

CERVICAL CANCER IN THE REPUBLIC OF PANAMA

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Cervical cancer is more common in Latin America than elsewhere in the world. Previous work indicated that Panama also had a high incidence of cervical cancer and that the disease clustered in rural Herrera Province; to document this and collect detailed information on risk factors, the authors established a population-based Cervical Cancer Registry in Panama. Cervical cancer cases diagnosed between 1974 and 1979 were identified by visiting every major hospital in the country. The registry abstracted epidemiologic, clinical, and other information from patients' hospital charts. It recorded an age-adjusted invasive cervical cancer incidence of 28.4/100,000 between 1974 and 1979; rural Herrera Province supported the highest rate (79.1/100,000), while urban Panama Province had a low rate (24.6/100,000); in situ disease followed a similar pattern (48.7/100,000 in Herrera Province and 17.6/100,000 in Panama Province). Women born in Herrera Province retained high cervical cancer rates irrespective of residence at diagnosis (64.7/100,000), while women from Panama Province had low rates (12.4/100,000) which were comparable to those seen in US whites. In addition to having high cancer rates, women from Herrera Province developed invasive disease at an unusually young age; women between 35 and 39 years of age had an incidence of 151/100,000.

neoplasms

The incidence of invasive cervical cancer has significantly decreased over the last 20 years in the United States, Canada, and other industrialized countries. During this same period, invasive cervical cancer has become recognized as a leading cause of female death throughout Latin America (1). Cancer reg-

istries in Bolivia, Brazil, Chile, Colombia, Cuba, Jamaica, Panama, Peru, Puerto Rico, and the Antilles have documented the world's highest cervical cancer incidence rates (2-4). Several US registries report ethnic-specific statistics and "Hispanics" have about twice the invasive cervical cancer risk of "other white" women

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in the same age groups. Latin American registry data show that the number of invasive cervical cancers equals about half of all male cancers combined (2, 5). In these high-risk areas, approximately one in every 1000 women between 30 and 55 years of age develops cervical cancer each year. These are young, active women, most of whom are from lower socioeconomic levels and who are important for their families' support and community productivity. Cervical cancer patients also require prolonged hospitalization and costly medical care which many developing countries cannot afford.

The classic cervical cancer risk factors are poverty and a sexual history characterized by early age at first intercourse, multiple pregnancies, and multiple sex partners. These risk factors were identified by studies in industrialized countries where cervical cancer rates have subsequently declined (6, 7). Detailed population-based cervical cancer studies have not been attempted in Latin America where the disease clusters. Latin America comprises the Caribbean, continental Central America, and tropical and temperate South America and thus represents considerable variation in racial composition, socioeconomic conditions, culture, climate, and geography. To a large extent, those Latin American populations with high cervical cancer incidence rates are poor, minimally educated, live in crowded conditions, and support high birth rates beginning at an early age. Specific risk factors such as sexual customs (8), exposure to herpes simplex virus type 2 (9), or papillomavirus (10) have not been quantified in high-risk Latin American populations.

Preliminary investigations (5) indicated that the Republic of Panama had a high cervical cancer incidence rate (38/100,000); cervical cancer clustered in isolated, rural Herrera Province (85/100,000) and had a high incidence in women between 20 and 39 years of age.

Similarly, cancer of the penis clustered with high rates in Herrera Province (4.3/100,000). We have initiated a cervical cancer program in Panama to determine what etiologic factors are interacting to produce this pattern of high disease rates. The present study was conducted to collect detailed population-based data describing cervical cancer in Panama and includes all cervical cancer cases hospitalized in the Republic between 1974 and 1979. Information from the study will be used to implement case-control studies, to compare independent measurements of herpes simplex virus and papillomavirus prevalence, to monitor disease occurrence over time, and to evaluate health services systems and treatment modalities as they relate to different patient populations, cancer stage, and survivorship.

METHODS

The Cervical Cancer Registry identified women admitted to Panamanian hospitals between January 1, 1974 and December 31, 1979 with a diagnosis of *in situ* or invasive cervical cancer. To do this, we visited most government and private hospitals in the country. The exceptions were Darien Province and Comarca de San Blas, which are frontier areas with numerous small isolated settlements whose primary care facilities refer patients to Panama Province; Los Santos Province, which by Ministry of Health policy refers gynecology patients to hospitals in neighboring Herrera Province; Bocas del Toro Province, with only five gynecology beds, which refers patients to Chiriqui or Colon province; and two 100-bed private hospitals in Panama City (representing about 10 per cent of the city's adult hospital beds), which would not allow us access to their charts. At each hospital, we reviewed log books of discharge or death and pulled charts of possible cervical cancer cases for female patients older than 15 years admitted during the study period. We also screened

operating room logs for this time period to identify female patients receiving pelvic surgery. At the National Oncology Institute, the only hospital in Panama with radiotherapy facilities, we checked radiotherapy log books. In the provinces of Colon, Herrera, Los Santos, and Chiriqui, we also reviewed all Pap smear records between 1974 and 1979 and identified women with class 3 Pap smears or greater. Death certificates were not reviewed.

Once identified as a possible cervical cancer case, a woman's entire medical record was checked. Invasive cervical cancer was defined according to the physician's diagnosis irrespective of histopathologic confirmation. In situ cervical cancer was recorded only if histopathologic confirmation appeared in the medical record. Pertinent data from all cervical cancer patients were abstracted by a Cervical Cancer Registry adapted from the standard World Health Organization (WHO) Cancer Registry form (11). The Panama Cervical Cancer Registry contained all WHO core data, most of the optional information recommended by WHO, and additional locally important data. (The authors will provide English or Spanish versions of the registry upon request.)

Hospital charts were abstracted by data processing and epidemiology technicians from the Gorgas Memorial Laboratory. All registry forms and hospital charts were reviewed by the senior epidemiology technician. Discrepancies were resolved and unusual situations or other problems were discussed with appropriate oncologists or pathologists. Charts from patients with multiple admissions to different hospitals were compared so that each patient's registry form contained the most accurate data. Duplicate registration was avoided by cross-checking patients' names, cedula (a required national identification card), and social security numbers. Information was entered into a General Automation SPC 16/65 com-

puter, and data processing utilized the Conversational Computer Statistical System (12). Three years were required to complete case registration.

We obtained specially prepared 1974-1979 population data from the Census Bureau, Contraloria General de Panama. Panama maintains an extremely accurate and current census, partly because of the country's small size, the relative accessibility of most areas, and an unusually cooperative population. A complete national census was taken in 1970 and another in 1980. The Census Bureau estimates the population of each district at yearly intervals using standard methods. The intercensal estimates we used as denominators were prepared by means of the actual 1980 census to adjust previous calculations. During each census, the government makes a particular effort to tabulate accurately the rural population. To compare Panama's cancer incidence rates with those from other countries, we adjusted age to the standard world population (2).

RESULTS

Between 1974 and 1979, the Panama Cervical Cancer Registry recorded an invasive cervical cancer incidence of 28.4/100,000 women (age-adjusted to the standard world population). Incidence rates were not uniformly high throughout Panama; invasive cervical cancer clustered in rural Herrera Province (79.1/100,000) and Los Santos Province (33.7/100,000), while the urban provinces of Panama and Colon had low rates (figure 1). In situ cervical cancer (age-adjusted incidence 16.4/100,000) followed the same pattern, varying from 48.7/100,000 in Herrera Province to 17.6/100,000 in Panama Province.

To analyze how residence related to cervical cancer incidence, we calculated incidence rates according to province of birth. The Census Bureau provided 1980 data concerning immigration patterns,



FIGURE 1. Average annual invasive cervical cancer incidence 1974-1979 by province of residence; rates adjusted to standard world population.

which we used to estimate the number of women in each five-year age group who were born in each province. The Herrera Province birth cohort retained the country's highest invasive cervical cancer incidence (64.7/100,000). Women born in either Panama Province or Colon Province had considerably lower invasive cervical cancer rates irrespective of residence at the time of diagnosis (figure 2). Again, in situ disease showed a similar pattern.

Age-specific invasive cervical cancer presented a complex picture when analyzed by residence (table 1). Herrera Province showed a rapidly increasing incidence curve (151/100,000) for women between 35 and 39 years of age; women in the 55- to 59-year age category had the highest incidence (186/100,000). In the remainder of the country, rates increased uniformly with age, beginning at age 30, and reached 82 cases/100,000 among



FIGURE 2. Average annual invasive cervical cancer incidence 1974-1979 by province of birth; rates adjusted to standard world population.

TABLE 1

Age-specific annual incidence/100,000 of invasive cervical carcinoma by residence, Panama, 1974-1979

Age group (years)	Province				Republic of Panama	n
	Herrera	n	Panama	n		
15-19	0.0	0	0.0	0	0.0	0
20-24	20.8	4	1.6	4	2.9	14
25-29	125.2	21	11.9	24	16.7	64
30-34	135.7	19	33.5	52	33.0	101
35-39	150.6	18	38.9	52	49.7	134
40-44	98.1	10	47.2	54	54.7	121
45-49	147.2	12	58.5	58	67.8	130
50-54	157.8	11	42.1	36	53.8	89
55-59	186.1	11	74.8	53	82.3	111
≥60	183.4	23	70.6	109	77.9	235
Age-adjusted*	79.1		24.6		28.4	
No. for whom age is unknown		16		15		83
Total cases		145		457		1082

* Incidence/100,000 adjusted to standard world population.

those aged 55-59 years. Age-specific in situ cervical cancer rates also varied by residence, but the overall patterns were similar, with uniformly increasing rates up to ages 30-34 and then a decline (table 2).

Invasive and in situ cervical cancer incidence rates remained relatively stable for the whole country between 1974 and 1979 (table 3). However, in Herrera Province, incidence of invasive cervical cancer declined and the ratio of in situ to invasive disease became larger. This could represent a trend or artifact due to small numerators; thus, we analyzed stage-specific invasive cervical cancer rates among patients seen at the National Oncology Institute Hospital (the country's only cancer center and the only hospital with radiotherapy equipment). All cervical cancers are clinically staged at the Oncology Institute by a small group of gynecologic oncologists. The proportion of cancers in each stage has not changed over time (table 4).

The Oncology Institute is the final referral center for most invasive cervical cancer cases irrespective of residence, so-

cial class, or prepaid medical insurance. Its patient population thus represents the general cancer patient population. Panamanian public and Social Security hospitals operate as an integrated triage system so that cases are rapidly transferred to the appropriate level medical facility (table 5). Eighty-nine per cent of invasive cervical cancer patients were evaluated at least once in one of Panama City's three major teaching hospitals. The proportion of patients with invasive disease whose final referral was in their home province (other than Panama Province) ranged from 14-15 per cent in the provinces of Colon and Chiriqui (sites of the country's second and third largest cities) to between 1 and 2 per cent in the other provinces (table 6). Women with in situ cervical cancer were more frequently diagnosed and treated in their home province (table 6); only 63 per cent of these patients were referred to Panama City (table 5).

All in situ diagnoses were confirmed by biopsy as were 1030 of 1082 (95 per cent) invasive cancers; 987 invasive cancers (91 per cent) were squamous cell and 95 were

TABLE 2

Age-specific annual incidence/100,000 of in situ cervical carcinoma by residence, Panama, 1974-1979

Age group (years)	Province				Republic of Panama	n
	Herrera	n	Panama	n		
15-19	0	0	1.4	4	0.7	4
20-24	46.7	9	8.9	23	9.1	43
25-29	107.3	18	37.8	76	31.9	122
30-34	135.7	19	49.0	96	51.3	157
35-39	133.9	16	51.6	69	44.9	121
40-44	166.8	17	55.0	63	49.3	109
45-49	61.4	5	27.2	27	24.5	47
50-54	43.0	3	14.0	12	15.1	25
55-59	0	0	16.9	12	18.5	25
≥60	39.9	5	12.3	19	11.9	36
Age-adjusted*	48.7		17.6		16.4	
No. for whom age is unknown		1		5		8
Total cases		93		406		697

* Incidence/100,000 adjusted to standard world population.

microinvasive; 35 (3 per cent) were invasive adenocarcinomas and three were mixed cell types. To establish a reference against which to compare histologic diagnoses made in Panama, we sent a selection of cervical biopsies to Dr. Henry J. Norris, Department of Gynecologic Pathology, Armed Forces Institute of Pathology, for an independent evaluation. Slides were selected randomly to represent in situ and invasive cervical cancer biopsies read between 1974 and 1978 at the Social Security or Santo Tomas Hospital pathology departments. Slides from 73 cases were reviewed; 34 cases had been

classified carcinoma in situ; of these, 28 (82 per cent) were similarly classified by Dr. Norris and six were classified as miscellaneous benign. Thirty-nine cases were classified in Panama as invasive cervical cancer; of these, 26 (67 per cent) were verified by Dr. Norris and 13 were termed in situ. Dr. Norris also stated that there was a great deal of condylomatous atypia in the slides, alone or associated with varying degrees of dysplasia.

DISCUSSION

The Republic of Panama supported a high invasive cervical cancer incidence

TABLE 3

Ratio of annual incidence rates of in situ/invasive cervical cancer by residence, Panama, 1974-1979

	1974 n = 81/173	1975 n = 104/163	1976 n = 154/172	1977 n = 128/207	1978 n = 129/195	1979 n = 101/172
Republic of Panama	12.8/30.7* (0.42)†	15.7/30.0 (0.52)	22.7/30.1 (0.75)	18.1/35.1 (0.52)	17.7/30.8 (0.57)	18.4/21.8 (0.84)
Panama Province	18.4/29.2 (0.63)	16.7/24.5 (0.68)	30.3/29.4 (1.03)	27.1/36.3 (0.75)	23.5/26.2 (0.90)	6.2/18.0 (0.34)
Herrera Province	21.1/97.1 (0.22)	37.6/95.6 (0.39)	48.0/68.6 (0.70)	26.2/69.4 (0.38)	68.2/68.8 (0.99)	82.2/58.0 (1.42)

* Rates are cases/100,000 adjusted to standard world population.

† Ratio.

TABLE 4
Per cent of cervical cancer cases in each stage according to residence and year of diagnosis, Panama, 1974-1979*

	1974			1975			1976			1977			1978			1979			
	Stage			Stage			Stage			Stage			Stage			Stage			
	1	2	3-4	1	2	3-4	1	2	3-4	1	2	3-4	1	2	3-4	1	2	3-4	
Republic of Panama	28	39	33	34	34	32	34	26	40	34	20	42	38	27	36	37	31	36	33
Province	29	49	22	32	34	34	20	48	32	16	49	35	22	43	35	26	34	40	
Herrera Province	48	30	22	48	20	32	58	26	16	16	47	21	32	60	30	10	53	29	18

* Stages 1-4 are invasive cervical cancers clinically staged (International Union against Cancer (UICC)) at the National Oncology Institute.

(28.4/100,000). Among Latin American cancer registries whose data are published by the World Health Organization-International Agency for Research on Cancer, only those of Cali, Colombia (52.9/100,000), São Paulo, Brazil (37.5/100,000), and Kingston-St. Andrews, Jamaica (29.8/100,000) have reported higher rates (2). It is impossible to compare accurately cancer rates between different registries since many variables differ. For example, most registries collect incidence data at the county or city level and represent areas with modern medical facilities which attract patients from a larger geographic area, so that accurate denominator data are difficult to define and apply, and locality-specific rates cannot be precisely determined. Also, most registries do not ascertain province of birth or link information from different hospital charts. The Panama Cervical Cancer Registry included all of Panama. By reviewing hospital records, we were able to determine patients' residence and thus accurately calculate residence-specific disease rates. Residents of Panama Province are comparable to those of Cali, São Paulo, or Kingston-St. Andrews regarding lifestyle; yet, Panama Province showed low invasive cervical cancer incidence. Panama's highest rates were in rural provinces, such as Herrera, where the age-adjusted risk (79.1/100,000) was 3.2 times greater than that in Panama Province. It is important to know whether a similar urban-rural difference exists in other Latin American areas.

It is even more striking that women born in the urban provinces of Panama and Colon had age-adjusted cervical cancer incidence rates (12.4 and 14/100,000, respectively) comparable to those of US white women, while women born in Herrera and other rural provinces retained high risks regardless of residence. Panama is a small geographically

TABLE 5
Final referral center for cervical cancer by region and medical facility, Panama, 1974-1979

	In situ		Invasive				Total	
	n	%	Microinvasive		Squamous		n	%
			n	%	n	%		
Panama								
Oncology Institute	148	21	40	42	812	82	852	79
Social Security	202	29	37	39	49	5	86	8
Santo Tomas	88	13	7	8	20	2	27	2
Colon								
6 hospitals	50	7	1	1	10	1	11	1
Chiriqui								
6 hospitals	77	11	4	4	16	2	20	2
Herrera								
5 hospitals	123	18	1	1	2		3	
Los Santos*								
4 hospitals	0		0		0			
Cocle								
3 hospitals	2		1	1	0		1	
Veraguas								
3 hospitals	0		0		1		1	
Bocas del Toro†								
3 hospitals	0		0		0			
No. for whom referral center is unknown	7	1	4	4	77	8	81	7

* Cervical cancer cases are referred to Herrera Province for initial treatment.

† Cervical cancer cases are referred to Chiriqui Province or Colon Province for initial treatment.

isolated country with 1.8 million inhabitants tabulated in 1980. The government collects extremely detailed census data which include information concerning in-

ternal migration patterns. Census data from 1960, 1970, and 1980 show increasing emigration from rural provinces to Panama, Colon, and the frontier areas.

TABLE 6

Proportion of number treated/number diagnosed for cervical cancer among residents of each province who received definitive care at a hospital in that province, Panama, 1974-1979

	In situ*		Invasive*					
	No. treated/ no. diagnosed	%	Microinvasive		Squamous		Total	
			No. treated/ no. diagnosed	%	No. treated/ no. diagnosed	%	No. treated/ no. diagnosed	%
Panama	402/402		46/46		395/395		441/441	
Colon	47/54	87	1/9	11	10/65	15	11/74	15
Chiriqui	77/81	95	4/5	80	16/135	12	20/140	14
Herrera	85/92	92	2/24	8	1/105	1	3/129	2
Los Santos	23†/36	64	0/4		1†/45	2	1/49	2
Cocle	2/16	13	1/1	100	0/70		1/71	1
Veraguas	1/2	50	0/0		0/66		0/66	
Bocas	0/2		0/1		0/10		0/11	
No. for whom data are unknown	12		5		96		101	

* All cases not receiving definitive care in their province were treated in Panama Province and have been summed with Panama Province residents.

† These 23 in situ and one invasive cancer cases were treated in Herrera.

About 10 per cent of emigrants are between 10 and 19 years of age and 45 per cent between 20 and 39 years of age (13). Thus, most women who emigrate from their birthplace do so after puberty and presumably after initiating sexual activity. The fact that locality of birth is a risk factor independent of residence is compatible with the excess cervical cancer risk detected for Hispanics in several US registries (2).

Women from rural areas of Panama are, in general, more poorly educated, are from a lower socioeconomic stratum, and live under less hygienic environmental conditions than their urban counterparts. Data concerning sex habits of Panamanian or other Latin American women have not been widely published. Within Panama, women from rural areas tend to become pregnant at a slightly younger age and utilize less formal medical care during pregnancy, delivery, and the postpartum period than urban women (14). Limited data collected in Panama City indicated that 342 women between 20 and 50 years of age who were interviewed during a Pap smear screening campaign had initiated sexual activity between 14 and 32 years of age; the average age was 15 years. A smaller study of 142 women attending an inner city barrio prenatal clinic documented similar figures, which is comparable to US data. However, the women in both studies had, on the average, 1.8 lifetime sex partners, with a range between one and 10 (15), considerably lower than US figures.

Popular theory is that Latin males are more promiscuous than women, but quantitative comparative data do not exist to substantiate this. Two recent papers pointed out that promiscuous males could constitute a cervical cancer risk factor for less sexually experienced female sex partners (16, 17). Both Kessler (18) and Singer et al. (19) have presented data supporting male causal factors for cervical

cancer. Prostitution is legal in Panama and throughout much of Latin America, including the areas whose registries were cited above; the prostitute population is mobile and a common pool rotates throughout the region. Penile cancer, which may reflect similar risk factors (20), is also common in Panama and other Latin American areas (2, 5), and studies in Puerto Rico found that wives of men with penile cancer had an excess risk of cervical cancer (21).

Limited information exists concerning sexually transmitted disease agents in Latin American populations. We screened 1182 prostitutes working in Panama City between 1978 and 1979 and found that only 1 per cent were culture-positive for herpes simplex virus type 2 (22). Rawls et al. (9) have summarized serologic data from various sources which show that herpes simplex virus type 2 prevalence rates between 21 and 28 per cent existed in normal Latin American women. Studies by Latin American investigators concur with these values (23, 24). Population data on genital papillomavirus infection have not been published from high-risk cervical cancer areas; therefore, it is difficult to assess their rate (25, 26) or to evaluate the high occurrence of papillomatous changes noted by Dr. Norris.

The fact that a group of young women from Herrera Province developed invasive cervical cancer may indicate that an unusual combination of risk factors is operating there (9, 27). Seroepidemiologic case-control studies would be very profitable in such an area. The apparently bimodal age-specific incidence curve may be due to small numbers of cases.

The possible decrease in Herrera Province cervical cancer incidence is also interesting. Unfortunately, accurate data have not been collected over time that would allow us to evaluate the extent to which Pap smear screening campaigns have caused a reduction in apparent in-

cidence, such as that which probably occurred in North America (28, 29). It may be possible to test critically cervical cancer control programs with prospective studies in Latin America.

It is difficult to account satisfactorily for the differences between tissue diagnoses done in Panama and at the Armed Forces Institute of Pathology, but two comments are in order. First, identical slides were not read by both groups. The material sent to the Armed Forces Institute of Pathology was taken from the histopathology archives of two hospitals. It became apparent during the review that many conization and hysterectomy specimens were negative but contained evidence of an earlier biopsy. The appropriate tissue may have been resected in the original biopsy. We are designing a prospective histopathology evaluation program. Second, there is a lack of comparative data; the International Agency for Research on Cancer and other groups stress the importance of histologic verification but, to date, no program has been established to facilitate formal exchange of histopathology material. We would like to see international collaboration to devise standard histologic criteria. Until this is possible, we must assume that histopathology standards followed in Panama are comparable to those represented in most published cancer registries.

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