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Original Paper

The Influence of Reproductive and Hormonal Factors on the Risk of Colon and Rectal Cancer in Women

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A case–control study was conducted between 1992 and 1996 in six Italian areas. It included 537 women with colon cancer, 291 women with rectal cancer and 2081 control women in hospital for acute conditions, unrelated to hormonal or gynaecological diseases. A higher age at menopause was associated with increased colon cancer risk (odds ratio (OR) for $\geq$ 53 years compared with < 50 years = 1.39, 95% confidence interval (CI) 1.04–1.87). Among parous women, a significant trend of decreasing colon cancer risk with increasing number of births was seen for colon (OR for $\geq$ 4 births compared with 1 birth = 0.62, 95% CI 0.42–0.90), but not for rectal cancer. Nulliparous women, however, were at lower risk than women with a single birth, and age at first birth was directly associated with risk. While oral contraceptive use showed no significant influence, ever users of hormone replacement therapy had a reduced risk of rectal cancer (OR = 0.56, 95% CI 0.31–1.01). Thus, the association of colorectal cancer with reproductive and menstrual factors is neither strong nor consistent.

Key words: colon cancer, rectal cancer, parity, oral contraceptives, hormone replacement therapy
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INTRODUCTION

COLORECTAL CANCER is the most common cancer in non-smokers in Western countries [1]. While dietary habits and physical activity are thought to be major determinants of colorectal cancer risk [2], female hormones have also received considerable attention [3, 4]. Hormonal and reproductive factors have been suspected of playing a role in women since differences exist in the distribution by subsite [5] and in incidence trends by gender and age [6, 7]. In England and Wales, for instance, a decline in the sex ratio of colorectal cancer incidence for cohorts born from 1915–1919 to the mid-1940s paralleled increases in female fertility [7]. Endogenous and exogenous female hormones may influence colorectal cancer risk by interfering with hepatic bile acid metabolism [3].

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Results from analytical studies are not totally consistent. Since 1979 at least 34 studies have provided information on reproductive and hormonal factors in relation to colorectal cancer: 27 were case–control investigations [8–34] and seven were cohort studies [35–41]. Ten case–control studies showed significant decreasing risks with increasing parity [8, 15, 18–20, 23, 24, 28, 32, 34]. In five studies, increased risks were seen in parous women [10, 11, 13, 14, 16], but only in one study was the trend significant [14]. With respect to cohort studies, no clear associations with parity were found in four investigations [35, 36, 40, 41]. Chute and colleagues [37] and Kravdal and associates [38] showed a significant inverse association between parity and cancer risk, whereas Bostick and co-workers [39] reported a direct association.

As for age at first birth, three case–control studies were consistent with a reduced risk for higher age at first birth [11, 14, 30], whereas five studies showed an elevated risk in women with delayed childbearing [15, 19, 23, 28, 32]. Among

cohort studies, the Nurses' Health Study [40] suggested that women with a higher age at first pregnancy may have an approximately 50% higher risk.

The role of menstrual variables in colorectal cancer aetiology is unclear. Three studies [13, 29, 40] found that risk was significantly decreased in women with a higher age at menarche. With respect to age at menopause, no consistent risk pattern has emerged, although a significant direct association was reported by Wu-Williams and colleagues [25] for rectal cancer.

A few investigations [19, 23, 25, 26, 33, 37, 40, 42] have provided information on the relationship between oral contraceptive use and colorectal cancer. In five studies, risk reductions in women who had ever used oral contraceptives compared with never users were found [19, 25, 26, 40, 42]. Three studies [18, 23, 30] suggested a non-significant increased risk for short-term use of oral contraceptives.

At least 16 studies [12, 14, 18, 19, 24, 30, 31, 33–35, 37, 39–43] have provided data on the relationship between hormone replacement therapy (HRT) and colorectal cancer, of which seven [14, 30, 31, 33, 40, 42, 43] showed significant risk reductions.

In order to elucidate further the role of endogenous and exogenous female hormones in the aetiology of cancer of the colon and the rectum, we took advantage of a large case–control study on colorectal cancer carried out in Italy.

MATERIALS AND METHODS

A case–control study of cancer of the colon and the rectum was conducted between January 1992 and June 1996 in six Italian areas: the provinces of Pordenone and Gorizia in northeastern Italy; the urban areas of Milan and Genoa, and the province of Forlì, in the north of the country; the provinces of Rome and Latina and the urban area of Naples in the south [44]. Cases had histologically confirmed colorectal cancer, diagnosed no longer than 1 year prior to the interview, and with no previous diagnoses of cancer at other sites. Anatomical subsites were defined as those specified at the individual four-digit level 153.0–154.1 and 159.0 of the *International Classification of Disease: 9th Revision* [45]. A total of 537 women with cancer of the colon (median age 61 years, range 24–74 years) and 291 with cancer of the rectum and recto-sigmoid junction (median age 62 years, range 24–74 years) were included in the study [44].

Controls were patients with no history of cancer admitted to major teaching and general hospitals in the same catchment areas. They had acute, non-neoplastic, non-gynaecological conditions, unrelated to hormonal or digestive tract diseases. They included 2081 women (median age 56 years, range 23–74 years) belonging to the following diagnostic categories: traumas, mostly fractures and sprains (27%); other orthopaedic disorders, such as low back pain and disc disorders (24%); acute surgical conditions (18%); eye diseases (24%); and other miscellaneous diseases, such as ear, nose and throat, skin and dental conditions (7%). The controls were somewhat younger than the cancer cases [44], but the age imbalance was carefully adjusted for in the statistical analyses (see below). Approximately 4% of cases and controls who were contacted during their hospital stay refused to be interviewed.

The same structured questionnaire and coding manual were used in each centre, and all interviewers were centrally trained and routinely supervised. Data checking for consistency and reliability was also conducted centrally. The questionnaire included information on sociodemographic characteristics, such as education and occupation, lifetime smoking and alcohol drinking habits, physical activity and body mass indices at various ages, a problem-oriented personal medical history and family history of cancer. Dietary habits were investigated through a validated food frequency consumption section.

Information was collected on menstrual and reproductive histories (e.g. age at menarche, characteristics of menstrual cycles, menopausal status, age at menopause, type of menopause, number of births, miscarriages and induced abortions, age at first pregnancy and birth). A history of the use of oral contraceptives, HRT and female hormones for other indications was also elicited, including information on age at first use, duration, and time since last use. Women were considered postmenopausal if they reported no menstrual periods in the 12 months prior to colorectal cancer diagnosis or hospital admission (controls) or had undergone hysterectomy and/or bilateral oophorectomy. Women who were experiencing signs of menopause (e.g. menstrual irregularities) were classified as perimenopausal and were grouped with premenopausal women, except for HRT use analyses. Pregnancies of fewer than 180 days were classified as miscarriages or induced abortions, according to whether they ended spontaneously or were voluntarily interrupted.

Odds ratios (OR), and the corresponding 95% confidence intervals (CI), were computed using unconditional multiple logistic regression models [46]. Women with cancer of the colon, but not the rectum, were significantly more educated and reported a lower level of physical activity than control women. Cases of both subsites had higher total energy intake than control women [44]. Therefore, all regression equations included terms for age (as a continuous variable and in quinquennia, in order to allow finer adjustment), study centre, years of education, physical activity and total energy intake.

Separate assessments in different strata of menopausal status, age (< 65 and ≥ 65 years), and study centre were performed. Colon cancer cases were also analysed separately according to whether the proximal colon (i.e. caecum, ascending, transverse colon and flexures) or the distal colon (i.e. descending or sigmoid colon) was reported as the subsite of origin.

RESULTS

The influence of menstrual characteristics is considered in Table 1. No clear associations of either colon or rectal cancer with age at menarche emerged. Women with colon cancer were more frequently postmenopausal than controls, and the risk was greater for menopause at age 50–52 years, as compared with earlier menopause (OR = 1.43, 95% CI 1.11–1.84), but was stable thereafter. Rectal cancer risk was not influenced by age at menopause. Artificial, instead of natural, menopause did not modify the risk of either subsite (Table 1). Duration or regularity of menstrual cycles and duration of menstrual bleeding did not influence cancer risk (not shown).

Reproductive variables are shown in Table 2. Among parous women, a significant trend of decreasing risk of colon, but not rectal, cancer with increasing number of births was seen (colon cancer OR for ≥ 4 births compared with 1 birth = 0.62, 95% CI 0.42–0.90). However, nulliparous women seemed at lower risk for rectal cancer than those with a single birth (OR = 0.65, 95% CI 0.42–1.02). Miscarriages

and induced abortions were not related to either colon or rectal cancer risk. Age at first birth showed a moderate direct association with cancer of the colon (OR for ≥ 28 years versus < 22 years = 1.31, 95% CI 0.99–1.72) as well as the rectum (OR = 1.39, 95% CI 0.99–1.96), although the risk trend was significant for colon cancer only (Table 2). After allowing for number of births, a higher age at first birth retained a borderline significance association (OR for ≥ 28 years versus

Table 1. *Odds ratio (OR)* and* 95% *confidence interval (CI) of colon and rectal cancer according to menstrual characteristics, Italy,* 1992–1996†

	Colon			Rectum			Controls
	n	OR	95% CI	*n*	OR	95% CI	*n*
Age at menarche (years)							
< 12	97	1‡		52	1‡		404
12–13	225	0.97	(0.73–1.27)	127	0.94	(0.67–1.33)	952
≥ 14	214	1.06	(0.79–1.40)	109	0.92	(0.64–1.32)	719
χ^2_1 for trend		0.29	$P = 0.59$		0.04	$P = 0.84$	
Menopausal status							
Premenopausal	87	1‡		49	1‡		647
Postmenopausal	450	1.88	(1.21–2.92)	240	1.11	(0.63–1.96)	1433
Age at menopause (years)							
< 50	176	1‡		106	1‡		691
50–52	164	1.43	(1.11–1.84)	85	1.10	(0.80–1.50)	453
≥ 53	109	1.39	(1.04–1.87)	48	0.89	(0.61–1.30)	285
χ^2_1 for trend		5.65	$P = 0.02$		0.10	$P = 0.75$	
Type of menopause							
Natural	365	1‡		194	1‡		1103
Artificial	85	0.91	(0.70–1.20)	45	0.91	(0.64–1.28)	324

*Estimates from multiple logistic regression equations, including terms for age, centre, education, physical activity and total energy intake. †Some strata do not add up to the total because of missing values. ‡Reference category.

Table 2. *Odds ratio (OR)* and* 95% *confidence interval (CI) of colon and rectal cancer according to reproductive characteristics, Italy,* 1992–1996†

	Colon			Rectum			Controls
	n	OR	95% CI	*n*	OR	95% CI	*n*
Number of births							
Nulliparae	84	0.87	(0.6–1.22)	35	0.65	(0.42–1.02)	323
1	112	1‡		64	1‡		422
2	180	0.81	(0.62–1.08)	93	0.74	(0.52–1.05)	713
3	101	0.81	(0.58–1.12)	51	0.73	(0.48–1.10)	370
≥ 4	58	0.62	(0.42–0.90)	45	0.86	(0.56–1.34)	252
χ^2_1 for trend		5.33	$P = 0.02$		0.04	$P = 0.84$	
Miscarriages							
0	404	1‡		226	1‡		1557
1	98	1.03	(0.79–1.33)	45	0.84	(0.59–1.19)	365
≥ 2	35	0.77	(0.52–1.15)	20	0.83	(0.50–1.36)	158
χ^2_1 for trend		0.81	$P = 0.37$		1.24	$P = 0.27$	
Induced abortions							
0	482	1‡		265	1†		1864
1	39	1.43	(0.96–2.13)	14	0.97	(0.54–1.75)	116
≥ 2	15	0.61	(0.34–1.09)	12	0.97	(0.52–1.83)	99
χ^2_1 for trend		0.38	$P = 0.54$		0.01	$P = 0.91$	
Age at first birth (years)							
< 22	79	1‡		53	1‡		449
22–24	124	1.17	(0.89–1.53)	67	1.16	(0.82–1.65)	485
25–27	123	1.35	(1.03–1.78)	60	1.20	(0.84–1.72)	416
≥ 28	127	1.31	(0.99–1.72)	76	1.39	(0.99–1.96)	407
χ^2_1 for trend		6.73	$P = 0.01$		2.02	$P = 0.15$	

*Estimates from multiple logistic regression equations, including terms for age, centre, education, physical activity and total energy intake. †Some strata do not add up to the total because of missing values. ‡Reference category.

< 22 years = 1.5, 95% CI 1.0–2.1 for colon cancer and 1.3, 95% CI 0.9–2.0 for rectal cancer).

The effect of number of births on colon cancer was re-examined for separate strata of age at diagnosis, level of education, physical activity, and colon subsite, yielding similar risk patterns (Table 3). The lowest risk estimates for women with four or more births emerged among younger and better educated women.

The relationship between oral contraceptive use and colorectal cancer risk was assessed only in women below 65 years of age (Table 4), since older women had, in Italy, little chance of using oral contraceptives in their fertile years. The risk of colon or rectal cancer was not modified significantly by oral contraceptive use (OR in ever users versus never users = 0.88, 95% CI 0.59–1.31 for colon, and 0.65, 95% CI 0.36–1.15 for rectum), including use at an early age or recent use.

Table 5 gives the numbers and ORs concerning the use of HRT and is restricted to peri- and postmenopausal women. HRT use did not influence the risk of colon cancer (OR = 1.0, 95% CI 0.69–1.46), while it was associated with a decreased risk for rectal cancer (OR = 0.56, 95% CI 0.31–1.01). Such protection was confirmed after exclusion, from the control group, of women admitted to hospital for traumas

Table 3. Odds ratio and 95% confidence interval (CI) of colon cancer by age, level of education and physical activity, and anatomical subsite, Italy,* 1992–1996

	Number of births (Odds ratio (95% CI))					
	Nulliparae	1†	2	3	≥ 4	χ^2_1 (trend)
Age (years)						
< 65	0.98 (0.64–1.49)	1	0.91 (0.64–1.28)	0.82 (0.55–1.24)	0.53 (0.32–0.90)	5.68 $P = 0.02$
≥ 65	0.69 (0.39–1.22)	1	0.66 (0.41–1.08)	0.76 (0.44–1.31)	0.70 (0.39–1.25)	0.52 $P = 0.47$
Education (years)						
< 7	0.85 (0.51–1.40)	1	0.75 (0.51–1.10)	0.82 (0.54–1.25)	0.67 (0.43–1.06)	1.49 $P = 0.22$
≥ 7	0.86 (0.54–1.36)	1	0.92 (0.61–1.39)	0.78 (0.45–1.34)	0.29 (0.11–0.74)	5.95 $P = 0.01$
Physical activity						
Low	0.82 (0.51–1.31)	1	0.85 (0.55–1.31)	0.65 (0.36–1.17)	0.55 (0.25–1.25)	4.89 $P = 0.03$
Intermediate or high	0.95 (0.58–1.55)	1	0.77 (0.53–1.11)	0.85 (0.56–1.26)	0.59 (0.38–0.94)	2.42 $P = 0.12$
Subsite‡						
Proximal	0.97 (0.54–1.76)	1	0.67 (0.40–1.12)	0.74 (0.40–1.37)	0.72 (0.36–1.44)	0.68 $P = 0.41$
Distal	0.87 (0.54–1.39)	1	0.82 (0.56–1.22)	0.94 (0.60–1.47)	0.83 (0.50–4.39)	0.46 $P = 0.50$

*Estimates from multiple logistic regression equations, including terms for age, centre, education, physical activity and total energy intake. †Reference category. ‡174 women with colon cancer of unspecified site of origin were excluded.

Table 4. Odds ratio (OR) and 95% confidence interval (CI) of colon and rectal cancer according to oral contraceptive use, Italy,* 1992–1996†

	Colon			Rectum			Controls
	n	OR	95% CI	*n*	OR	95% CI	*n*
Oral contraceptive use							
Never	289	1‡		162	1‡		1323
Ever	40	0.88	(0.59–1.31)	16	0.65	(0.36–1.15)	225
Age at first use (years)							
Never	289	1‡		162	1‡		1323
< 30	20	0.84	(0.49–1.44)	7	0.50	(0.22–1.15)	131
≥ 30	20	0.95	(0.56–1.61)	8	0.73	(0.34–1.58)	92
χ^2_1 for trend		0.26	$P = 0.61$		1.68	$P = 0.19$	
Duration of use (years)							
Never	289	1‡		162	1‡		1323
< 1	10	0.67	(0.33–1.37)	3	0.38	(0.11–1.28)	68
≥ 1	29	0.97	(0.62–1.53)	12	0.72	(0.38–1.38)	152
χ^2_1 for trend		0.05	$P = 0.82$		1.35	$P = 0.24$	
Time since last use (years)							
Never	289	1‡		162	1†		1323
< 10	9	0.74	(0.35–1.57)	5	0.85	(0.32–2.28)	72
≥ 10	29	0.91	(0.58–1.43)	10	0.56	(0.28–1.13)	143
χ^2_1 for trend		0.85	$P = 0.36$		0.04	$P = 0.84$	

*Estimates from multiple logistic regression equations, including terms for age, centre, education, physical activity and total energy intake. †Only women below age 65 years were included. Some strata do not add up to the total because of missing values. ‡Reference category.

Table 5. *Odds ratio (OR)* and* 95% *confidence interval (CI) of colon and rectal cancer according to hormone replacement therapy (HRT) use, Italy,* 1992–1996†

	Colon			Rectum			Controls
	n	OR	95% CI	*n*	OR	95% CI	*n*
HRT use							
Never	417	1‡		234	1‡		1421
Ever	41	1.00	(0.69–1.46)	13	0.56	(0.31–1.01)	147
Age at first use (years)							
Never	417	1‡		234	1‡		1421
< 50	26	1.10	(0.69–1.77)	7	0.51	(0.23–1.14)	88
≥ 50	14	0.79	(0.43–1.46)	6	0.62	(0.26–1.47)	59
χ^2_1 for trend		0.00	$P = 0.95$		3.67	$P = 0.06$	
Duration of use (years)							
Never	417	1‡		234	1‡		1421
< 1	18	0.93	(0.54–1.61)	8	0.75	(0.35–1.61)	73
≥ 1	21	1.06	(0.63–1.78)	5	0.42	(0.17–1.08)	70
χ^2_1 for trend		0.28	$P = 0.59$		1.82	$P = 0.18$	
Time since last use (years)							
Never	417	1‡		234	1‡		1421
< 10	22	1.49	(0.88–2.51)	5	0.61	(0.24–1.56)	69
≥ 10	17	0.68	(0.39–1.19)	8	0.56	(0.26–1.21)	74
χ^2_1 for trend		0.85	$P = 0.36$		1.48	$P = 0.22$	

*Estimates from multiple logistic regression equations, including terms for age, centre, education, physical activity and total energy intake. †Only peri- and postmenopausal women were included. Some strata do not add up to the total because of missing values. ‡Reference category.

and orthopaedic conditions (OR = 0.45, 95% CI 0.25–0.83) (not shown). A trend of decreasing risk with the increase of HRT use duration was present. A lowered risk from HRT use seemed to persist over time (OR for ≥ 10 years since last use = 0.68, 95% CI 0.39–1.19 for colon, and 0.56, 95% CI 0.26–1.21 for rectum).

DISCUSSION

This paper provides further quantitative estimates on the effects of reproductive and menstrual factors on colorectal cancer risk. Moderate inverse associations of colon cancer risk with the number of pregnancies or births were found, as in several other studies [8, 18, 20, 23, 24, 28, 32, 34], including a previous case–control study from Italy [15]. A lower age at first birth was associated with a lowered risk, even after allowing for number of births. Age at first pregnancy or birth did not emerge consistently as a determinant of risk in previous investigations, although it has been found in some studies [15, 19, 21, 28, 40].

While our results are of particular interest, because allowance for several risk covariates (e.g. education, physical activity and total energy intake) has been possible, they suggest that the relationship of colorectal cancer with reproductive factors is not a simple one. Multiparous women showed a significant reduction of colon cancer risk, but nulliparous women seemed also at a somewhat lower risk for colon as well as rectal cancer compared with women with a single birth.

An association of parity with colon cancer risk in men similar to the one seen in women was found in our study, with the highest risk in males with a single child, and a lowered risk in those with no children (OR = 0.7) or with four or more children (OR = 0.7). When parity effect estimates are similar in the two sexes, parity-related differentials in lifestyle factors are considered a more likely explanation than hormone-related ones [38]. Residual confounding by socioeconomic correlates is conceivable, since colon cancer has a direct social class correlation [1, 44]. In fact, albeit not restricted to, the apparent protection from multiparity seemed more marked among more educated women.

We did not confirm the suggestion by Slattery and colleagues [28] that age at cancer diagnosis may be an important modifier of reproductive factors, since the effect of parity was not greater in older women. Also, the role of parity seemed similar in the proximal and distal colon. It has been suggested that the composition of enterohepatically circulating bile acids should be reflected maximally in altered risk of cancer of the proximal colon [47]. Our findings, therefore, as well as those of a few previous studies which showed similar results by colon subsite [32, 33, 40], do not lend clear support to a specific effect of reproductive factors via bile acid alterations.

Age at menarche seemed to have no effect, as in most previous work, while age at natural menopause was directly associated with colon, but not rectal cancer risk. There is, however, little consistent evidence relating age at menopause with risk of colon or rectal cancer [13, 30, 40].

With respect to exogenous female hormones, our data suggest that the use of oral contraceptives does not alter colon cancer risk, whereas HRT may lower rectal cancer risk. The inverse association with ever use of HRT was significant, although caution is required due to the low numbers of users on whom the association was based (only 13 HRT users among rectal cancer cases and 147 among controls).

Overall, previous data on oral contraceptive use are consistent with lack of effect [37, 41] or moderate inverse associations [25, 40]. With respect to HRT, evidence of a favourable influence on colon and/or rectal cancer is more consistent. Furner and associates [14] (90 cases of colorectal and 208 controls) found an OR of 0.5 (95% CI 0.3–0.9) for colorectal cancer in HRT users, which seemed more marked

for rectal cancer. Jacobs and colleagues [30] (193 cases of colon cancer and 194 controls) reported a lowered risk in HRT users (OR = 0.6, 95% CI 0.4–1.0), particularly among women with more than 5 years of use (OR = 0.5, 95% CI 0.2–0.9). Newcomb and Storer [31] (694 cases of colorectal cancer and 1622 controls) found an inverse association between HRT and colorectal cancer risk which was particularly marked for colon cancer among recent users (OR = 0.5, 95% CI 0.3–0.9). Kampman and associates [33] (894 cases of colon cancer and 1120 controls) reported a lowered risk in HRT users (OR = 0.7, 95% CI 0.6–0.9). The protection from HRT appeared to be more pronounced for those with a higher age at diagnosis and for those with a relatively low body mass index [33]. Another Italian case–control study [42], which included 702 women with colorectal cancer from Milan, northern Italy, showed an OR of 0.4 for ever use of HRT, which, as in the present investigation, persisted at least up to 10 years since last use. Risks of colorectal cancer were also associated with past HRT use in the American Nurses' Health Study cohort (RR = 0.5, 95% CI 0.3–1.0) [37] and in the American Cancer Society prospective study (RR for fatal colon cancer in ever HRT users = 0.7, 95% CI 0.6–0.8) [43].

Finally, evidence of protective effects can also be derived from a few cohort studies of women on HRT. One was a cohort of approximately 40 000 postmenopausal women from the U.S.A. [48], where an adjusted RR of colon cancer of 0.8 (95% CI 0.6–1.1) in former users and 0.7 (95% CI 0.5–1.1) in current users emerged. Another study [49] included approximately 23 000 Swedish women and disclosed a significantly reduced mortality from colorectal cancer in HRT users (RR = 0.7, 95% CI 0.5–0.9). Results from the Breast Cancer Detection Demonstration Project cohort (approximately 40 000 postmenopausal women), U.S.A., did not show variations in colorectal cancer risk by ever use of HRT [41]. Some lowering of risk emerged, however, among recent HRT users of long duration, most notably for distal colon and rectal cancer [41].

Postulated mechanisms for HRT use included reduction of bile acid production or direct hormonal effect on the intestinal mucosa [1, 50]. However, at variance with cancer of the breast [49], the effects of HRT use and delayed menopause are not consistent for colorectal cancer. An increased chance of early detection of colorectal cancer in HRT users or former users is not likely, since colorectal cancer screening in Italy was uncommon in the study period.

Our study was hospital-based. The broad range of acute conditions, unrelated to hormonal or reproductive factors included among controls subjects should have avoided selection bias. Refusals to participate among cases and controls were very few and the results were consistent across the six Italian areas under study and when separate comparisons of cases with each of the major diagnostic categories of control were performed. Furthermore, the hospital setting should have improved the comparability of information on drug use [51], whereas it is unlikely that information bias had any noticeable impact on reproductive factors.

In conclusion, the association of colorectal cancer with reproductive and menstrual factors seems neither strong nor consistent in the available literature. The effect of parity reported in this study closely paralleled the one observed among men with cancer of the colon. Of importance are, however, the lack of colorectal cancer excess in oral contraceptive users and additional evidence that HRT use may confer a moderate, but persistent, reduction of rectal cancer risk.

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