A Prospective Study of Reproductive Factors, Oral Contraceptive Use, and Risk of Colorectal Cancer[1]

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Abstract

To explore the roles of reproductive factors and oral contraceptive use in the etiology of colorectal cancer, we examined incident cases of colorectal cancer (n = 501) that occurred during 1,012,280 person-years of follow-up between 1980 and 1992 in the Nurses' Health Study. The women completed mailed, self-administered questionnaires every 2 years to update information on the risk factors and major medical events. In multivariate analysis, the relative risk (RR) of colorectal cancer among women who experienced menarche at age 14 or older was 0.83 (95% confidence interval (CI) = 0.64–1.08) compared with women who had menarche at age 13; women whose menarche occurred under age 12 were at higher risk (RR = 1.22; 95% CI = 0.96–1.55, P for trend = 0.01). Compared with women whose first pregnancy was before age 24, the risk for colorectal cancer was significantly increased among women whose first pregnancy was at age 30 or older (RR = 1.57; 95% CI = 1.15–2.14; P for trend = 0.02). No important associations were seen for parity or age at menopause. Women who used oral contraceptives for 96 months or longer had a 40% lower risk of developing colorectal cancer (RR = 0.60; 95% CI = 0.40–0.89; P for trend = 0.02) compared with women who never used oral contraceptives. These prospective data suggest that a later age at menarche and use of oral contraceptives may reduce risk of colorectal cancer, whereas women with a later age at first pregnancy may have a higher risk.

Received 6/4/96; revised 10/16/96; accepted 10/16/96.

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[1] This work was supported by Faculty Research Award FRA-398 (to G. A. C.), Special Institution Grant No. 18 from the American Cancer Society, and Grants HL 35464 and CA40356 from NIH.

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Introduction

Interest in the role of female reproductive factors in the etiology of colorectal cancer originated from various lines of indirect evidence. Incidence and mortality rates of colon and breast cancers are positively correlated internationally (1, 2) as well as within countries (3, 4). Howell (2) has suggested that cancer of the colon may share common etiological factors with cancers of the breast and reproductive organs in women. Nuns, who experience higher-than-expected mortality rates for cancers of the breast, ovary, and uterus, have also been reported to have higher-than-expected rates of colon cancer (5). Also, in the Third National Cancer Survey (6), single women experienced a higher incidence rate of colon cancer than married women. Furthermore, incidence rates in men and women cross around the age of menopause with male rates, formerly lower, subsequently exceeding female rates (7).

Several mechanisms have been hypothesized to explain the association of female hormonal factors with colorectal cancer, including modifications of estrogen profile secondary to pregnancies and their effects on bile acid metabolism (7, 8), immunological effects of pregnancies (9), and increased physical activity associated with large families (10). McMichael and Potter (7) have further proposed in a study of time trends of colon cancer mortality that the generation of women that experienced both a substantial increase in fertility in the late 1950s and exposure to early high-dose oral contraceptives in the early 1960s subsequently experienced a transient decline in colon cancer mortality.

Results of the considerable number of analytic epidemiological studies on reproductive factors and colorectal cancer have been conflicting (8–38). Previously, we have reported data on this topic based on 8 years of follow-up of this cohort, including 240 cases of colorectal cancer (15). Given the scarcity of prospective studies, we present findings of reproductive factors and oral contraceptive use based on 12 years of follow-up as they relate to cancer of the colorectum that included an additional 261 cases.

Materials and Methods

The Nurses' Health Study. The Nurses' Health Study Cohort was established in 1976 when 121,700 female, married, registered nurses ages 30–55 responded to a mailed questionnaire. The questionnaire included information about suspected and established risk factors for cancer and cardiovascular disease and a variety of health conditions, including any previous cancer. Every 2 years, follow-up questionnaires are mailed to the participants to update risk factor information and to ascertain whether major medical events have occurred. In 1980, a dietary questionnaire was included.

Study Population. The present analysis is based on 89,448 women who completed the 1980 dietary questionnaire and who had no history of cancer (except nonmelanoma skin cancer), ulcerative colitis, or Crohn's disease in 1980. In 1992, more

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than 94% of the participants had responded to follow-up questionnaires. The 12-year follow-up analyses included 501 verified incident cases of colorectal cancer (396 colon and 105 rectal cancers), which accrued over the 1,012,280 person-years of follow-up.

Identification of Colorectal Cancer. The ascertainment of cases of colorectal cancer has been described in detail elsewhere (39). On each biennial follow-up questionnaire, we asked whether cancer of the colon or rectum has been diagnosed during the previous 2 years. We also used the National Death Index and the Postal Service to identify fatalities; we estimate that more than 98% of deaths were ascertained (40). When a participant (or next of kin for decedents) reported a diagnosis of cancer of the colon or rectum on our follow-up questionnaire, we asked her (or next of kin) for permission to obtain hospital records and pathology reports regarding this diagnosis. A study physician blinded to the exposure information reviewed the medical records to extract information on the histological type, the anatomic location, and the stage of the cancer. Cancers other than adenocarcinoma were excluded from analyses. We included 52 cases with missing information for anatomic location with the colon cancer group because the majority of colorectal cancers occur in the colon; analyses limited to colon cancer cases with complete information yielded results virtually identical to those of analyses including these cases.

Exposure Data. Responses to the baseline and biennial follow-up questionnaires were used to define exposure categories. Age at menarche was recorded by whole-number years; we excluded women whose reported age at menarche was ≤ 8 or ≥ 22. A complete history of oral contraceptive use, including dates of beginning and stopping use, was obtained from respondents and was categorized as never or ever (current or past use). Virtually all use in the follow-up period was past use. A history of parity was established if participants had one or more pregnancies lasting 6 months or longer; parous women were categorized by the number of pregnancies lasting 6 months or more. Age at first pregnancy was defined as age of first pregnancy lasting at least 6 months. We classified a woman as postmenopausal from the time she returned a questionnaire on which she reported natural menopause or hysterectomy with a bilateral oophorectomy. In addition, for women who reported hysterectomy without bilateral oophorectomy, we assigned their menopause to the age when natural menopause had occurred in 90% of the cohort (54 years for current cigarette smokers and 56 years for nonsmokers).

Statistical Analysis. For each participant, person-months of follow-up were computed from the month of return of the 1980 questionnaire to the date of colorectal cancer diagnosis, death from any cause, May 31, 1992, or whichever came first. For 1980–1982, person-months of follow-up were allocated according to exposure status in 1980, and for subsequent 2-year follow-up intervals, person-months were allocated after updating exposure information on each biennial questionnaire. Allocation to categories of age at menarche was made according to the 1976 questionnaire only. The report of menopausal status was updated every 2 years. For parity, age at first pregnancy, and use of oral contraceptives, exposure data were updated every 2 years up to 1984. Incidence rates were calculated as the number of cases in each category divided by the person-years in that category, and the rate ratio was computed as the incidence rate in a specified category divided by the incidence rate in the reference category. To obtain the most stable estimates of rate ratios, we used the mode of the group as the reference category: 13 for age at menarche, three pregnancies for parity, less than 24 for age at first pregnancy, and 48–51 for age at menopause. We calculated the 95% CI[4] for each rate ratio estimate. The Mantel extension test was used to evaluate linear trends across categories of exposure. The P values for the trends are two sided.

We used multiple logistic regression models to control simultaneously for several potentially confounding variables (41). Covariates that are a priori potential risk factors for colorectal cancer were included in the models. In the multivariate models, we included age (in six 5-year categories), history of colorectal cancer in a parent or sibling, body mass index (in five categories), cigarette smoking (pack-years of smoking more than 35 years before diagnosis), leisure-time physical activity (metabolic equivalents per week), aspirin use (times per week), postmenopausal hormone use (never, premenopausal, past use, or current use), and quintiles of intake of red meat and alcohol. Because several dietary factors have been shown to be associated with risk of colorectal cancer (42, 43), we used the follow-up period beginning in 1980 when the first dietary questionnaire was administered.

Results

Table 1 presents the multivariate RRs for colorectal, colon, and rectal cancer associated with age at menarche, parity, age at first pregnancy, and age at menopause. Results with age-adjusted models only were very similar to those from the multivariate models. A later age at menarche was associated with a lower risk for colorectal cancer. Compared with women who experienced menarche at age 13, the RR for those whose menarche occurred before age 12 was 1.22 (95% CI = 0.96–1.55), whereas that for those whose menarche occurred at age 14 or older was 0.83 (95% CI = 0.64–1.08). A statistically significant trend was observed across the categories ($P = 0.01$). The association between age at menarche and colon cancer was not substantially different from that for colorectal cancer, and no important association was seen for rectal cancer.

Because the proportion of nulliparous women in this cohort was low (7%), we restricted the analysis of parity to parous women. The RR for colorectal cancer for women who reported only one pregnancy lasting 6 months or more was 0.72 (95% CI = 0.48–1.07) compared with those reporting three pregnancies, whereas women who had more than four pregnancies had a RR of 1.13 (95% CI = 0.87–1.47). The P value across levels of parity was 0.10. Similar results were seen for colon and rectal cancer. No important association was seen for parity overall (RR = 1.06; 95% CI = 0.74–1.51, comparing parous to nonparous women).

Among parous women, those who reported a first pregnancy at age 30 or older had a RR for colorectal cancer of 1.57 (95% CI = 1.15–2.14) compared with those with an age at first pregnancy of under 24 (P for trend = 0.02). The corresponding RR for colon cancer was stronger (RR = 1.65; 95% CI = 1.16–2.33) and that for rectal cancer was weaker (RR = 1.24; 95% CI = 0.61–2.50).

As of 1990, 78% of the women in this cohort were postmenopausal. There was no consistent pattern for the relation between age at menopause and risk of colorectal cancer. Compared with women who experienced menopause at ages 48–51, a significantly lower risk for colorectal cancer was seen among women with an earlier age at menopause (RR = 0.56; 95% CI = 0.40–0.78) and among those with a later age at meno-

[4] The abbreviations used are: CI, confidence interval; RR, relative risk.

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Table 1 RR[a] for colorectal, colon, and rectal cancer by selected reproductive factors

Risk factor	Person-years[b]	Colorectum		Colon		Rectum	
		No. cases[b]	RR (95% CI)	No. cases	RR (95% CI)	No. cases	RR (95% CI)
Age at menarche							
<12	225,975	127	1.22 (0.96–1.55)	106	1.26 (0.97–1.64)	21	1.05 (0.60–1.83)
12	268,900	129	1.00 (0.79–1.26)	96	0.92 (0.70–1.20)	33	1.30 (0.80–2.14)
13	309,860	151	1.00	121	1.00	30	1.00
14+	199,450	88	0.83 (0.64–1.08)	68	0.80 (0.59–1.07)	20	0.96 (0.54–1.68)
P for trend[c]			0.01		0.01		0.56
Parity[d]							
1	72,304	31	0.72 (0.48–1.07)	25	0.72 (0.46–1.13)	6	0.70 (0.29–1.74)
2	279,797	116	0.87 (0.68–1.11)	87	0.82 (0.61–1.08)	29	1.06 (0.63–1.78)
3	273,957	139	1.00	110	1.00	29	1.00
4	165,837	71	0.76 (0.57–1.01)	58	0.79 (0.57–1.08)	13	0.65 (0.34–1.25)
>4	140,633	101	1.13 (0.87–1.47)	79	1.13 (0.84—1.51)	22	1.14 (0.64–2.00)
P for trend			0.10		0.08		0.85
Age at first pregnancy[d]							
<24	390,852	153	1.00	120	1.00	33	1.00
24–25	246,640	116	1.05 (0.82–1.33)	93	1.07 (0.81–1.40)	23	0.93 (0.55–1.59)
26–29	213,743	123	1.20 (0.94–1.53)	92	1.14 (0.86–1.50)	31	1.35 (0.82–2.24)
30+	80,668	66	1.57 (1.15–2.14)	54	1.65 (1.16–2.33)	12	1.24 (0.61–2.50)
P for trend			0.02		0.06		0.10
Age at menopause[e]							
<44	112,975	47	0.56 (0.40–0.78)	35	0.51 (0.35–0.75)	12	0.70 (0.36–1.37)
44–47	99,661	81	1.02 (0.78–1.34)	68	1.09 (0.81–1.46)	13	0.77 (0.41–1.47)
48–51	140,547	130	1.00	99	1.00	31	1.00
>51	107,055	80	0.70 (0.53–0.91)	63	0.71 (0.52–0.96)	17	0.65 (0.37–1.17)
P for trend			0.44		0.38		0.98

[a] Adjusted for age, body mass index, physical activity, family history of colorectal cancer, aspirin use, cigarette smoking, alcohol consumption, intake of red meat, oral contraceptive use, postmenopausal hormone use, and the other reproductive factors.
[b] Number of cases and person-years do not always add up to the total due to missing information for the risk factors.
[c] Test for trend conducted by modeling the variable as a continuous variable.
[d] Includes parous women only.
[e] Includes postmenopausal women only.

pause (RR = 0.70; 95% CI = 0.53–0.91). Similar results were observed for colon cancer and rectal cancer. When we stratified by postmenopausal hormone use, risk of colorectal cancer was not related to age at menopause among ever users (RR = 0.93, 1.48, 1.00, and 0.83) or nonusers (RR = 0.56, 0.82, 1.00, and 0.74). We also evaluated the association of age at menopause and colorectal cancer by type of menopause. Among women who experienced natural menopause (n = 39,031), the RRs for the categories of age at menopause were 0.45, 1.03, 1.00, and 0.73. Among women with surgical menopause (n = 28,053), the corresponding RRs were 0.92, 0.91, 1.00, and 0.63; however, the upper category included only five cases. Because we conducted these analyses among postmenopausal women only, we examined age at menopause among women over age 60. These results yielded substantially the same results, although with wider CIs reflecting the smaller sample size (RR = 0.70; 95% CI = 0.44–1.11 comparing upper to lower categories).

The prevalence of use of oral contraceptives in this cohort was 32%, and virtually all use was in the past. Compared with never use, ever use of oral contraceptives was associated with a lower risk for colorectal cancer (Table 2). Women who used oral contraceptives for 96 months or more were at significantly lower risk of developing colorectal cancer compared with never users (RR = 0.60; 95% CI = 0.40–0.89; *P* for trend = 0.02). The results for colon cancer were not appreciably different from those of the colorectum (RR = 0.64; 95% CI = 0.40–1.02 for 96 months or more of use compared with never users). The RR for rectal cancer associated with ever use of oral contraceptives was 0.76 (95% CI = 0.49–1.18); however, there were insufficient data to examine duration of use.

The hypothesis by McMichael and Potter (7) suggests that if the hormonal effect of reproductive factors is acting by altering bile acid synthesis, the risk of colon cancer would be stronger for the proximal colon where fecal bile acids are reabsorbed. However, our data do not support this. Although we were limited by the number of cases for this analysis (237 distal and 159 proximal cases), the RRs were stronger for the distal than the proximal colon (data not shown).

Discussion

On the basis of epidemiological and animal data, McMichael and Potter (7) proposed that progestins, pregnancy, and exogenous estrogens may reduce bile acid production, thereby affecting colon carcinogenesis. Specifically, they proposed that endogenous estrogens increase colon cancer through increased bile acid production, whereas progestins, pregnancy, and high-dose oral contraceptives decrease risk of colon cancer by reducing bile acid synthesis. This mechanism is plausible given the evidence that increased concentrations of unabsorbed bile acids in the colon and their derivatives, secondary bile acids, act as promoters of colon carcinogenesis (44). A direct effect of steroid hormones on the colorectal epithelium is plausible given the identification of steroid hormone receptors in colorectal cancers and normal epithelium (45–47).

These prospective data support the inverse association between age at menarche and risk of colorectal cancer. Of the studies that have examined this association (10, 12, 15, 18, 20, 21, 26, 30–32, 36, 37), two cohort studies (10, 26) reported a weak, nonsignificant inverse relation for age at menarche and

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Table 2 RR[a] for colorectal cancer according to oral contraceptive use and duration

	No. cases[c]	Person-years[c]	RR (95% CI)	*P* for trend[b]
Use				
Never	335	509,683	1.00	
Ever	166	498,648	0.84 (0.69–1.02)	
Duration (months)				
1–11	40	112,653	0.85 (0.61–1.19)	
12–35	43	126,984	0.95 (0.69–1.32)	
36–95	45	153,644	0.79 (0.57–1.09)	
96+	23	81,940	0.60 (0.40–0.89)	0.02

[a] Adjusted for age, body mass index, physical activity, family history of colorectal cancer, aspirin use, cigarette smoking, alcohol consumption, intake of red meat, postmenopausal hormone use, age at menarche, parity, age at first pregnancy, and age at menopause.
[b] Test for trend was conducted by modeling the median of each category for duration of use as a continuous variable and including the never users.
[c] Information on oral contraceptive use was missing for 3,948 person-years, and an additional 15 cases and 23,427 person-years were missing information on duration.

risk of colon cancer, and five case-control studies (20, 30, 32, 36, 37) support this inverse association. It is unknown whether the effect of age at menarche on colorectal cancer risk is mediated through a hormonal mechanism. It is possible that age at menarche is not directly related to risk of colorectal cancer, but is merely a surrogate for an unidentifiable risk factor present at or near puberty (*i.e.*, diet, body weight/body fat, or physical activity). Abdominal-type obesity is recognizable in girls even before puberty (48), and some studies have shown this to be associated with hyperinsulinemia resulting from insulin resistance (49, 50), and an earlier onset of menarche (51). Because insulin is an important growth factor for colonic mucosal cells and colonic cancer cells *in vitro*, Giovannucci (52) has suggested that hyperinsulinemia is a colon cancer promoter. It is unknown, however, to what extent one or more of these factors present during puberty can alter risk of colorectal cancer decades later. Thus, the complex metabolic, endocrine, and hormonal mechanisms taking place in the pubertal period are difficult to assess in the context of colon cancer carcinogenesis.

A large number of studies have investigated the effect of parity on colon cancer risk (8–37). However, in fewer than half of the 24 case-control studies has there been evidence of a protective effect of parity (8, 9, 14, 18, 20, 23, 25, 32, 35–37) and in only four of these (8, 18, 32, 35) were the associations significant. Only two (10, 24) of the seven published cohort studies have shown an inverse, albeit nonsignificant, effect for parity and colon cancer. It is interesting that two studies (24, 25) reported a protective effect of wife's parity among males. Our results do not support a protective association for the group of parous women. All but four (22, 26, 34, 37) of the published studies of parity have used the group of nulliparous women as the referent. In the present study, eligibility criteria included being married at the time of enrollment. It is possible that the nulliparous group comprised a higher proportion of infertile women than nulliparous women from a sample that included never-married women. It has been suggested that women who are unable to bear children have a hormone profile or other features that increase the risk of colon cancer (8). Although we have limited power to assess the association with nulliparity, we have substantial power to detect an association with parity among parous women.

Our results indicate that a later age at first pregnancy is associated with almost a 60% increase in risk for colorectal cancer. These data are supported by three of the six published cohort studies (15, 24, 26), although none of these was significant. Furthermore, 7 (8, 18, 22, 25, 30, 36, 37) of the 19 case-control studies reported a positive association, but in only two (8, 22) were the results significant.

In the present study, both an earlier (<44 years) and a later (>51 years) age at menopause were significantly associated with a lower risk of developing colorectal cancer compared with the age group of 48–51 years. Results of studies that have assessed the effect of age at menopause and colon cancer risk (10, 18, 20, 23, 26, 30–32, 36, 37) have been inconsistent, with approximately half reporting nonsignificant lower risks associated with higher age at menopause (10, 18, 30–32, 36). In one of these studies (36), the shape of the association was consistent with the results of our study.

To our knowledge, this is the first study to show a significant reduction in risk of colorectal cancer associated with use of oral contraceptives. Longer duration of use was associated with the lowest risk. Only two prospective (12, 15) and six case-control studies (8, 18–19, 23, 35, 38) have reported results for use of oral contraceptives and risk of colon or colorectal cancer. All but three (12, 35, 38) are consistent with the present study, but none was statistically significant. However, only four of these (8, 15, 23, 35) assessed duration of use, and none evaluated a period longer than 5 years. The majority of these studies is limited by small study samples. Since the introduction and first widespread use of oral contraceptives in the 1960s, the hormone dosages used have decreased substantially. Most of the oral contraceptive use among the members of this cohort took place at a time when relatively high doses were common.

The results of this study provide some support to the hormonal role of colorectal carcinogenesis in women. These suggest that an earlier age at first birth, but not a higher parity, is protective for colorectal cancer. Although our data suggest an inverse association between age at menarche and colorectal cancer, it is unknown to what extent this directly influences risk. Our findings also support the hypothesis by McMichael and Potter (7), which suggests that use of exogenous hormones, including high-dose oral contraceptives, lower the risk of colon cancer. Future studies are needed to assess the relation of oral contraceptives currently available as they relate to risk of colorectal cancer. A beneficial effect could be potentially important given the current widespread use of this method of contraception.

Acknowledgments

We thank Gary Chase, Karen Corsano, Lisa Dunn, Barbara Egan, Stefanie Parker, Kate Saunders, Mark Shneyder, and Lori Ward for their expert assistance.

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Cancer Epidemiol Biomarkers Prev 1997;6:1-5.

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