64. McThernan A, Weiss NS, Daling JR. Incidence of thyroid cancer in women in relation to known or suspected risk factors for breast cancer. *Cancer Res* 1987, **47**, 292.
65. Bielschowsky F. Neoplasia and internal environment. *Br J Cancer* 1955, **9**, 80.
66. Swelstadt J, Scanlon ER, Murphey ED. Thyroid disease following irradiation for benign conditions. *Arch Surg* 1977, **112**, 380.
67. Lindsay S, Sheline GE, Potter GD, Chaikoff L. Induction of neoplasms in the thyroid on the rats by X-irradiation of the gland. *Cancer Res* 1961, **21**, 9.
68. Strand SE, Erlandsson K, Löwenhielm P. Thyroid uptake of iodine-131 and iodine-133 from Chernobyl in the population of Southern Sweden. *J Nucl Med* 1988, **29**, 1719.
69. Conard RA. Summary of thyroid findings in Marshallese 22 years after exposure to radioactive fallout. In DeGroot LJ, ed. *Radiation-associated Thyroid Carcinoma*. New York, Grune & Stratton, 1977, 241.
70. Conard RA, Dobyns BM, Sutow WW. Thyroid neoplasia as late effect of exposure to radioactive iodine in fallout. *JAMA* 1975, **232**, 1356.
71. Ramalingaswami V. Iodine and thyroid cancer in man. In Hedinger C, ed. *Thyroid Cancer*. Berlin, Springer, 1969.
72. Franssila KO, Harach R. Occult papillary carcinoma of the thyroid in children and young adults. A systemic autopsy study in Finland. *Cancer* 1986, **58**, 715.
73. Doll R, Payne P, Waterhouse J. *Cancer Incidence in Five Continents*. Berlin, Springer, 1966, 512.
74. Buttfield JH, Hetzell BS. Endemic goiter in Eastern New Guinea with special reference to the use of iodised oil in prophylaxis and treatment. *Bull World Health Org* 1967, **36**, 243.
75. Ramalingaswami V. Endemic goitre. In Pitt-Rivers R, Trotter WR, eds. *The Thyroid Gland*. London, Butterworths, 1964, 71.
76. Studer H, Hunziker HR. Ätiologie, Pathogenese und Diagnostik des Kropfes. *Helv Chir Acta* 1977, **44**, 699.
77. Correa P, Cuello C, Eisenberg H. Epidemiology of different types of thyroid cancer. In Hedinger C, ed. *Thyroid Cancer*. Berlin, Springer, 1969, 81.
78. Riccabona G. Epidemiologie der Struma maligna. *Schweiz Rundschau Med* 1982, **71**, 523.
79. Funkunaga FH. Occult thyroid cancer. In DeGroot LJ, Frohman LA, Kaplan EL, Refetoff S, eds. *Radiation-associated Thyroid Carcinoma*. New York, Grune & Stratton, 1977, 161.
80. Schröder S, Kastendieck H, Böcker W. Das okkulte papilläre Schilddrüsenkarzinom. Klinische Bedeutung und Morphologie eines häufigen Tumors. *Deutsch Med Wochenschr* 1986, **111**, 582.
81. Lang W, Borrusch H, Bauer L. Occult carcinomas of the thyroid. *Am J Clin Pathol* 1988, **90**, 72.
82. Fukunaga FH, Yatani R. Geographic pathology of occult thyroid carcinomas. *Cancer* 1975, **36**, 1095.
83. Ramalingaswami V, Subramanian TAV, Deo MG. The aetiology of Himalayan endemic goiter. *Lancet* 1961, **1**, 791.
84. Pedersen E, Hougen A. Thyroid cancer in Norway. In Hedinger C, ed. *Thyroid Cancer*. Berlin, Springer, 1969, 71.
85. Bross ID, Shimaoka K, Tidings J. Some epidemiological clues in thyroid cancer. *Arch Intern Med* 1971, **128**, 755.
86. Shore RE, Woodard E, Hildreth N. Thyroid tumors following thymus irradiation. *J Natl Cancer Inst* 1985, **74**, 1177.
87. Wahner HW, Cuello C, Correa P, Urribe LF, Gaitan E. Thyroid carcinoma in an endemic goiter area. Cali, Colombia. *Am J Med* 1966, **40**, 58.
88. Ron E, Curtis R, Hoffman DA, Flannery JT. Multiple primary breast and thyroid cancer. *Br J Cancer* 1984, **49**, 87.
89. Breslow NE, Enstrom JE. Geographic correlations between cancer mortality rates and alcohol–tobacco consumption in the United States. *J Natl Cancer Inst* 1974, **53**, 681.
90. Williams ED. The aetiology of thyroid tumours. *Clin Endocrinol Metab* 1979, **8**, 193.
91. Riccabona G. *Thyroid Cancer*. Berlin, Springer, 1987.

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# Colon Cancer in Seven Siblings

**Parviz Ghadirian, Marcel Cadotte, André Lacroix, Jacques Baillargeon and Chantal Perret**

**In a case–control study of cancer of the colon it was found that 96 out of 332 (29%) cases had a positive family history of cancer of the colon (2 cases and more) as compared with 19 out of 473 (4%) controls. 3 colon cancer cases reported that 6 of their respective relatives were also affected with the same cancer. We were able to do a complete follow-up study of one family where 7 out of 12 sibling ($P < 0.05$) had confirmed pathological diagnoses of cancer of the colon. The mean age at diagnosis among these familial colon cancer cases was 64 years (60 years for females and 73 years for males) and all tumours were located in the caecum or right colon (a common characteristic of colon cancer in this family). There was no history of familial adenomatous polyposis in this family. It is unlikely that the significantly high proportion of familial colon cancer found could be due to chance. This suggests that both environmental and genetic factors play an important role in the aetiology of colon cancer.**
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## INTRODUCTION

CANCER OF the large bowel is the second most common cancer both in terms of incidence and mortality for both men and women in most of the developed countries of the world. The highest incidence rates are from the U.S.A., Canada and New Zealand, while the lowest rates have been reported from Asia, Africa and Latin America [1].

The highest rates of colorectal cancer appear among those aged 65 years and over, and male:female ratios of less than unity are more frequently observed for cancer of the colon than for other cancers [2]. Countries with high rates of stomach cancer tend to have low mortality rates from colorectal cancer, and vice versa [3]. People living in rural areas tend to have lower rates of colorectal cancer: a prominent feature of large bowel cancer is that urban populations are at high risk [4–7].

American Indians have a rate less than half that for U.S.A. whites [8]. Mormons in the U.S.A. have lower rates of colorectal cancer than the population as a whole [9, 10]. This is also true

for Seventh Day Adventists [11]. These cancers are also less evident among black and oriental populations [2]. There does not appear to be a clear connection between social division and cancer of the colon, whereas a higher mortality from rectal cancer is apparent among lower social classes [12]. Migrant studies show low rates for colorectal cancers among Japanese living in Japan; the incidence rates rise for first and second generations of immigrants to the U.S.A. [13].

Colon cancer occurs more frequently among first-degree relatives of cases [14–28] and it has been estimated that heritable predisposition is responsible for 5% of colorectal cancer [16]. The first family aggregation of cancer of the colon was reported in 1913 [24], and during the 1970s and 1980s two hereditary non-polyposis syndromes characterised by autosomal dominant inheritance, Lynch syndrome I (hereditary site-specific colon cancer) and Lynch syndrome II (cancer family syndrome), were postulated [20]. Familial colon cancer occurs more frequently among first-degree relatives who suffer from either Lynch syndrome. In addition to familial polyposis coli [29], there is increased evidence of familial colonic cancer among those suffering from other syndromes with multiple colonic adenoma (Garner's and Turcot's syndromes) or other hereditary large bowel diseases (coeliac disease, Crohn's disease and ulcerative colitis) [30]. It has been suggested that large bowel cancers are more likely to follow appendectomies [31] and ureterosigmoidostomies [32]. Furthermore, an epidemiological study showed a positive correlation between the risks for cancer of the breast and of the large bowel [33].

The 5-year survival rate for early-stage colorectal cancer is 77% [35]. Mortality rates for colon cancer in the low-risk countries have risen, while the colonic cancer rates in some former high-risk populations, such as Scotland and England, have declined. In general, differences in time trends between countries at the two extremes of the spectrum of risk are clearly evident [2].

## MATERIALS AND METHODS

*Case ascertainment*

During 1989–1992 all patients aged between 35 and 79 years with histological diagnosis of cancer of colon were identified through admission offices, pathology departments, gastroenterological services, and medical record departments of six French-speaking hospitals located in Greater Montreal, five of which are members of the Réseau Inter-hospitalier de Cancérologie de l'Université de Montréal (RICUM).

Once an eligible case was identified the attending surgeon or physician was approached for permission to interview the patient. If permission was given, the patient was then contacted by letter, followed by a telephone call to arrange an interview.

*Control ascertainment*

Population-based controls matched for age (within 5-year age-group), sex and place of residence were selected from the telephone directory in which the corresponding case was listed (all patients studied had a listed telephone number: only 1% of families in the Montreal region do not have a telephone). A page from the telephone directory was randomly selected from the sampling frame and the names and addresses of 10 individuals with the same first three digit telephone numbers as the patient were selected. These residences were then contacted by letter and the aims of the study explained. Approximately 1 week later the selected families were telephoned to see if they contained an individual who matched the original case for age and sex and who agreed to be interviewed. If so, an interview was arranged at the control's home. If not, the procedure was repeated. If more than one eligible control was reached at a given number, this information was kept in a data bank for further use. For cases without a telephone, a random digit dialing method would have been used to select the control.

For both cases and controls, interviews were carried out in the respondent's home. If either the case or control was hospitalised at the time of the scheduled interview and seemed unlikely to be available for home interview within 2 weeks, an in-hospital interview was attempted. If a patient was very ill, whether at home or in hospital, the interview was carried out in the presence of, and with the help of, any family members or other persons who were available and likely to have relevant information.

A total of 332 cases and 473 controls were interviewed in this study. Among cancer cases 96 (29%) had a positive family history (2 or more cases) of the same cancer (colon) as compared with only 19 (4%) among controls.

## RESULTS

The frequency of two subjects of colon cancer among the members of the family of cases was 26.2% as compared with 3.4% among controls (Table 1). These rates for 3 cases of colon cancer in the family were 5.1% and 0.6% in cases and controls, respectively. Among cases, there were eight families (2.4%) with a positive family history of 4 cases; two families (0.6%) with 5 cases and, finally, three families (0.9%) with 7 cases of the same cancer. A total of 288 relatives with colon cancer were affected

*Table 1. Distribution of cases and controls with positive family history of colon cancer by number of cases among the family (information obtained by interview)*

| Familial aggregation (1st and 2nd degree) | | Cases ($n$ = 96) | | Controls ($n$ = 19) | |
|---|---|---|---|---|---|
| | | Cases | Affected relatives | Controls | Affected relatives |
| 2 cases | No | 87 | 174 | 16 | 32 |
| | % | 26.2 | 52.4 | 3.4 | 6.8 |
| 3 cases | No | 17 | 51 | 3 | 9 |
| | % | 5.1 | 15.4 | 0.6 | 1.9 |
| 4 cases | No | 8 | 32 | 0 | 0 |
| | % | 2.4 | 9.6 | | |
| 5 cases | No | 2 | 10 | 0 | 0 |
| | % | 0.6 | 3.0 | | |
| 6 cases | No | 0 | 0 | 0 | 0 |
| | % | | | | |
| 7 cases | No | 3 | 21 | 0 | 0 |
| | % | 0.9 | 6.3 | | |
| Total | No | 96 | 288 | 19 | 41 |
| | % | 28.9 | 86.8 | 4.0 | 8.7 |

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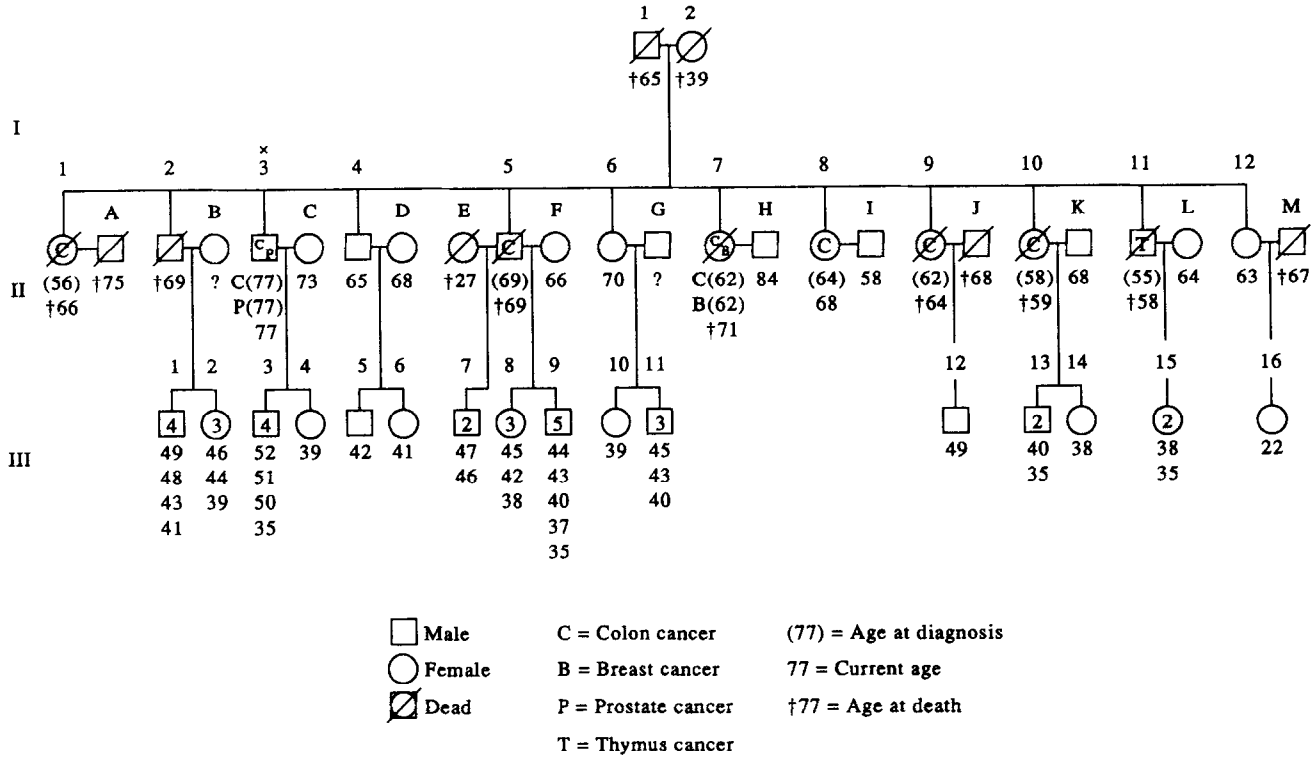


**Fig. 1. Pedigree of colon cancer patients: 7 brothers and sisters (1990).**

*Table 2. Clinical and related information on seven siblings with familial cancer of the colon*

| Case No. | Sex and year of birth | Age at diagnosis | Year of diagnosis | Diagnosis | Location of tumour | Histological type | Stage | Remarks |
|---|---|---|---|---|---|---|---|---|
| II- 1 | F 1909 | 56 | 1965 | Colon | Ascending colon | Adenocarcinoma | A | Died 1975 |
| II- 3 | M 1911 | 77 | 1989 | Colon and *prostate | Caecum | Well differentiated adenocarcinoma | B | Alive 1991 |
| II- 7 | F 1915 | 62 | 1977 | Colon and †breast | Ascending colon | Well differentiated partly colloid adenocarcinoma | C | Died 1986 |
| II- 9 | F 1917 | 62 | 1980 | Colon | Caecum | Moderately differentiated adenocarcinoma | C | Died 1981 |
| II- 5 | M 1918 | 69 | 1987 | Colon | Ascending colon | Moderately differentiated adenocarcinoma | B2 | Died 1987 |
| II- 8 | F 1922 | 64 | 1986 | Colon | Caecum | Poorly differentiated adenocarcinoma | B2 | Alive 1991 |
| II-10 | F 1926 | 58 | 1984 | Colon | Ascending colon | Well differentiated adenocarcinoma | B2 | Died 1985 |

* Age at diagnosis = 77; † Age at diagnosis = 62.

from those 96 index cases (an average of three relatives in each family) as compared with 41 relatives among 19 index controls (an average of two relatives in each family).

The mean age at diagnosis of the seven siblings, presented in this paper was 64 years (60 years for females and 73 years for males). The first case was born in 1909 and the last in 1926 (within a 17-year period). The youngest case was 56 years old and the oldest 77 years old (a 20-year difference between the occurrence of the first and last cancer).

## DISCUSSION

In this population-based case–control study of colon cancer 29% of cases and 4% of controls ($P < 0.05$) gave a positive history of the same cancer (2 or more cases among first and second degree relatives) in the family, of which 3 cases of colon cancer patients had 7 cases of the same cancer among relatives.

Among those with a positive family history of colon cancer we were able to identify a family with a history of confirmed colon cancer in seven siblings. The mother and father of this family of 12 children (7 brothers and 5 sisters) died at the age of 39 and 65, respectively, due to diseases other than cancer (Fig. 1).

Two members of the family (nos. 3 and 7) had multiple primary cancers diagnosed at almost the same time. The second primary cancers were breast and prostate, respectively. There was no history of familial adenomatous polyposis in the family studied.

Colorectal cancer has been reported in association with "Cancer Families" [22, 28, 64], where colorectal carcinoma is suspected to be transmitted in an autosomal dominant mode. Patients in this group are characterised by unusually early onset (around 40 years) of malignancy and multiple primary neoplasms. Although 2 out of 7 (29%) of the reported cases of colon cancer in the family studied had multiple primary cancers, the family genealogy (Fig. 1) showed that this family did not follow the pattern of early onset of malignancy (mean age of 64 years, range 56–77 years).

The pathological slides for all patients but one were reviewed by one of us (M.C.) and the tumours were classified according to gross anatomy, microscopy and Duke's stages. However, it could be an important observation that all tumours were located in the caecum or right colon, while 60–70% of colorectal carcinomas are located in the rectum, rectosigmoid or sigmoid colon (Table 2).


1. Muir C, Waterhouse J, Mack T, Powell J, Whelan S. Cancer incidence in five Continents. (IARC Sci. Publ.; No.88) Lyon, IARC, 1987.
2. Haenszel W, Correa P. Epidemiology of large bowel cancer. In Correa P, Haenszel W, eds. *Epidemiology of Cancer of the Digestive Tract. Developments in Oncology* The Hague, Martinus Nijhoff. 1982, 85–126.
3. Alderson M. *The Prevention of Cancer*. London, Edward Arnold Ltd. 1982, 20–79.
4. Kevin ML, Haenszel W, Carrol BJ, Gerhardt PR, Handy VH, Ingraham SC. Cancer Incidence in Urban and Rural Areas of New York State. *J Natl Cancer Inst* 1960, **24**, 1243–1257.
5. Registrar General of England and Wales: Registral's Statistical Review of England and Wales Supplement on Cancer. London: HMSO, 1965.
6. Teppo L, Hakama M, Hakulinen T, Lehtonen M, Saxen E. In *Cancer in Finland* 1953–1970: *Incidence, Mortality, Prevalence*. Copenhagen Munksgaard, 1975.
7. Clemmesen J. *Statistical Studies in Malignant Neoplasms*. Copenhagen, Munksgaard, 1977, vol 5.
8. Smith RL. Recorded and expected mortality among the Indians of the United States with special reference to cancer. *J Natl Cancer Inst* 1957, **18**, 385–396.
9. Estrom JE. Cancer Mortality Among Mormons. *Cancer* 1975, **36**, 825–841.
10. Kyon JL, Klauber MR, Gardner JW, Smart CR. Cancer Incidence in Mormons and non-Mormons: Utah, 1966–1970. *N Engl J Med* 1976, **294**, 129–133.
11. Phillips RL. Role of life-style and dietary habits in risk of cancer among Seventh-Day-Adventists. *Cancer Res* 1975, **35**, 3513–3522.
12. Registrar General of England and Wales: Occupational Mortality. London, HMSO, 1978.
13. Haenszel W, Kurihara M. Mortality from cancer and other diseases among Japanese in the United States. *J Natl Cancer Inst* 1968, **40**, 43–68.
15. Duncan JL, Kyle J. Family incidence of carcinoma of the colon and rectum in north-east Scotland. *Gut* 1982, **23**, 169–171.
16. Lynch HT, Rozen P, Schuelke GS. Hereditary colon cancer: polyposis and nonpolyposis variants. *Ca—Cancer J Clin* 1985, **35**, 95–145.
17. Lynch HT, Krush AJ. Differential diagnosis of the cancer family syndrome. *Surg Gynecol Obstet* 1973, **136**, 221–224.
18. Mecklin JP. Frequency of hereditary colorectal carcinoma. *Gastroenterology* 1987, **93**, 1021–1025.
19. Danes BS, Bulow S, Svendsen LB. Hereditary colon cancer syndromes: An *in vitro* study. *Clin Genet* 1980, **18**, 128–136.
20. Lynch HT, Schuelke GS, Kimberling WJ, *et al.* Hereditary nonpolyposis colorectal cancer (Lynch syndromes I and II) II. Biomarker studies. *Cancer* 1985, **56**, 939–951.
21. Bailey-Wilson JE, Elston RC, Shuelke GS, *et al.* Segregation analysis of hereditary nonpolyposis colorectal cancer. *Genet Epidemiol* 1986, **3**, 27–38.
22. Lynch HT, Lynch PM, Keathley J. Epidemiology of colon cancer. In Lynch PM, Lynch HT, eds. *Colon Cancer Genetics*. New York, Van Nostrand Reinhold, 1985, 1–16.
23. Mulvihill JJ. The frequency of hereditary large bowel cancer. In Ingal JRF, Mastromarino AJ, eds. *Prevention of Hereditary Large Bowel Cancer* New York, A.R. Liss 1983, 61–75.
24. Warthin AS. Heredity with reference to carcinoma as shown by the study of cases examined in the Pathological Laboratory of the University of Michigan, 1895–1913. *Arch Intern Med* 1913, **12**, 546–555.
25. Lynch PM, Lynch HT, Harris RE. Hereditary proximal colonic cancer. *Dis Colon Rectum* 1977, **20**, 661–668.
26. Levine EG, King RA, Bloomfield CD. The role of heredity in cancer. *J Clin Oncol* 1980, 7, 527–540.
27. Cameron BH, Fitzgerald GW, Cox J. Hereditary site-specific colon cancer in a Canadian kindred. *Can Med Assoc J* 1989, **140**, 41–45.
28. Jarvinen HJ. Familial cancer: a review on hereditary cancer traits with special regard to colorectal carcinoma. *Finland Acta Oncol* 1988, **27**, 783–786.
29. Russey HJR. *Familial Polyposis Coli*. Baltimore, Johns Hopkins University, 1975.
30. Wennstrom J, Pierce ER, McCusick VA. Hereditary benign and malignant lesions of the large bowel. *Cancer* 1974, **43**, 850–857.
31. Hyams L, Wynder EL. Appendectomy and Cancer Risk. *J Chron Dis* 1968, **21**, 391–415.
32. Haney MJ, McGarity WC. Ureterosigmoidostomy and neoplasms of the colon. *Arch Surg* 1971, **103**, 69–72.
33. Bjelke E. *Epidemiologic Studies of Cancer of the Stomach, Colon, and Rectum, with Special Emphasis on the Role of Diet* Ann. Arbor, Michigan, University Microfilms, 1973, 1–5.
34. Fink DJ. Facts about colorectal cancer detection. *Ca—Cancer J Clin* 1983, **33**, 366–367.
35. Lynch HT. Cancer families (endometrial and colon carcinoma) and multiple primary malignant neoplasms. *Cancer Res* 1967, **12**, 125–142.


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