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Prevalence and standardized incidence rates of preclinical cervical pathology among 1,061 women sterilized with transcervical quinacrine hydrochloride pellets*

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Objective: To determine whether the incidence of in situ cervical carcinoma was increased among a cohort of women who received transcervical insertions of quinacrine hydrochloride pellets into the uterine cavity as a method of nonsurgical sterilization.

Design: Retrospective review of Papanicolaou (Pap) test results, comparing incidence of high-grade lesions among quinacrine acceptors with a comparison population.

Setting: Outpatient clinics, Santiago, Chile.

Subjects: Women attending a family planning clinic (quinacrine acceptors) and a comparison population from another area of Santiago.

Main Outcome Measure: Incidence of in situ cervical carcinoma.

Results: During 3,668 woman-years of follow-up, 8 women in the quinacrine group were found to have in situ carcinomas for an age-adjusted rate of 2.62 per 1,000 woman-years. The incidence in a comparison population was 1.62 per 1,000 woman-years, but the difference was not statistically different.

Conclusions: The age-standardized incidence of in situ carcinoma among the quinacrine sterilized women was not significantly different from the rate in a comparison population of women in Santiago. However, the study has a number of limitations.

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Key Words: Cervical cancer, quinacrine, Pap smears, epidemiology, retrospective cohort, sterilization.

Since the mid-1970s, a number of studies of voluntary nonsurgical sterilization have been done with the intrauterine application of quinacrine hydrochloride pellets in patients at the Family Planning Clinic of the Sotero del Rio Hospital in Santiago (1). In 1977, a cytology laboratory and a pathology service were established in the hospital. Since that time, periodic (generally annual) Papanicolaou (Pap) examinations were carried out among this group of women.

The present analysis was undertaken because of concerns that have been raised about the mutagenicity of quinacrine and its potential carcinogenicity in humans (see Sokal et al. [2], this issue). The purpose of this report is to evaluate the results of the Pap smear screening program in which these women were participating and compare their results with available data for a similar population in Santiago.

MATERIALS AND METHODS

We reviewed all cytologic records of women sterilized with intrauterine quinacrine in the Sótero del

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Rio Hospital between March 1977 and October 1990, as well as the results of the histopathologic studies obtained from the archives of the hospital pathology service. Lesions were classified using the Bethesda system. Cervical intraepithelial neoplasia (CIN) grades II and III were grouped together as high-grade squamous intraepithelial lesions. In this report, we will refer to high-grade lesions as in situ carcinomas. The Bethesda classification of low-grade lesions refers to "cellular changes associated with human papilloma virus" and "mild dysplasia/CIN I." We did not compare rates of low-grade lesions for two reasons. First, there were changing criteria for diagnosis and interpretation of low-grade abnormalities among different cytologists during the study period. Second, agreement and uniformity among cytologists is better for the diagnosis of high-grade lesions.

Incidence rates of in situ carcinomas were calculated for only those women who had had a single negative Pap smear before quinacrine sterilization and were compared with rates for a similar group of Santiago women. Because the age distributions of the two groups were different, the rates were standardized on the basis of the female population of Chile in the 1970 national census (3).

Comparison data were taken from a previous report on the incidence of preclinical cervical pathology in metropolitan Santiago (4). A program for Pap screening was started in Santiago in 1966. In 1977 the program was incorporated into routine maternal and child care programs of the Ministry of Health, and in 1981 a computerized data base including all cytologic examinations was established. The previous report included data from 36,520 women who had a Pap smear in 1981 or 1982 and had at least one subsequent Pap smear in the succeeding 5 years, i.e., through 1986 or 1987, respectively. For the estimation of the incidence rate of in situ carcinoma per 1,000 woman-years, only women with a negative smear at the first exam were included. Due to changes in computer systems, we no longer had access to individual data records for the previous report, so to calculate the number of women years of exposure for each age group, we multiplied the number of women in each group by the average length of follow-up, which was 2.4 years. The two groups are from two different geographic areas, southeast Santiago (quinacrine group) and northeast Santiago (control group), but the communities have similar socioeconomic levels and cervical cancer mortality rates, and both groups receive health services from government clinics.

In the earlier study, rates were calculated separately for women with one or two negative smears, and for women with three, four, and five negative smears. Because the women in the quinacrine study were included in this analysis if they had had a single negative smear at the time of sterilization, they were compared with data for women with one or two negative smears in the earlier study. Due to various factors, perhaps including behavioral factors related to good compliance, incidence rates of in situ carcinoma are higher after only one or two negative Pap smears than after three or more negative smears (4, 5).

The methods of follow-up between the two groups were different. The quinacrine-sterilized women were participants in clinical studies and were followed-up actively. Women in the comparison group were from the general population, and no special effort was made to follow up women with negative smears. The average length of follow-up was 3.5 years in the quinacrine group and 2.4 years in the control group. To take into account the differing lengths of follow-up, rates were calculated per 1,000 woman-years. The comparison of the incidence density of in situ cancers between the quinacrine and comparison groups was performed using a maximum likelihood estimate of the rate ratio.

Table 1 Distribution By Age and Woman-Years of Observation of Women Sterilized With Quinacrine Pellets in Sótero del Rio Hospital, Santiago, Chile, 1977 to 1990

Age group	No. of women	Women-years of cytologic observation*	Intraepithelial lesions, high grade
15 to 19	1	0	0
20 to 24	8	8	0
25 to 29	84	186	0
30 to 34	243	729	3
35 to 39	301	975	3
40 to 44	266	1,047	1
45 to 49	115	536	1
50 to 54	34	I54	0
55 to 59	5	24	0
60 to 64		2	0
Unknown	3		0
Total	1,061	3,668	8

* Time in years between first and last cytologic examination.

RESULTS

The available cytologic records include a group of 1,061 women whose distribution by age at the time of the first cytologic examination and lengths of observation is shown in Table 1.

In this group of women, there were 19 patients in whom an in situ carcinoma, or cervical cancer, was found at the time of the first quinacrine pellet insertion (prevalence = 1.8%). Of these women, 18 had in situ cancers and 1 had invasive cancer. The woman with invasive cancer was diagnosed subse-

quently with adenocarcinoma of the cervix, was treated surgically, and was alive at the last follow-up in 1992. One of the women with an in situ carcinoma was lost to follow-up and was diagnosed with cervical cancer 12 years later at a different hospital. She died despite treatment.

A second group of nine women showed a change from their first cytology examination after the first insertion of intrauterine quinacrine. In this incident group, we found one patient with squamous cell carcinoma surgically treated in 1986. She was alive and free of illness at her last follow-up visit in 1990. The eight other women were found to have carcinoma in situ. Their distribution by age at the time of the first cytologic exam is shown in Table 1. The three women with unknown ages did not have any lesions and were not included in the age-adjusted analysis.

For the comparison population, the previously reported incidence rates of high-grade cervical pathology found among women ages 30-49 years in another area of Santiago and the 1970 census female population, both by 5-year age groups, are shown in Table 2. The crude incidence rates are 2.18 per 1,000 woman-years for the quinacrine group and 1.78 for the comparison group, for a crude rate ratio of 1.37, with 95% confidence limits of 0.61 to 3.07. The age-standardized rates for both groups are as follows: quinacrine group 8.62/3,285 = 2.62 per thousand woman-years; comparison group, 19.96/12,355 = 1.62 per thousand woman-years. The resulting rate ratio is 1.62, with 95% confidence limits of 0.73 and 3.61, indicating no significant difference between the two groups.

Table 2 Comparison of The Number of In Situ Carcinomas and Woman-Years of Exposure By Age Among Quinacrine-Sterilized and Comparison Women in Santiago, Chile

Age group	Quinacrine in situ cancer	Woman-years	Comparison in situ cancer	Woman-years	Chile 1970 female population*
30 to 34	3	729	13	4,951	299,200
35 to 39	3	975	5	3,374	259,400
40 to 44	1	1,046	1	2,309	248,100
45 to 49	1	535	3	1,721	200,200
Total	8	3,285	22	12,355	1,006,900

* Population used for age adjustments.

DISCUSSION

The age-adjusted incidence rate of in situ cervical carcinoma in patients treated with quinacrine (2.62 per 1,000 woman-years) is not significantly higher than the incidence rate in the comparison group (1.62 per 1,000 woman-years). While this analysis has shown no increased risk, this study has a number of limitations. The quinacrine group and comparison group were not recruited or followed in the same manner. They are from two separate geographic areas of Santiago. We do not have comparable data from the two groups on risk factors for cervical cancer such as age at first intercourse or number of sexual partners. The difference in the length and intensity of follow-up between the two groups might be a source of bias.

The relatively short average length of follow-up in the quinacrine group limits the study's generalizability. We are not aware of any data on chemically induced cervical cancer or carcinoma in situ in humans that would permit one to estimate a latent period. However, based on the latent period for known human carcinogens, it is certainly possible that insufficient time has passed since quinacrine insertion to see an effect.

The biologic plausibility of quinacrine causing cervical cancer is probably low, as most human cancers of the cervix are associated with infection by human papilloma virus. However, quinacrine is mutagenic and has the theoretic potential of being a carcinogen or cocarcinogen. The potential carcinogenicity of quinacrine is discussed in more detail by Sokal et al. (2). Additional toxicologic studies of quinacrine are being planned to better assess its potential carcinogenicity.

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REFERENCES

1. Zipper J, Cole LP, Goldsmith A, Wheeler R, Rivera M. Quinacrine hydrochloride pellets: preliminary data on a non-surgical method of female sterilization. Int J Gynaecol Obstet 1980; 18:275-9.
2. Sokal DC, Zipper J, Guzman-Serani R, Aldrich, TE. Cancer risk among women sterilized with transcervical quinacrine hydrochloride pellets, 1977 to 1991. Fertil Steril 1995; 00:000-000.
3. Instituto Nacional de Estadisticas. Poblacion 1960- 1975. Ministerio de Economia, Fomento y Reconstruccion, Republica de Chile (National Institute of Statistics. Population 1960-1975, Ministry of Economy, Public Works and Reconstruction, Republic of Chile, 1977:232. (Spa). 1977:232.
4. Dabancens OA. Tasas estandarizadas de patolo gia cervical preclinica obtenidas por el programa de control precoz de cancer cervico-uterino, en el area metropolitana de Santiago [Standardized tables of preclinical cervical pathology obtained by the program for early diagnosis of cervical-uterine cancer in the metropolitan area of Santiago]. Rev Chil Obstet Gineco 1989;54(4):217-24. (Spa).
5. Pettersson F, Naslund I, Malker B. Evaluation of the effect of papanicolaou screening in Sweden: record linkage between a central screening registry and the national cancer registry. In: Hakama M, Miller AB, Day NE. Screening for cancer of the uterine cervix. World Health Organization, International Agency for Research of Cancer, No. 76, 1986.