

Cancer risk among women sterilized with transcervical quinacrine in Chile: an update through 1996

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Objective: To determine whether further follow-up of a cohort of Chilean women would demonstrate an increased risk of invasive cancer associated with quinacrine sterilization.

Design: Cohort study. Cancer cases were evaluated using cohort analyses.

Setting: Santiago and Valdivia, Chile

Subject(s): Fourteen hundred ninety-two women who received transcervical quinacrine pellets for contraceptive sterilization between 1977 and 1989.

Method(s): Interviews and reviews of medical records.

Main Outcome Measure(s): Age- and site-specific incidence of invasive cancers.

Result(s): During 13,444 person-years of follow-up, 25 invasive cancers were identified, including 8 new cases. This compares with 21.9 expected cancers, based on age-specific rates from the Cali, Colombia, cancer registry. Eight cases of cervical cancer were observed, compared with the 6.3 expected. Since the initial study's confirmation of a single case of leiomyosarcoma, no other noncervical uterine cancers have been diagnosed. The number of observed person-years gives an expectation of 0.62 noncervical uterine cancers. One case of ovarian cancer was diagnosed, compared with the 0.99 expected.

Conclusion(s): Rates of cancer among women exposed to intrauterine quinacrine are not significantly different from population-based rates. (*Fertil Steril*® 2000;74: 169-71. ©2000 by American Society for Reproductive Medicine.)

Key Words: Quinacrine, cancer incidence, cohort analysis, tubal sterilization, follow-up studies

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The transcervical insertion of quinacrine pellets has been proposed as a potentially safer and less expensive method of voluntary female sterilization than surgery. However, since quinacrine is a mutagen, there has been some concern about the potential risk of cancer. We conducted a retrospective cohort study to evaluate the occurrence of an apparent cancer cluster among women in Chile who had received quinacrine pellets. That study concluded that the cluster was not related to quinacrine (1).

MATERIALS AND METHODS

Since the initial report, we have gathered 4 additional years of follow-up data. The cohort includes 1,341 women from Santiago and 151 from Valdivia. In the initial study, we interviewed 138 (9.14%) women from Valdivia and 664 (49.5%) women from Santiago. During the

additional years of follow-up, we made further efforts to find and interview more women.

The study's procedures involved [1] clinic record reviews of all women; [2] active tracing of these women and interviews with them to identify cancer occurrences through the 1995 calendar year and part of 1996; [3] hospital record reviews for all cancer cases identified; and [4] review of pathology slides for all gynecologic cancers by an independent pathologist.

This follow-up study was initially approved by FHI's institutional review board in June 1990. The collection of the additional follow-up data reported here was approved in August 1993.

We estimated the expected cancer risk for the cohort using direct standardization with the age- and gender-specific incidence rates from

Cali, Colombia (2). Additional details regarding identification of study participants, choice of the Cali cancer registry for calculation of expected numbers, and survey and statistical methods were described in a previous publication (1). We also used data from nine US cancer registries to calculate the number of expected cases of uterine leiomyosarcomas (3). An independent pathologist reviewed the pathology slides and confirmed the diagnosis for the new cases of gynecologic cancers that we identified.

RESULTS

From 1977 through 1989, 1,492 women in Chile received voluntary sterilization via transcervical quinacrine pellets and thus were eligible for the retrospective cohort. Since the initial report, an additional 441 women were located and interviewed. Thus we located and interviewed a cumulative total of 1,243 (83%) women: 1,100 (82%) from Santiago and 143 from Valdivia (95%). At least 6 months of follow-up are available for 97.5% of the cohort.

We found 8 additional cancers: one new case in Valdivia and 7 in Santiago. Thus the present analysis is focused on a cumulative total of 25 observed invasive cancers: 9 from Valdivia and 16 from Santiago. Of the 25 women with invasive cancers, 9 were dead at the time the data were gathered.

We observed 13,444 person-years and calculated an expected rate of 7.86 gynecological cancers per 10,000 person-years based on data from the Cali, Colombia, cancer registry. Thus, for a one-tailed test with a .05 significance level, our study has 73% power to detect a two-fold or greater excess of all gynecologic cancers (relative risk [RR] = 2) and 65% power to detect an increase of cervical cancers.

Comparisons-Interviewed Versus Noninterviewed Subjects

We compared the characteristics of the 1,100 Santiago cohort members who were interviewed and the 241 who were not interviewed (data not shown). Interview status in Santiago varied sporadically by year with a range of 8.7%-28.5% not interviewed. Women who were younger when they were sterilized were less likely to be interviewed than older women, ranging from 28.0% not interviewed among 257 women ages <30 years to 10.8% among 158 women ages 240. There was no significant difference in interview status by years of education, number of live births, or previous contraceptive method. At the Valdivia site, 143 of 151 women were interviewed, so a tabulation of interviewed versus noninterviewed women was not considered useful.

There were two cancers in the noninterviewed women, a cervical cancer and a bile-duct cancer. Using a one-tailed test, there was no significant difference in cancer incidence per 1,000 person-years between the Santiago women interviewed and not interviewed (1.32 vs. 2.89, $P = .86$).

TABLE 1

Observed and expected cancer diagnoses for all breast, cervical, uterine, and ovarian cancers, quinacrine cohort 1977-1996.

Site	Observed	Expected ^a	Ratio	95% Confidence limits
All	25	21.92	1.14	0.74-1.68
Breast	6	6.11	0.98	0.36-2.14
Cervix	8	6.25	1.28	0.54-2.53
Ovary	1	0.99	1.01	0.10-5.66
Other uterine	1	0.62	1.61	0.16-9.03

^a Expected numbers were calculated from age- and gender-specific incidence rates from the Cali, Colombia, cancer registry. Volume V rates were used for person-years contributed during 1977-1981. Volume VI rates were used for years 1982-1986. Volume VII. See ref. (2).

Sokal. Cancer risk and quinacrine. Fertil Steril 2000.

Temporal Evaluations

We examined the time elapsed from sterilization to cancer diagnosis for the most frequent cancers, breast (6 cases) and cervical (8 cases). The women with breast cancer were an average of 45 years of age, and the time elapsed since their first quinacrine insertion averaged 7 years. The women with cervical cancer were an average of 43 years of age, and the time elapsed since their first quinacrine insertion averaged 8 years. Both breast and cervical cancers varied widely in terms of the interval from first quinacrine insertion to cancer diagnosis (data not shown).

Cohort-Observed Versus Expected

Based on the age distribution and person-years of exposure over the 20-year interval, 21.9 new cancer cases would be expected. The 25 cancer cases observed are not significantly different from the number expected (observed/expected ratio = 1.14; 95% CI = 0.74, 1.68). With respect to geographic location, there were 16 observed and 18.3 expected in Santiago, for a ratio of 0.87; 95% CI = 0.51, 1.42, and 9 observed and 3.6 expected in Valdivia, for a ratio of 2.49; 95% CI = 1.11, 4.74.

Site-Specific Evaluation

The 8 new cancers included 3 cervical cancers and one each of the following: breast, ovary, gall bladder, multiple myeloma, and stomach. For breast cancer, the observed/expected ratio was 0.98, with a 95% confidence interval of 0.3-2.14 (Table I). For cervical cancer the ratio was 1.28 with a 95% confidence interval of 0.54-2.53. Neither of these results provides evidence of a significant association. We observed one case of ovarian cancer in this cohort, while 0.99 cases were expected.

A case of uterine leiomyosarcoma was identified in the first study (1). No additional cases of leiomyosarcoma or other non-cervical cancers of the uterus have been identified. Based on the Cali data, one would expect about 0.48 cases of

cancer of the body of the uterus if "unspecified uterine" cancers are excluded or 0.62 cases if unspecified uterine cancers are included. Based on US data, the number of expected uterine leiomyosarcomas would be approximately 0.17 or 0.29, using rates for white or black women, respectively (3). These are not significantly different from the one case observed.

DISCUSSION

In the current analysis, we had a power of 73.5% to detect a two-fold increase in all gynecologic cancers ($RR = 2$). The results reported here still show evidence of the Valdivia cluster, but the cluster effect has weakened with the inclusion of additional data. Two of us (AD, JZ) recently published an analysis of a slightly larger group of women from Santiago only, using a hospital-based comparison group. That report listed one additional case of cancer, an oral cancer (4). However, on further review of hospital records, we found that that cancer had been diagnosed prior to the woman's quinacrine insertion. The inferences that can be drawn from this study are limited because of the relatively small number of women in this cohort; however, we have not found a significantly increased risk of cancer associated with the transcervical administration of quinacrine pellets.

Compared with our original report, the rate of follow-up interviews has improved. It seems unlikely that the differences between the interviewed and noninterviewed women in Santiago would significantly bias the analysis.

If we followed this cohort for an additional 10 years through 2006, assuming a 20% loss to follow-up, the power of the study would increase. We would have 80% power to detect a 40% increase in all gynecologic cancers ($RR = 1.4$) or a 45% increase in cervical cancers ($RR = 1.45$). For other

' "Well established" is defined as registries that have had data included in both Volumes VI and VII of the IARC series.

uterine cancers and ovarian cancers, we would have the power to detect increased relative risks of about 1.5.

Compared with the United States, cervical cancer rates in the Cali registry are high. However, in comparison with other South American cancer registries, the cervical cancer rates in Cali are about average. Of the five well-established South American cancer registries whose results have been reported by the International Agency for Research on Cancer (IARC), Cali's cervical cancer rate is in the middle. Two registries, Goiana, Brazil, and Trujillo, Peru, report higher cervical cancer rates than Cali, and two, Quito, Ecuador, and Porto Alegre, Brazil, report lower rates (2). Furthermore, the IARC editors note that three of these five registries, but not Cali or Trujillo, are probably subject to under-ascertainment. Cali was chosen for comparison because it has had the best-established cancer registry in South America, with regular reporting to IARC from 1962 through 1991 (2).

Despite the reassuring results of this follow-up study, additional animal studies of quinacrine's carcinogenic potential are needed before the US Food and Drug Administration would consider approving quinacrine pellets for non-surgical sterilization.

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