Reproductive and Menstrual Factors and Risk of Colorectal Cancer

Eva Negri, Carlo La Vecchia, Fabio Parazzini, Renzo Savoldelli, Antonella Gentile, Barbara D'Avanzo, Annamaria Gramenzi, and Silvia Franceschi

INTRODUCTION

There are considerable similarities in the epidemiology of cancers of the colorectum and breast (1, 2). Incidence of and mortality from these neoplasms are positively correlated on both an international (3) and intranational scale (4). Further, there are consistent and similar correlations between rates from these neoplasms and per capita gross internal product, total fat, animal fat, animal protein, meat, milk, and dairy products consumption (5–7).

These epidemiological similarities may thus be explained in terms of similar dietary correlates, but little is known about the relation of any specific aspect of diet to the occurrence of either breast or intestinal cancers, and other risk factors may be important as well.

Reproductive factors have been associated with breast cancer for over two centuries (8), but evidence has recently been produced suggesting associations between reproductive factors and female colon cancer, too (9). Analyses of rates of various cancers in nuns (10), and data from case-control studies found an inverse relation with parity and a direct one with age at first birth (11–14). Some influence of reproductive factors on intestinal carcinogenesis is biologically plausible, since female sex hormones influence hepatic cholesterol metabolism and bile production (9), and estradiol and progesterone receptors have been found in colorectal cancers (15), but epidemiological evidence is not totally consistent. At least three formal case-control studies (16–18), however, including the largest one (16), found no association between parity or age at first birth and intestinal cancer in females, while a cohort investigation (19) found an association with parity for both females and males, casting doubts on the biological causality of the relation.

To provide further epidemiological data on the issue, we consider in this article the relation between reproductive and menstrual factors and female colorectal cancer, using data from a case-control study conducted in Northern Italy.

SUBJECTS AND METHODS

The data considered were derived from an on-going case-control study of digestive tract neoplasms, based on a network of teaching and general hospitals of the Greater Milan area. Recruitment of cases of colorectal cancer started in January 1985 and the present report is based on data collected before December 1988.

The general design of this investigation has already been described in a paper on dietary factors (20). Briefly, trained interviewers identified and questioned subjects admitted to university and general hospitals in the area under surveillance for cancers of the colorectum, and for a wide spectrum of other conditions. On the average, less than 2% of eligible subjects (cases and controls) refused to be interviewed.

The structured questionnaire included information on sociodemographic factors and general lifestyle habits (smoking, coffee, and alcohol consumption), a brief diet history including 29 indicator foods, a problem-oriented medical history, and history of use of selected drugs. For women, information was obtained on menstrual factors (age at menarche, type and age at menopause, and menstrual cycle patterns), reproductive variables (number of births, of spontaneous and induced abortions, age at first pregnancy, at first and last birth), and use of female hormone preparations for contraception or other purposes.

Cases. The cases were women below the age of 75 with histologically confirmed cancer of the colon or rectum whose original diagnosis dated back no more than 1 year before interview ("incident cases"), who had been admitted to the National Cancer Institute, to several specialized university clinics and to the Ospedale Maggiore, which includes the four largest teaching and general hospitals in Milan. A total of 279 women with colon cancer (aged 32–74, median age 61 years) and 153 with rectal cancer (aged 34–74, median age 62 years) were considered for the present analysis.

Controls. The controls were women admitted to the Ospedale Maggiore and the same network of university clinics for a wide spectrum of acute diseases. They were included for diseases other than neoplasms, digestive tract disorders, or any condition related to alcohol or tobacco. A total of 386 controls aged 28 to 74 (median age, 61 years) were interviewed. Among them, 48% were admitted for traumatic conditions (not directly related to alcohol), 22% had nontraumatic orthopaedic disorders, 15% acute surgical diseases (including plastic surgery) and 15% various other illnesses, such as ear, nose and throat, skin, or dental disorders.

The catchment area of cases and controls was comparable: overall, 83% of the cases and 78% of the controls came from the same region; Lombardy, 86% of the cases and 83% of the controls from northern Italy.
Data Analysis. The relative risks of cancer of the colon and rectum, together with their 95% approximate confidence intervals, were first derived from data stratified for decade of age by the usual Mantel-Haenszel procedure (21). Secondly, to account simultaneously for the potential confounding effect of age, geographical area, marital status, education, and smoking, multiple logistic regression models were used, fitted by the method of maximum likelihood (22). The significance of the trends in risk was based on chi-square values for trend, computed, in the logistic models, considering the recoded factors as continuous terms (22, 23).

RESULTS

The distribution of cases of cancer of the colon, rectum, and controls according to age and selected covariates is given in Table 1. There was no appreciable difference in relation to marital status, but cases tended to be somewhat less educated and less frequently smokers. Although, after allowance for age, none of the differences was statistically significant, the potential confounding effect of all these covariates was allowed for in multivariate analyses.

Table 2 gives the absolute number and percentage distribution of cases and controls according to the reproductive and men- strual factors considered. The corresponding relative risks are given in Table 3 for reproductive and Table 4 for menstrual factors.

There was no consistent association between parity and colorectal cancer. Compared with nulliparous women, the age-adjusted relative risks of colon cancer were 1.1 for one and two births, 1.3 for three or four and 1.1 for five or more. Corresponding values for rectal cancer were 0.9 for one, 1.1 for two, 1.4 for three or four and 0.8 for five or more livebirths. Likewise, no consistent relation emerged with number of abortions.

With reference to age at first birth, compared to women who first gave birth at age 20 or less, the point estimates tended to be above unity for colon and below unity for rectal cancer, but no consistent trend in risk emerged. Likewise, in relation to age at last birth, the point estimates were above unity for all subsequent age groups above 25, but, again, there was no consistent pattern of trends for colon or rectal cancer.

Women whose menarche occurred at age 15 or over were at significantly reduced risk of colon cancer and the point estimate was below unity (though nonsignificantly) for right colon (13). Evidence on anatomical subsites, moreover, is largely inconsis-
tent: for instance, in a case-control study where an association appeared to have a greater effect on right colon cancer, and age at last birth for either site.

One limitation of this study lies in the absence of information on anatomical subsites, since it has been suggested that the influence of sex hormones should be greater, or restricted, to the right side of the colon (9, 13, 24–28). The lack of any overall association, however, provides little scope for etiological inferences on subsites. Direct epidemiological evidence on anatomical subsites, moreover, is largely inconsistent: for instance, in a case-control study where an association was found between large bowel cancer and reproduction, parity appeared to have a greater effect on right colon cancer, and age at first birth on the left colon (13).

DISCUSSION

The present study provided no evidence that reproductive factors are related to colorectal cancer in this population. With this sample size, it was possible to exclude relative risks compared to nulliparae below 0.8 for women with three or more births for colon cancer, and below 0.7 for cancer of the rectum, and there was no evidence of trend in risk with age at first or last birth for either site.

One limitation of this study lies in the absence of information of specific subsites of origin in the colon, since it has been suggested that the influence of sex hormones should be greater, or restricted, to the right side of the colon (9, 13, 24–28). The lack of any overall association, however, provides little scope for etiological inferences on subsites. Direct epidemiological evidence on anatomical subsites, moreover, is largely inconsistent: for instance, in a case-control study where an association was found between large bowel cancer and reproduction, parity appeared to have a greater effect on right colon cancer, and age at first birth on the left colon (13).

The absence of positive findings could be related to other
potential biases in the study, which was a typical hospital-based case-control study and, as such, has all the relative strengths and weaknesses. It is unlikely however, that information, selection, or confounding biases played any major role, since (a) information on reproductive factors is usually reliable; (b) cases and controls came from comparable catchment areas (i.e., controls subjects would probably have been referred, if affected by colorectal cancer, to the hospitals where cases were identified, and participation was almost complete; (c) the distribution of major variables of interest was similar across various diagnostic categories: for instance, women with three or more births were included), they had diseases requiring hospital admission, and participation was almost complete; (d) the reduced risk of colon cancer among women whose menarche occurred at age 15 or over. The result was statistically significant, and the pattern of risk, with an apparent threshold effect around age 15, was similar to that observed for breast cancer in this and other populations (29, 31, 32). This may suggest a role of nutrition in childhood and adolescence on subsequent colorectal cancer risk. In consideration of the inconsistent findings on other menstrual and reproductive factors considered, it is nonetheless inappropriate to draw any etiological or biological inference from this single positive result.

In conclusion, this study, although largely negative, in consideration of the relatively large size of the dataset, provides further important documentation on the intestinal cancer/reproductive and hormonal factor issue. The definition and general applicability of any potential association to various populations, as shown by the inconsistencies from published studies, is however still largely unsettled.

Table 3 Relation between reproductive factors and cancers of the colon and rectum. Milan, Italy, 1985-1988

<table>
<thead>
<tr>
<th>Variables</th>
<th>M-H&lt;sup&gt;a&lt;/sup&gt;</th>
<th>M-H&lt;sup&gt;b&lt;/sup&gt;</th>
<th>M-H&lt;sup&gt;c&lt;/sup&gt;</th>
<th>M-H&lt;sup&gt;d&lt;/sup&gt;</th>
<th>M-H&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of births</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1.00 (0.89-1.12)</td>
<td>1.00 (0.89-1.12)</td>
<td>1.00 (0.89-1.12)</td>
<td>1.00 (0.89-1.12)</td>
<td>1.00 (0.89-1.12)</td>
</tr>
<tr>
<td>1</td>
<td>1.05 (0.86-1.28)</td>
<td>1.05 (0.86-1.28)</td>
<td>1.05 (0.86-1.28)</td>
<td>1.05 (0.86-1.28)</td>
<td>1.05 (0.86-1.28)</td>
</tr>
<tr>
<td>2</td>
<td>1.07 (0.88-1.29)</td>
<td>1.07 (0.88-1.29)</td>
<td>1.07 (0.88-1.29)</td>
<td>1.07 (0.88-1.29)</td>
<td>1.07 (0.88-1.29)</td>
</tr>
<tr>
<td>3-4</td>
<td>1.27 (1.08-1.51)</td>
<td>1.27 (1.08-1.51)</td>
<td>1.27 (1.08-1.51)</td>
<td>1.27 (1.08-1.51)</td>
<td>1.27 (1.08-1.51)</td>
</tr>
<tr>
<td>≥5</td>
<td>1.10 (0.90-1.35)</td>
<td>1.10 (0.90-1.35)</td>
<td>1.10 (0.90-1.35)</td>
<td>1.10 (0.90-1.35)</td>
<td>1.10 (0.90-1.35)</td>
</tr>
<tr>
<td>χ&lt;sup&gt;2&lt;/sup&gt; (trend)</td>
<td>0.39 (NS)</td>
<td>0.39 (NS)</td>
<td>0.39 (NS)</td>
<td>0.39 (NS)</td>
<td>0.39 (NS)</td>
</tr>
</tbody>
</table>

Table 4 Relation between menstrual factors and cancers of the colon and rectum. Milan, Italy, 1985-1988

<table>
<thead>
<tr>
<th>Variables</th>
<th>M-H&lt;sup&gt;a&lt;/sup&gt;</th>
<th>M-H&lt;sup&gt;b&lt;/sup&gt;</th>
<th>M-H&lt;sup&gt;c&lt;/sup&gt;</th>
<th>M-H&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at menarche (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12-14</td>
<td>1.00 (0.89-1.12)</td>
<td>1.00 (0.89-1.12)</td>
<td>1.00 (0.89-1.12)</td>
<td>1.00 (0.89-1.12)</td>
</tr>
<tr>
<td>≥15</td>
<td>1.00 (0.89-1.12)</td>
<td>1.00 (0.89-1.12)</td>
<td>1.00 (0.89-1.12)</td>
<td>1.00 (0.89-1.12)</td>
</tr>
<tr>
<td>χ&lt;sup&gt;2&lt;/sup&gt; (trend)</td>
<td>0.02 (NS)</td>
<td>0.02 (NS)</td>
<td>0.02 (NS)</td>
<td>0.02 (NS)</td>
</tr>
</tbody>
</table>

Table 5 Relation between menstrual factors and cancers of the colon and rectum. Milan, Italy, 1985-1988

<table>
<thead>
<tr>
<th>Variables</th>
<th>M-H&lt;sup&gt;a&lt;/sup&gt;</th>
<th>M-H&lt;sup&gt;b&lt;/sup&gt;</th>
<th>M-H&lt;sup&gt;c&lt;/sup&gt;</th>
<th>M-H&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at menopause (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;45-49</td>
<td>1.00 (0.89-1.12)</td>
<td>1.00 (0.89-1.12)</td>
<td>1.00 (0.89-1.12)</td>
<td>1.00 (0.89-1.12)</td>
</tr>
<tr>
<td>≥50</td>
<td>1.00 (0.89-1.12)</td>
<td>1.00 (0.89-1.12)</td>
<td>1.00 (0.89-1.12)</td>
<td>1.00 (0.89-1.12)</td>
</tr>
<tr>
<td>χ&lt;sup&gt;2&lt;/sup&gt; (trend)</td>
<td>0.02 (NS)</td>
<td>0.02 (NS)</td>
<td>0.02 (NS)</td>
<td>0.02 (NS)</td>
</tr>
</tbody>
</table>

Potential biases in the study, which was a typical hospital-based case-control study and, as such, has all the relative strengths and weaknesses. It is unlikely however, that information, selection, or confounding biases played any major role, since (a) information on reproductive factors is usually reliable; (b) cases and controls came from comparable catchment areas (i.e., confounding factors did not materially modify any of the results.

Further, a case-control study of breast cancer conducted in the same population and using the same design and method found a consistent direct relation with age at first birth, and a significantly lower risk in multiparous women (29). Finally, the proportion of nulliparous women in our control population was 11.9% among married women. This is comparable with the figure of 12.5% given by the last National Fecundity Survey (30), where only figures for married women were given.

The hypothesis that reproductive and hormonal factors might be related to the risk of intestinal cancer probably originated from the similarities in the descriptive and ecological epidemiology of cancers of the intestines and breast (1-6). Only one of the results of this study was in agreement with available knowledge on breast cancer epidemiology, i.e., the reduced risk of colon cancer among women whose menarche occurred at age 15 or over. The result was statistically significant, and the pattern of risk, with an apparent threshold effect around age 15, was similar to that observed for breast cancer in this and other populations (29, 31, 32). This may suggest a role of nutrition in childhood and adolescence on subsequent colorectal cancer risk. In consideration of the inconsistent findings on other menstrual and reproductive factors considered, it is nonetheless inappropriate to draw any etiological or biological inference from this single positive result.

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REFERENCES

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