Oral contraceptives, hormone replacement therapy and the risk of colorectal cancer

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Summary The relationship between oral contraceptives (OCs), menopausal hormone replacement therapy (HRT) and the risk of colorectal cancer was investigated in a case–control study conducted in northern Italy between 1985 and 1992 on 709 women with incident colorectal cancer and 992 controls admitted to hospital for a wide spectrum of acute, non-neoplastic, non-digestive tract, non-hormone-related disorders. A reduced risk of colorectal cancer was observed in women who had ever used OCs (multivariate odds ratio (OR) = 0.58, 95% confidence interval (CI): 0.36–0.92). The OR was 0.52 (95% CI 0.27–1.02) for use over 2 years. For women ever using HRT, the multivariate OR was 0.40 (95% CI 0.25–0.66). The risk was inversely related to duration of use, with ORs of 0.46 for 2 years or less and 0.25 for more than 2 years of use. No consistent pattern of trends was observed with dose (first or last use). This study provides, including informal OC and HRT do not increase, and possibly decrease, the risk of colorectal cancer. These results, if confirmed, would have important implications for the ultimate risk–benefit assessment of female hormone preparations.

Keywords: oral contraceptive; hormone replacement therapy; large-bowel cancer; epidemiology

Cancer of the large bowel is the second leading site of cancer in women (WHO, 1992) and over the last few decades its incidence and mortality trends have been consistently more favourable in women than in males in North America and in most western European countries (Ries et al., 1991; La Vecchia et al., 1992). This may be due to a healthier dietary and lifestyle pattern in women, but also to a potential protective effect of exposure to (exogenous) female hormones in women. Such an effect of female sex hormones on colorectal carcinogenesis is biologically plausible, as they influence hepatic cholesterol metabolism and bile production (McMichael and Potter, 1980), and steroid hormone receptors have been found in colorectal cancers and normal colonic mucosa (Singh et al., 1993; Hendrickse et al., 1993). Furthermore, an inverse relationship between parity and colorectal cancer risk (Potter and McMichael, 1983), as well as an increased incidence of colorectal cancer in nuns (Fraumeni et al., 1969), has been reported.

Several cohort and case–control studies have investigated reproductive factors and colorectal cancer in women (La Vecchia and Franceschi, 1991; Potter et al., 1993) but only few have considered use of oral contraceptives and/or hormone replacement therapy (Potter and McMichael, 1983; Wu et al., 1987; Adami et al., 1989; Chute et al., 1991; Bostick et al., 1994; Weiss et al., 1981; Rosenberg et al., 1987; Davis et al., 1989; Furnet et al., 1989; Peters et al., 1990; Kune et al., 1990; Wu-Williams et al., 1991; Gerhardsson de Verdier and London, 1992; Newcomb and Storer, 1995; Jacobs et al., 1994; Risch and Howe, 1995; Calle et al., 1995; Folsom et al., 1995). Among these, two studies have reported some (although inconsistent) increased risk of colorectal cancer among women who had used oral contraceptives (OCs) (Weiss et al., 1981; Kune et al., 1990), and one showed a moderate protection (Potter and McMichael, 1983). In six studies an inverse relationship was observed for hormone replacement therapy (HRT) (Chute et al., 1991; Furner et al., 1989; Gerhardsson de Verdier and London, 1992; Jacobs et al., 1994; Newcomb and Storer, 1995; Calle et al., 1995). In summary, most evidence suggests that OC and HRT use do not increase the risk of colorectal cancer, and some data even indicate a possible protective effect of HRT.

Given the widespread use of OCs and HRT in developed countries, it is a major public health issue to further elucidate this relationship. Thus, this investigation was aimed at assessing the relationship between OC and HRT use and colorectal cancer, using data from a case–control study conducted in northern Italy.

Subjects and methods

The data were derived from a case–control study of colorectal cancer conducted in northern Italy, based on a network of teaching and general hospitals in the Greater Milan area (the largest urban area in northern Italy, with approximately 4 million inhabitants), and the province of Pordenone, in north-east Italy. Recruitment of colorectal cases and of the corresponding controls began in January 1985, and the present analysis is based on data collected before June 1992.

The general design of this investigation has been described previously (Negri et al., 1989; Franceschi et al., 1991). Briefly, trained interviewers identified and questioned cases of colorectal cancer and controls admitted to hospital using a structured questionnaire, including information on socio-demographic factors, personal characteristics and lifestyle habits (such as smoking, alcohol, coffee and other methylxanthine-containing beverage consumption), frequency of consumption of 29 indicator foods, and a problem-oriented medical history. For women, information was also collected on menstrual and reproductive factors, and on use of oral contraceptives, non-contraceptive oestrogens for menopausal replacement therapy and female hormones for other indications. The time of each episode of use was noted, together with the brand name, whenever available.

Cases

The cases included in the present analysis were 709 women aged less than 75 years (median age, 61 years) with histologically confirmed incident (i.e. diagnosed within the year before
interview) cancers of the colorectum. They were admitted to the National Cancer Institute, to several university hospitals, or the Ospedale Maggiore of Milan, which includes the four largest teaching and general hospitals in Milan, to the Aviano Cancer Center and to all other general hospitals in the area of Pordenone. All the interviews were conducted in hospital, and restricted to identified surviving patients.

Controls
The comparison group included 992 women aged less than 75 years (median age, 58 years) admitted for a wide spectrum of acute, non-neoplastic, non-digestive, non-hormone-related disorders to the same network of hospitals in which cases were recruited. Forty per cent were admitted for traumatic conditions, 20% had non-traumatic orthopaedic disorders, 16% had acute surgical conditions, 13% eye conditions and 11% had other miscellaneous diseases, such as ear, nose and throat, skin, or dental disorders. About 80% of cases and controls resided in the same regions, Lombardy and Friuli Venezia-Giulia, and more than 90% came from northern Italy. As for cases, all the data were collected by direct interview during a hospital stay. Less than 3% of subjects approached (cases and controls) refused to be interviewed.

Data analysis and control for confounding
Odds ratios (ORs), as estimators of relative risks, together with the corresponding 95% confidence intervals (CIs), for various measures of use of OCs and HRT were derived from unconditional multiple logistic regression equations, fitted by the method of maximum likelihood (Breslow and Day, 1980; Baker and Nelder, 1978). Since separate analysis of colon and rectal cancer provided similar results, only combined ORs are shown. The variables included in the regression equations were age (in decades, except for the first group defined by age <40 years), area of residence, social class (based on the head of the household's occupation), family history of colorectal cancer, age at menarche (≤11, 12–14, ≥15 years) and parity (0, 1, 2, 3 ≥4 births). Allowance for other potential confounding variables (total energy intake; an indicator variable of food consumption score based on a diet rich in cereals and poor in vegetables and fruit; meat and alcohol consumption; fat intake; body mass index; and smoking) did not substantially modify any of the estimates. Allowance for physical activity was not possible since the questionnaire used did not comprise this factor.

Results
The distribution of colorectal cancer cases and controls according to age and selected covariates is shown in Table I. No significant difference was observed in social class and parity, but cases more frequently reported a family history of colorectal cancer (OR = 1.80; 95% CI: 1.17–2.77), and an early menarche (OR for ≥15 years vs ≤11 years = 0.56; 95% CI: 0.39–0.79).

Various measures of OC use are considered in Table II. A total of 30 (4.2%) cases and 92 (9.3%) controls had ever used OCs, yielding a multivariate OR of 0.58 (95% CI: 0.36–0.92), and of 0.52 (95% CI: 0.27–1.02) for use >2 years. The OR was 0.74 in women who had begun to use OCs 15 years ago or less, and 0.42 for women who had begun more than 15 years ago. The OR was 0.64 for women who had stopped OC use 10 or less years ago, and 0.48 for those who had stopped 10 or more years ago.

HRT is considered in Table III. Twenty-three (3.2%) cases vs 75 (7.6%) controls reported having ever used HRT, corresponding to an OR of 0.40 (95% CI: 0.25–0.66). The risk was inversely related to duration of use, with an OR of 0.46 (95% CI: 0.27–0.80) for 2 or less years and 0.25 (95% CI: 0.08–0.77) for more than 2 years of use. Similarly to OC use, no consistent pattern of trends was observed with reference to time since first or last HRT use.

No interaction was apparent when the association between OCs, HRT and colorectal cancer was investigated in separate strata of age at diagnosis (<60, ≥60 years), menopausal status (pre, post-menopausal) and parity (0, 1–2, ≥3 births).

| Table I Distribution of 709 female cases of colorectal cancer and 992 controls according to age and selected covariates, Italy, 1985–92 |
|---|---|---|
| Age (years) | Colorectal cancer | Controls |
| | n (%) | n (%) |
| <40 | 41 (5.8) | 106 (10.7) |
| 40–49 | 78 (11.0) | 163 (16.4) |
| 50–59 | 193 (27.2) | 278 (28.0) |
| 60–69 | 253 (35.7) | 339 (34.2) |
| ≥70 | 144 (20.3) | 106 (10.7) |
| Social class | | |
| Professional and managerial | 50 (7.0) | 88 (8.9) |
| Non-manual and manual skilled | 251 (35.4) | 348 (35.1) |
| Manual non-skilled | 309 (43.6) | 442 (44.6) |
| Farmers | 26 (3.7) | 26 (2.6) |
| Other, not classified | 73 (10.3) | 88 (8.8) |
| Family history of colorectal cancer* | | |
| No | 659 (92.9) | 951 (95.9) |
| Yes | 50 (7.1) | 41 (4.1) |
| Age at menarche (years) | | |
| ≤11 | 119 (16.8) | 152 (15.3) |
| 12–14 | 487 (68.7) | 640 (64.5) |
| ≥15 | 103 (14.5) | 200 (20.2) |
| Parity | | |
| Nulliparæ | 129 (18.2) | 195 (19.6) |
| 1 | 166 (23.4) | 218 (22.0) |
| 2 | 213 (30.1) | 330 (33.3) |
| 3 | 154 (21.7) | 182 (18.3) |
| ≥4 | 47 (6.6) | 67 (6.8) |

*In first-degree relatives.
The study indicates that... consistent time-risk relationship. The data presented here are consistent with the observation that female hormones are protective against colorectal carcinogenesis, and may be related to the hypothesis that exogenous female hormones confer a protection against colorectal cancer as a result of changes in bile acids and lipids (McMichael and Potter, 1980; Potter and McMichael, 1983; McMichael and Potter, 1985). One limitation of the present investigation is the lack of...
information on specific subites of origin of the neoplasm in the colon. However, separate analysis of colon and rectal cancer did not show appreciable differences in the risk pattern.

Further, this is a typical case-control study and, as such, has all the related limitations and strengths (Breslow and Day, 1980). Among the strengths of the study, the comparable catchment area of cases and controls (i.e. control subjects would have been referred, if affected by colorectal cancer, to the same hospitals where cases were identified), together with the almost complete participation, are reassuring against selection bias. A distortion of the observed OR, by over-estimation of the risk cannot be disregarded, as 40% of controls were admitted for traumatic conditions, and the use of HRT has been associated with a protective effect against osteoporotic fractures (Meyer et al., 1993; Hutchinson et al., 1979). However, separate comparison of cases with each of the major diagnostic categories of controls yielded similar results, thus providing reassurance against potential selection bias. Cases and controls were directly interviewed in the same setting, thus allowing reasonably comparable information to be obtained. This may be particularly relevant for reporting history of drug use, since cases and hospital controls are similarly sensitised towards recalling medical information (Colombo et al., 1977; Kelly et al., 1990).

Information bias is unlikely to have led to a systematic underreporting of hormone use by cases, because a potential relationship between female hormones and colorectal cancer risk was unknown to the interviewers and probably to the subjects interviewed. With reference to confounding, the results were virtually unmodified after allowance for several covariates, including body mass index, total energy intake and other dietary indicators. As the cases are somewhat older than the controls, it is possible that the cases had less opportunity to be treated with HRT. No temporal confounding effect by the calendar time of advent of HRT was apparent, however, after the analysis in separate age strata (i.e. OR = 0.31 among women aged <60 years and OR = 0.44 among women aged ≥60 for ever vs never HRT use). Still, the results might be confounded owing to the fact that women using OCs and HRT have greater access to medical care and are more likely, at least in principle, to be screened for colorectal cancer. This would however have biased the observed effect towards reducing any protective effect.

From the data presented, and according to previous research (Potter and McMichael, 1983; Potter et al., 1993; Furner et al., 1989; Chute et al., 1991; Gerhardsen de Verder and London, 1992; Jacobs et al., 1994; Calle et al., 1995; Newcomb and Storer, 1995) it is clear that OCs and HRT do not elevate the risk of colorectal cancer. Indeed, these results would suggest a protective role of these female hormone preparations on colorectal cancer risk. These findings are consistent with the descriptive epidemiology of the disease, showing declining trends in women over recent decades in several developed countries, and might have important public health implications for the ultimate risk–benefit evaluation for female hormone preparation use.

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