Comparison of Long Term Cancer Risk Between Vietnamese Women Undergoing QS vs. IUD Contraceptive Procedures

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BACKGROUND

Vietnam began researching the use of quinacrine hydrochloride pellets for non-surgical sterilization of women in 1989. They halted use of the procedure in 1993 after concerns were raised about a risk of cancer associated with the method.

OBJECTIVE

Earlier studies found non-significant differences in cancer incidence between women who underwent quinacrine hydrochloride sterilization (QS) and non-QS treated women. This study's goal was to compare the long-term risk of reproductive cancer diagnosis between women who underwent QS vs. those who had tubal ligation (TL) or Copper (Cu++) T IUD procedures without exposure to QS.

METHODS

A retrospective cohort study of cancer and other serious gynecological outcomes was conducted among a group of Vietnamese women who were either sterilized with QS or tubal ligation, or fitted with a Cu++ T IUD between 1989 and 1993. Clinic log books identified women for interviews in the northern provinces of Nam Dinh, Ha Nam, Ninh Binh and Thai Binh. Missing IUD and TL log books in Nam Dinh required researchers to conduct a community survey to identify potential controls in that province. QS exposed women were matched (1:1) to women who underwent TL or IUD placement (without exposure to QS) by quarter and year of contraceptive procedure, age at procedure, and clinic.

General health status interviews were conducted, with follow-up questions about reported outcomes of interest. Personal and family medical and health histories, as well as information about exposures to potential carcinogens, were also solicited. When available, hospital records were reviewed to validate self-reported outcomes.

Cox Proportional Hazards regression (CPH) was used to compare the risk among the QS vs. IUD groups of having a diagnosis, during their follow-up intervals, for reproductive cancer only (uterine, cervical and ovarian), breast cancer only, or any type of cancer.

Age at the time of procedure and exposure to X-ray radiation were included as covariates in all of the CPH models. Province of residence was added in the multivariate models, with women living in Nam Dinh serving as the reference group. Each CPH model was also run with the addition of a propensity score variable, designed to account for potential differences in baseline characteristics of women choosing the different contraceptive methods.

SURVEY RESULTS

Between 2007 and 2009, over 21,000 Vietnamese women who had received QS, IUD or TL were interviewed to assess their health status.

Average follow-up time from procedure to interview exceeded 16 years (**Table 1**). Study participants were in their early fifties at the time the interviews were conducted, on average, having had their procedures in their mid-thirties. Most women were married, and worked as farmers or fishermen. The study population's mean level of education was more than 6 years.

RISK ANALYSIS

A total of 115 cancers were identified among the women interviewed (0.33 / 1,000 woman years of follow-up time, 95% CI=0.28-0.40) (**Table 2**). Twenty of the reported cancers (17%) were in reproductive tract organs, and breast cancers accounted for 27 (23%) of the total.

The median time from procedure to any cancer diagnosis was 13 years. This statistic was shorter among the QS women, and longer for the TL and IUD cohorts.

Due to the relatively small proportion of patients in the TL cohort, coupled with enough differences in women's characteristics to preclude combining them with the IUD patients, the control group for the CPH analyses was limited to women in the IUD group.

Looking at QS vs. IUD study participants, no significant association of QS with the risks of reproductive or breast cancers, during the follow-up time period, was found in either the univariate or multivariate CPH analyses (**Table 3**). While QS, by itself, was associated with a significantly higher risk of any cancer diagnosis during the elapsed interval, that difference was not significant after controlling for other risk factors.

Exposure to X-rays and age at procedure stood out as the two risk factors most strongly associated with the risk of developing cancer during the follow-up period, for the women in this study population. X-ray exposure was significantly associated with the risk of cancer over time for each of the cancer groups examined. Similarly, each additional year of age at procedure significantly increased the risk of cancer in every model.

Women interviewed in Ha Nam had higher risks of breast cancer, or any type of cancer, than otherwise similar women in Nam Dinh. Thai Binh women were also significantly more likely to report any type of cancer diagnosis after their procedures, as compared to the Nam Dinh group.

The propensity score adjustment had virtually no effect on any of the CPH results.

Table 1. Characteristics at the Time of Study Interview for Women Who Underwent QS, IUD or TL Procedures in Vietnam between 1989 and 1996.*

	QS		IUD		TL	
	N	%	N	%	N	%
Total Patients	10,503	100.00	9,203	100.00	1,331	100.00
Follow-up Time**						
Mean ± SD	16.33 ± 1.27		16.62 ± 1.02		16.04 ± 1.20	
Age at Procedure						
Mean ± SD	34.71 ± 4.25		34.61 ± 4.32		35.03 ± 3.95	
Age at interview						
Mean ± SD***	51.08 ± 4.32		50.89 ± 4.38		50.84 ± 3.97	
Residency						
NAM DINH	4,979	47.41	4,926	53.53	48	3.61
HA NAM	2,017	19.20	1,309	14.22	733	55.07
THAI BINH	1,921	18.29	1,521	16.53	424	31.86
NINH BINH	1,586	15.10	1,447	15.72	126	9.47
Marriage Status						
Married	9,976	94.98	8,967	97.44	1,267	95.19
Single, Divorced, Separated, Widowed	421	4.00	193	2.10	59	4.43
Missing	106	1.01	43	0.46	5	0.38
Education						
Mean ± SD	6.66 ± 1.78 (10325)		6.84 ± 1.88 (9124)		6.63 ± 1.61 (1317)	
Occupation						
Farmer/Fisher	10,057	95.76	8,736	94.93	1,310	98.42
Other occupations	446	4.22	467	5.08	21	1.59

* Except for IUD and TL cohorts in Nam Dinh, data are from logbook records.
** Years from Index Procedure to interview, death or latest medical event.
*** Age as of 2007 for women with non-missing date of birth.

Table 2. Number and rate of reported cancer diagnoses and median time from procedure to cancer diagnosis, in years, by procedure and type of cancer: reproductive (uterine, cervical and ovarian), breast, and the group of all cancers

	All Women (N=21,037)			QS (N=10,503)			IUD (N=9,203)			TL (N=1,331)		
Type of cancer	N	Rate / 1000 woman years (95% CI)	Median yrs to diagnosis	N	Rate / 1000 woman years (95% CI)	Median yrs to diagnosis	N	Rate / 1000 woman years (95% CI)	Median yrs to diagnosis	N	Rate / 1000 woman years (95% CI)	Median yrs to diagnosis
All Cancers	115	0.33 (0.28-0.40)	13.00	69	0.40 (0.32-0.51)	12.00	40	0.26 (0.19-0.36)	14.00	6	0.28 (0.13-0.62)	13.50
Reproductive	20	0.06 (0.04-0.09)	12.00	12	0.07 (0.04-0.12)	12.00	8	0.05 (0.03-0.10)	14.00	0	-	-
Non-reproductive*	93	0.27 (0.22-0.33)	13.00	56	0.32 (0.25-0.42)	11.00	31	0.20 (0.14-0.29)	14.00	6	0.28 (0.13-0.62)	13.50
Breast	27	0.08 (0.05-0.11)	12.00	15	0.09 (0.05-0.14)	9.00	9	0.06 (0.03-0.11)	13.00	3	0.14 (0.04-0.44)	14.00

* Non-reproductive cancers include breast cancer, and exclude reproductive and skin cancers.

Table 3. Results of Cox Proportional Hazards Regression for risk of cancer following QS sterilization or IUD insertion for Vietnamese women who had those procedures between 1989 and 1996 (N=19,706)

	Univariate Results					
	Unadjusted			Adjusted for Propensity Score		
Outcomes \\ Covariates	Reproductive tract cancer	Breast cancer	Any cancer	Reproductive tract cancer	Breast cancer	Any cancer
X-ray exposure	3.08 (1.10-8.64)	4.32 (1.72-10.82)	2.92 (1.81-4.70)	3.08 (1.10-8.66)	4.28 (1.70-10.76)	2.90 (1.80-4.68)
Age at procedure	1.12 (1.01-1.24)	1.13 (1.02-1.24)	1.10 (1.05-1.14)	1.12 (1.01-1.24)	1.13 (1.02-1.24)	1.10 (1.05-1.14)
QS Procedure	1.37 (0.56-3.35)	1.53 (0.67-3.50)	1.66 (1.12-2.45)	1.74 (0.62-4.86)	1.44 (0.55-3.78)	1.88 (1.20-2.96)

	Multivariate Results					
	Unadjusted			Adjusted for Propensity Score		
Outcomes \\ Covariates	Reproductive tract cancer	Breast cancer	Any cancer	Reproductive tract cancer	Breast cancer	Any cancer
X-ray exposure	4.52 (1.07-19.21)	5.07 (1.10-23.33)	4.19 (2.04-8.60)	4.56 (1.08-19.30)	5.02 (1.09-23.16)	4.24 (2.07-8.68)
Age at procedure	1.15 (1.02-1.29)	1.14 (1.03-1.28)	1.10 (1.04-1.16)	1.15 (1.02-1.29)	1.14 (1.02-1.28)	1.10 (1.04-1.16)
QS Procedure	1.42 (0.55-3.66)	1.02 (0.42-2.47)	1.48 (0.96-2.29)	1.66 (0.53-5.18)	0.94 (0.33-2.74)	1.67 (0.99-2.80)
Lives in Ha Nam	0.97 (0.20-4.68)	7.02 (1.98-24.89)	2.44 (1.33-4.47)	0.95 (0.20-4.60)	7.07 (1.99-25.07)	2.40 (1.31-4.40)
Lives in Ninh Binh	0.62 (0.14-2.86)	2.08 (0.43-10.07)	1.03 (0.49-2.16)	0.62 (0.14-2.85)	2.08 (0.43-10.12)	1.03 (0.49-2.15)
Lives in Thai Binh	1.80 (0.52-6.21)	1.20 (0.35-11.31)	2.89 (1.59-5.23)	1.79 (0.52-6.17)	2.01 (0.36-11.38)	2.88 (1.59-5.21)

CONCLUSIONS

Analysis of these study data indicate that, after controlling for other known cancer risk factors, no significant association exists between QS and the specific outcomes of reproductive cancer, breast cancer, or the group of all reported cancers. Findings of earlier studies are reinforced by these conclusions.

Highly significant associations between X-ray exposure and age at procedure with the risk of diagnosis with these cancers, during the follow-up interval, suggest that any cancer risk that might be associated with the QS procedure is overshadowed by other factors in women's backgrounds that influence their selection of QS as a means of permanent contraception. The failure of the propensity score to reveal any differential risk of cancer between the QS and IUD groups also suggests that environmental and cultural factors are likely to exist, not measured in the interviews, which influence this study population's risk of cancer over time. The finding of a significant association between QS and the group of all cancers in a univariate model, that is not significant when controlling for other risk factors, highlights the importance of considering all potential contributing variables in evaluating risk of malignancies, or other outcomes.