experience, education as a social worker, previous survey research work). We also emphasized the need for the interviewers to be personable, well organized, amenable to performing tasks in a standardized fashion, and (most important) adaptable to new and challenging situations.

In hiring there was also a need to be aware of cultural sensitivities. For example, at most sites we found that male study subjects were usually receptive to being interviewed by a female. However, this was found entirely unacceptable in Mexico, a circumstance that required the hiring of additional male interviewers. In addition, there was need at all of the sites for a male physician to perform the physical examinations on the male subjects.

RESULTS

Response Rates

The response rates obtained are shown in Table 3. The 99% response rate among the female cervical cancer subjects and the 96% response rate among the female controls attest to the extremely cooperative nature of these subjects and the persistence of our personnel in encouraging participation. Extensive resources were devoted to increasing participation, and field trips were often made to remote areas to locate as few as one or two subjects. On occasion, transportation and other expenses were paid to participants willing to visit the appropriate study hospital or clinic. Among female controls, the 3% who refused to participate accounted for most of the nonresponse.

The response rates for the male subjects were considerably lower (67% for the case husbands and 62% for the control husbands). The major reasons for nonresponse among males were death (14% of the case husbands and 13% of the control husbands had died) and inability to locate the subject (in 14% of the cases in both groups). Despite extensive attempts to locate the maximum possible number of male subjects, many no longer lived with their wives and were ex-

Table 3. Interview response rates of eligible cervical cancer patients, matched female controls, and male partners of monogamous female subjects.

	Cervical cancer patients and husbands		Female controls and husbands	
	No.	%	No.	%
Female subjects:				
Eligible subjects	766	100.0	1,532	100.0
Interviewed	*759*	*99.1*	*1,467*	*95.8*
Not interviewed:				
Refusals	0	0.0	41	2.7
Deaths	3	0.4	0	0.0
Communication problems	2	0.3	10	0.7
Incompetence	1	0.1	8	0.5
Inability to locate	1	0.1	6	0.4
Male subjects:				
Eligible subjects	304	100.0	778	100.0
Interviewed	*204*	*67.1*	*485*	*62.3*
Not interviewed:				
Refusals	11	3.6	79	10.2
Deaths	44	14.5	102	13.1
Communication problems	0	0.0	2	0.3
Incompetence	3	1.0	5	0.6
Inability to locate	42	13.8	105	13.5

tremely difficult to find. Most of the men we could locate did agree to participate, the refusal rates being low (4% for the case husbands and 10% for the control husbands).

Comparison of Hospital and Community Controls

To determine whether the use of hospital controls might produce different risk estimates than use of community controls, we compared the distribution of cervical cancer risk factors for these two groups in Costa Rica and Panama. As Table 4 shows, we encountered surprisingly few differences. Similar distributions were observed for number of sexual partners, age at first intercourse, history of a venereal disease, number of pregnancies, interval since last Pap smear, detection of human papillomavirus types 16 or 18, number of cigarettes smoked per day, alcohol consumption, household appliances, and socioeconomic status. The only risk factor that differed substantially was use of oral contraceptives, which was more commonly reported by community controls, although the difference between the two groups was not statistically significant (Chi square $p = 0.07$).

Laboratory Studies

Nearly all subjects who agreed to the interview were willing to provide the requested biologic specimens (Table 5). However, the true overall response rate to this phase of the study depended on a positive response at both the interview and collection phases. Thus, the overall response rate for blood samples was 98% among the female subjects with cervical cancer (the 99.1% interview response rate multiplied by the 99.3% collection rate) and 91% among the female controls (95.8% x 95.2%). The overall response rates were only somewhat lower for the cervical swabs (98% among the cases, 87% among female controls).

Table 4. A comparison of interview data on female hospital and community control subjects regarding major cervical cancer risk factors. Unknowns in each category were excluded from the analysis.

	Hospital controls		Community controls		Chi-square
	No.	%	No.	%	p value
Number of sexual partners:					
0	9	2.5	8	2.1	0.286
1	163	44.9	193	51.7	
2–3	140	38.6	126	33.8	
4–5	33	9.1	24	6.4	
≥6	18	5.0	22	5.9	
Age at first sexual intercourse (years):					
Virgin	9	2.5	8	2.2	0.988
>20	115	31.9	123	33.1	
18–19	72	19.9	75	20.2	
16–17	80	22.2	86	23.1	
14–15	64	17.7	60	16.1	
<14	21	5.8	20	5.4	
History of venereal disease:					
No	340	93.7	344	92.0	0.376
Yes	23	6.3	30	8.0	
Number of pregnancies:					
0–1	50	13.8	37	9.9	0.257
2–3	70	19.3	82	21.9	
4–5	77	21.3	92	24.6	
≥6	165	45.6	163	43.6	
Interval since last Pap smear (years):					
<2	113	33.8	109	31.5	0.77
2–3	75	22.5	90	26.0	
4–5	23	6.9	21	6.1	
≥6	46	13.8	42	12.1	
Never	77	23.1	84	24.3	
Reaction with HPV 16/18 DNA probes:					
Negative	204	66.0	209	67.4	0.71
Positive	105	34.0	101	32.6	
Cigarettes smoked per day:					
0	290	79.9	292	78.1	0.47
<10	45	12.4	56	15.0	
≥10	28	7.7	26	7.0	
Ever drunk alcohol:					
No	307	84.6	322	86.6	0.44
Yes	56	15.4	50	13.4	
Number of household appliances:					
≥6	149	41.0	163	43.6	0.37
4–5	108	29.8	119	31.8	
≤3	106	29.2	92	24.6	
Ever used oral contraceptives:					
No	277	76.3	262	70.1	0.07
Yes	86	23.7	112	29.9	

Table 5. The numbers and percentages of the study subjects interviewed who provided the indicated biologic specimens and assented to physical examination.

	Cervical cancer patients and husbands		Female controls and husbands	
	No.	%	No.	%
Female subjects:				
Blood sample	754	99.3	1,396	95.2
Cervical swab	753	99.2	1,324	90.3
Pap smear	0	0.0	1,323	90.2
Male subjects:				
Blood sample	200	98.0	467	96.3
Physical examination	198	97.1	463	95.5
Penile swab	198	97.1	463	95.5

Among the male subjects, response rates for the blood specimens were 66% among the case subject husbands (67.1% interview response rate x 98.0% collection rate) and 60% among the control subject husbands (62.3% x 96.3%). Comparable response rates for penile swabs were 65% and 59%, respectively.

Problem Situations

Transportation was a major logistical problem in most study areas, particularly in Costa Rica and Panama, where interviews were often sought in extremely rural places. Although four-wheel-drive vehicles were provided in these two countries, it was often necessary to travel by such means as boat, foot, or horseback. Obviously, such travel demanded that staff members be fit, adventuresome, and adaptable. In Bogotá, the purchase of an automobile facilitated transport to the control hospitals and subjects' homes, which were widely dispersed; but travel to parts of the city with high crime rates remained a problem. This necessitated caution on the part of the interviewers, who often traveled in pairs.

Largely because work on the study was often regarded as a temporary job for a physician and the work required unusual challenges (e.g., absences from home during field trips), changes in personnel occurred that required training new personnel in the middle of the study. Other noteworthy problems included the earthquake in Mexico City, which occurred during the pilot phase of the study, other natural disasters (e.g., floods), and disbursement of funds, especially since a contract with the U.S. Government was involved.

DISCUSSION

The data collection phases of two multicenter case-control studies in the U.S. have previously been reported (*10, 11*). Although we experienced a number of concerns in common with those studies, we also encountered various situations in the four developing countries that were different from those found in the U.S. studies.

It turned out that a major advantage of conducting our study in the areas chosen was the exceptionally high response rates obtained, 99% from the female subjects with cervical cancer and 96% from the female controls. Very few eligible subjects refused to be interviewed; indeed many felt privileged to be included. Such a situation is quite different than that typically encountered in the U.S., where, despite different tactics to increase participation,

response rates to epidemiologic studies now hover around 60–70%. Possible reasons for the strong Latin American response are that individuals are used to participating in health-related activities that include home visits, and physicians are viewed with a fair amount of respect as authority figures. (In the case of our study, it seems clear that the enthusiasm and strong commitment of our study personnel also contributed to the high response rates.)

Another important asset engendered by our study design and locales was the ease with which we were able to identify and locate appropriately matched control subjects. Frequently updated censuses in Panama and Costa Rica permitted ready identification of controls matched by age and area of residence to the eligible cases. Limited migration kept these census lists valid for some time after the censuses were taken; but even when female subjects had moved, the small, close-knit communities where they had resided often knew of their whereabouts and were willing to volunteer this information. Computerization of the lists facilitated not only selection of an initial control, but also selection of a replacement if such were needed. This situation contrasts with that found in the U.S., where similar lists usually do not exist, necessitating the use of laborious control selection procedures such as random digit dialing (*12, 13*), which may be associated with certain response biases.

Our study presented challenges regarding identification of appropriate hospital controls, because of uncertain referral patterns as well as frequent admissions for chronic diseases, many of which were related to the exposures of interest. In order to eliminate associated biases, we excluded several diagnostic groups from consideration as controls. This complicated the selection process, particularly when selections were made from hospitals in distant rural areas. Multiple visits to small centers were often needed to find eligible controls, and the potential for selection bias was high. Therefore, a rigorous system for selecting controls that would provide little flexibility for the interviewers was required.

Given the complexities of choosing appropriate hospital controls, it is reassuring for future studies that we found so few differences between the hospital and community controls. Although a previous cervical cancer study in Utah (*14*) found the two types of controls to differ, particularly with respect to risk factors related to social class, our exclusion diagnoses and selection of controls from primary referral hospitals may have led to inclusion of a group more representative of the healthy population. A previous bladder cancer study (*15*) found that excluding conditions related to the exposure of interest (obesity-related conditions and use of artificial sweeteners) from the control group led to estimates comparable to those derived using population controls. Thus, our results indicate that use of a restricted hospital control group may be appropriate for assessing many risk factors, although some caution should be exercised with respect to assessing the effects of oral contraceptives (*16*).

Our study also collected biologic specimens for laboratory testing. The increasing ability to quantify exposures to hypothesized infectious, environmental, and genetic risk factors adds considerable power to epidemiologic studies. It is thus important to fully understand issues pertaining to the agents being investigated. For example, infection with HPV may be a risk factor for cervical cancer, but important and basic biologic issues remain unresolved (*17*). It is only after resolving such issues that one can be sure of properly collecting and processing specimens and applying appropriate assay systems.

In the case of the present study, we developed procedure manuals, trained study personnel to perform simple pelvic examinations and collect specimens in a standardized fashion, provided equipment for field transport and storage of specimens, and arranged for international shipment to collaborating laboratories. We also employed detailed documentation, labeling, and tracking procedures directed toward successful processing of varied specimens destined for a variety of required assays.

It is also true that basic predetermined methodologic principles apply in obtaining biologic specimens. In particular, it is important to recognize that the positive response rate of the subjects must be high at both the interview and specimen collection phases in order to eliminate associated biases. For this reason, by being able to obtain blood specimens from 98% of the eligible cases and 91% of the eligible female controls, the present investigation came to possess special virtues. This situation is quite different from those tending to prevail in other studies, where adequate response rates have been hard to achieve (*18*), and where those willing to donate specimens have tended to exhibit unusual behavioral features (*19*).

CONCLUSION

While there may be certain drawbacks to conducting epidemiologic studies in developing countries, there are also major advantages. In our four-country study the major advantages were the cooperativeness of the study subjects in answering long questionnaires and donating laboratory specimens, and the ease of selecting population controls. However, anyone contemplating a similar endeavor should very definitely be prepared for some challenges, especially with respect to access problems and difficulties involved in identifying appropriate hospital controls.

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III Teleconference on AIDS

PAHO is sponsoring the III Pan American Teleconference on AIDS, which will originate from Caracas, Venezuela, 13–15 March 1991, for four hours during each of the three days. Like the two previous teleconferences, this forum will permit health workers, educators, decision makers, and others to have access to the latest information about AIDS and HIV infection without incurring the high costs associated with travel to international meetings.

Each day's presentations will focus on a different facet of the challenges posed by AIDS. Session I will deal with policies implemented in response to AIDS and is directed toward decision makers. Issues to to discussed include the burden of AIDS on the health care system and the problem of discrimination. Session II is aimed toward workers involved in AIDS prevention and control and will concern prevention of sexual and perinatal transmission, lessons learned from attempts to change behavior, and the question of who needs to know the infection status of a patient. Session III will deal with the care of HIV-infected persons, a topic of special importance to health services personnel. Specific presentations in this session will focus on clinical and social management, risks to and obligations of health workers, and protection of the blood supply. Two press conferences are also included in the agenda, one at the end of the first session and the other at the close of the teleconference.