

# Contraceptive methods and induced abortions and their association with the risk of colon cancer in Shanghai, China

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## Abstract

267 400 female textile workers in Shanghai, who were administered a questionnaire at enrollment into a randomised trial of breast self-examination between October 1989 and October 1991, were followed up until the middle of 2000. Based on the 655 women who developed colon cancer, rate ratios (RRs) were estimated and trends in risk assessed using Cox Proportional Hazards Models. Risk was increased in women who used oral contraceptives for over 3 years (RR = 1.56, 95% Confidence Interval (CI) 1.01–2.40). A possible increase in risk was also observed in women who received progestational injections during pregnancy (RR = 1.24, 95% CI 0.95–1.62), but not in relation to the use of injectable contraceptives. A possible reduction in risk was associated with tubal ligation (RR = 0.86, 95% CI 0.71–1.03) and ever having had an induced abortion (RR = 0.84, 95% CI 0.71–1.00). No trends in risk were observed in relation to the duration of hormonal contraceptive use or the number of induced abortions. Additional studies of the possible roles contraceptives may play in the aetiology of colon cancer in women at low risk of this disease are warranted.

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## 1. Introduction

A reduction in the risk of colon cancer with increasing parity has been observed in most studies conducted in developed countries [1,2], but not in China [3]. Most previous studies have also found a decreased risk with long-term exposure to oral contraceptives [4] and hormone replacement therapy [5,6]. These observations suggest that there may be a hormonal component to the aetiology of colon cancer.

## 2. Patients and methods

A randomised trial of breast self-examination was initiated in 1989 [7]. The trial included 30–64-year-old current and retired employees associated with 519 factories in the Shanghai Textile Industry Bureau (STIB).

The women received their primary medical services from medical workers in clinics located within their assigned factories. After receiving training from study workers, the medical workers in each factory orally administered a baseline questionnaire to all eligible women between October 1989 and October 1991. This four-page, optically-scanned questionnaire ascertained information on breast cancer risk factors, induced abortions, and contraceptive use, including oral and injectable contraceptives, intrauterine devices, and tubal ligations. Comparisons between the baseline questionnaire and a breast cancer case-control study questionnaire (administered by study workers) showed at least an 85% agreement for live births and induced abortions and at least a 90% agreement for other contraceptive variables (data not shown).

When cancer was suspected, the women were referred to one of three hospitals operated by the STIB, or to other hospitals with contracts with individual factories. The STIB Tumour and Death Registry received annual reports from each factory of all cases of cancer and deaths that had occurred among the cohort members. This information was supplemented by periodic reviews

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of the records of the Shanghai Cancer Registry that meets the standards for inclusion of data in *Cancer Incidence in Five Continents* [8]. These methods of cancer detection were shown to result in a high level of case ascertainment for breast cancer in the cohort [9]. Hospital records were reviewed if the diagnosis of cancer at the Shanghai Cancer Institute, prior to 1998, were different from the STIB Tumour and Death Registry.

The data-set used for this analysis included information on the follow-up of 267 400 women in the cohort through to 31 July, 2000. Information on censored observations was obtained from personnel records (i.e. whether the woman changed jobs and left the STIB) and from the STIB Tumour and Death Registry (i.e. deaths). Information on incident colon cancer cases International Classification of Diseases (ICD9 153.0–153.9) was obtained from the STIB Tumour and Death Registry. The hospital records of 167 cancers ascertained from the STIB Registry, which were originally coded as ‘intestinal cancer, unspecified’, were reviewed and 98 were reassigned as colon cancer. There was a 92.6% follow-up over the period of the study (i.e. 7.4% of the subjects transferred out of the STIB).

Cox Proportional Hazards models were used to analyse the data with length of follow-up being the time-scale variable [10]. Missing observations (less than 0.1% of any data item) were deleted from the analyses. All models were controlled for the potentially confounding effect of age (using linear splines with knots at 5-year periods). Parity, ages at first live birth and menarche, menopausal status, various contraceptive methods, induced and spontaneous abortions, and type of factory, were considered as possible risk factors and confounders. Variables that altered an estimate of the relative risk (RR) of colon cancer in relation to a factor of interest by more than 5% were retained as confounding variables in the model for that factor.

This study was approved by the Institutional Review Boards of the Fred Hutchinson Cancer Research Center, the University of Illinois at Urbana-Champaign, and the Station for Prevention and Treatment of Cancer of the STIB and was also approved by the Office for the Protection from Research Risks (OPPR) of the National Institutes of Health.

### 3. Results

As expected, the risk of colon cancer ( $N=655$ ) increased with age (Table 1). There was a decreasing trend in risk with the number of live births (parity), which was not statistically significant. A reduction in the risk of borderline significance was observed in women who had ever had an induced abortion, but there was no trend in risk with the number of induced abortions. Risk was not associated with spontaneous abortions.

Women who used oral contraceptives for more than 36 months had a significant elevation in the risk of colon cancer, but the possible trend in risk with duration of use was not statistically significant. The most common oral contraceptive used was the Chinese Pill No. 1, which contained 0.625 mg norethisterone and 0.035 mg ethinyl oestradiol until 1974, when the dosage was changed to 0.3 mg norethisterone and 0.03 mg ethinyl oestradiol.

There was no increase in risk associated with the use of monthly injectable contraceptives. The most common monthly injectable in China contains 250 mg of 17- $\alpha$  hydroxy-progesterone and 5 mg oestradiol-valerate.

An increase in risk of borderline statistical significance was also observed in women who reported receiving injections of progesterone during pregnancy for the prevention of miscarriage in women with vaginal bleeding. These injections were typically given in 10–20 mg doses for 5–10 days during the first trimester.

No association was observed with the use of intra-uterine devices. A borderline reduction in risk was observed for women who had had a tubal ligation.

### 4. Discussion

Our findings suggest that the risk of colon cancer may be slightly reduced in response to having a live birth. A decreased risk associated with increasing parity has been observed in some previous studies [1,2] and warrants further investigation.

Few studies have separated the effect of spontaneous and induced abortions. Of those that have, La Vecchia and colleagues [11] found a reduced risk associated with the number of induced abortions, but not with spontaneous abortions; but a later study by the same group [1] found no relationship with either type of abortion. We also did not observe trends in the risk of colon cancer with the numbers of induced abortions. It seems unlikely that abortions cause or protect against colon cancer.

Our findings suggest that exposure to exogenous sources of progestins (long-term oral contraceptive use, and injections of progestational compounds during pregnancy) may increase the risk of colon cancer. However, no association was found with injectable contraceptives, and previous investigations found either no or a negative association of oral contraceptive use with colon cancer risk [4].

The possible reduced risk associated with ever having had a tubal ligation is consistent with findings of Cape and Kreiger reported in Ref. [12]. They postulated that their findings were due to a decreased level of endogenous oestrogen exposure. However, this hypothesis is not consistent with previous observations of an association between postmenopausal oestrogen use and a reduced risk of colon cancer [5,6]. The role of oestrogen in the aetiology of colon cancer remains uncertain.

Table 1

Rate ratios for colon cancer with respect to contraceptive methods, induced abortions, and potential confounders, Shanghai Textile Industry Bureau Cohort, 1989–1997

Exposure	Category	Cases	Person years	RR	95% CI
Age (years)	≤35	28	549 851	1.00	
	36–40	37	471 628	1.53	0.94, 2.50
	41–45	52	294 230	3.37	2.12, 5.34
	46–50	59	130 207	4.31	2.56, 7.25
	51–55	88	226 375	7.44	4.86, 11.39
	56–60	220	420 665	10.14	6.84, 15.03
	61+	201	305 175	12.82	8.63, 19.03
				$P < 0.0001$	
Parity	0	32	116 414	1.00 <sup>a</sup>	
	1	111	1 145 488	0.89	0.58, 1.38
	2	124	394 487	0.92	0.62, 1.36
	3	149	308 131	0.91	0.61, 1.34
	4	121	224 825	0.89	0.60, 1.32
	5+	118	208 834	0.83	0.56, 1.23
				$P = 0.38^b$	
Induced abortions	Never	372	1 072 259	1.00 <sup>c</sup>	
	Ever	256	1 225 834	0.84	0.71, 1.00
	1	172	857 633	0.82 <sup>a</sup>	0.68, 0.98
	2	66	304 459	0.89	0.68, 1.16
	3+	18	63 742	1.01	0.62, 1.65
				$P = 0.20^b$	
Spontaneous abortions	Never	525	2 012 991	1.00 <sup>c</sup>	
	Ever	103	285 102	0.99	0.80, 1.23
	1	88	227 336	1.10	0.88, 1.39
	2	11	43 073	0.62	0.34, 1.13
	3+	4	14 694	0.62	0.23, 1.66
				$P = 0.34^b$	
Oral contraceptives	Never	563	2 045 338	1.00 <sup>d</sup>	
	Ever	92	352 851	1.09	0.86, 1.37
	≤6 months	25	134 048	0.97	0.64, 1.47
	7–24 months	32	133 308	0.96	0.67, 1.38
	25–36 months	13	426 625	1.13	0.65, 1.97
	37+ months	22	42 378	1.56	1.01, 2.40
				$P = 0.16^b$	
Monthly injectables	Never	627	2 285 262	1.00 <sup>d</sup>	
	Ever	27	111 392	1.12	0.75, 1.67
	1–6 months	11	51 319	1.10	0.56, 2.07
	7–12 months	6	23 277	1.30	0.58, 2.93
	13–24 months	6	14 910	1.73	0.77, 3.88
	25+ months	4	21 885	0.67	0.25, 1.80
				$P = 1.00$	
Injections during pregnancy	Never	564	2 047 489	1.00 <sup>c</sup>	
	Ever	64	250 604	1.24	0.95–1.62
Intrauterine device	Never	499	1 237 344	1.00 <sup>d</sup>	
	Ever	156	1 160 824	1.10	0.88, 1.38
Tubal ligation	Never	472	1 967 535	1.00 <sup>d</sup>	
	Ever	183	430 664	0.86	0.71, 1.03

95% CI; 95% Confidence Interval; RR, rate ratios.

<sup>a</sup> Adjusted for age using splines.

<sup>b</sup> Test for trend.

<sup>c</sup> Adjusted for age using splines and parity. Restricted to women who had ever been pregnant.

<sup>d</sup> Adjusted for age using splines and parity.

Our results are unlikely to be a result of uncontrolled confounding by other colon cancer risk factors related to nutrition or genetics because these factors are not likely to have been associated with the hormonal and contraceptive factors evaluated in this investigation.

There was no routine genetic screening for colon cancer in the study population; most women received equal pay and were largely of Han ethnicity, and therefore probably ate a relatively uniform diet; and all women had equal access to medical and contraceptive services.

Assessment of reproductive variables such as parity was probably acceptably accurate, since these variables showed the expected associations with breast cancer [13]. The roles of contraceptive and reproductive factors were assessed for many cancer sites, and observed associations with respect to colon cancer could be due to chance.

The prospective nature of this study eliminated the possibility of recall bias, which is especially important with respect to reporting of induced abortion in some cultures. Our findings are from a low-risk population, and associations that we observed could have been obscured in previous studies conducted in high-risk areas. However, it should be noted, that colon cancer rates are increasing in Shanghai [14] and rates for colon cancer were observed to be higher in female textile workers than in women with some other occupations in Shanghai [15] and that rates of colon cancer are slightly higher in our study cohort than in the general population of Shanghai [16]. Additional investigations of the role of contraceptives practices in the aetiology of colon cancer are warranted.

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