Association of colorectal adenoma with other malignancies in Swedish families

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Using the Swedish Family-Cancer Database covering over 11.5 million individuals, estimated relative risks (RRs) for colorectal adenoma were using Poisson’s regression. The RR of colorectal adenoma was found to be increased among first-degree relatives of patients with colorectal cancer (2.72; 95% confidence interval = 2.46 – 3.00) and among the offspring and siblings of patients with endometrial and prostate cancers. We also found an increased risk of colorectal adenoma for the offspring of individuals with stomach cancer and leukaemia, and for siblings of those with pancreatic cancer and multiple myeloma. Our results suggest that colorectal adenoma may share a genetic aetiology with cancer even at extracolorectal sites. Increases of colorectal adenoma in families affected by prostate cancer and acute leukaemia cannot be attributed to known cancer syndromes, although the play of chance cannot be excluded.

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Most colorectal cancers (CRCs) develop through sequential malignant transformations of adenomatous polyps (Bond, 2000). Mutations in the adenomatous polyposis coli gene are responsible for the early stage of adenoma formation in familial adenomatous polyposis (Houlston, 2001; Lynch and de la Chapelle, 2003; Molatore and Ranzani, 2004) and mutations in the mismatch-repair genes are associated with hereditary nonpolyposis CRC (HNPCC) (Lynch and de la Chapelle, 2003; Molatore and Ranzani, 2004). The later stages of adenoma development into CRCs include K-ras, p53 and mismatch-repair genes (Lynch and de la Chapelle, 2003; Molatore and Ranzani, 2004).

The adenoma–carcinoma sequence implies that colorectal adenomas and carcinomas have common risk factors. A family history of CRC increases the risk of CRC (Slattery and Kerber, 1994; Hemminki and Li, 2001; Andreu et al, 2004; Stefansson et al, 2006) and is a strong risk factor for adenoma growth (Lindgren et al, 2002; Almendingen et al, 2003). Although an association between CRC risk and a family history of extra-colorectal malignancies has been reported previously (Slattery and Kerber, 1994; Hemminki and Li, 2001; Andreu et al, 2004), little is known on the corresponding risk of colorectal adenoma.

We have therefore quantified the risk of colorectal adenoma among individuals with a family history of any cancer using the nationwide Swedish Family-Cancer Database with its unique capacity for accurate and unbiased assessment (Hemminki and Li, 2001; Hemminki et al, 2001b).

MATERIALS AND METHODS

The population-based Swedish Family-Cancer Database was created by linking the Multigeneration Register at Statistics Sweden to the Swedish Cancer Registry (Hemminki et al, 2001b). This is based on compulsory reports from pathologists and cytologists, on every cancer diagnosis on surgically removed tissues, biopsies, cytological specimens, bone marrow aspirates and autopsies (Center for Epidemiology, 2004). The Multigeneration Register includes individuals born in Sweden after 1931 and their biological parents and its latest update covers over 11.5 million individuals. Cancer/adenoma data were retrieved from the Swedish Cancer Registry from 1961 to 2004. Database coverage is practically complete but some familial links are missing from offspring born before 1941 and dying in 1960–1997 reducing the number of fatal cancers among offspring. This is unlikely to bias familial studies because familial and sporadic cases would be reduced proportionately (Hemminki et al, 1998; Hemminki and Vaithinen, 1999). The present study relies on individuals with information about both parents. Family history was restricted to first-degree relatives, parents, and siblings.

From International Classification of Diseases (ICD-7) the following codes were used: for colorectal adenomas 094; CRCs by anatomic site: 1530 (ascending), 1531 (transverse), 1532 (descending), 1533 (sigmoid), 1538 (multiple sites), 1534 and 1539 (other sites), 154 – excluding 1541 (rectum). Follow-up started from the date of birth, immigration or 1 January 1961, whichever occurred last. Follow-up ended on the date of diagnosis of CRC or colorectal adenoma, death, emigration, or the closing date of the study (31 December 2004), whichever came first. Relative risks (RRs) with 95% confidence intervals (CIs) were used to compare adenoma incidence among those whose family was
affected by cancer adenoma with adenoma incidence in the general population. Cases of adenoma and person-years were classified according to gender, family history of cancer, calendar year and age. The distribution of the number of cases in each group was modelled by Poisson’s regression. The Genmod procedure of the SAS software was used for the analysis (SAS Version 9.1; SAS Institute, Cary, NC, USA).

RESULTS

The Database included 2943 individuals diagnosed with colorectal adenoma and with information about both parents. The parental generation incorporated 12,458 individuals with colorectal adenoma. The incidence of colorectal adenoma in Sweden has been increasing since the 1960s; the site-specific age-adjusted incidence rates for 1990–1999 and 2000–2004 are displayed in Table 1. Table 2 shows some demographic characteristics and RRs. Women were at a slightly lower risk of colorectal adenoma compared to men (RR = 0.89; 95% CI = 0.82–0.94). As expected, age was associated with risk, which was also increased with a family history of CRC (RR = 2.72; 95% CI = 2.46–3.00) and particularly of colorectal adenoma (RR = 4.99; 95% CI = 4.12–6.05). Among the 108 patients with colorectal adenoma and also a family history of this, 55 individuals (in 27 families) had an affected sibling (RR = 9.41; 95% CI = 7.21–12.3).

Standard Poisson’s regression assumes independent observations. Because of possible overdispersion due to clustered family structure, s.e. were adjusted using Pearson’s $\chi^2$ divided by the degrees of freedom, resulting in slightly wider CIs. For example, the RR of colorectal adenoma for individuals with a positive family history was 4.99 (95% CI = 3.36–7.41). However, as this procedure may be sensitive to outlying observations to be expected in our large data set, we show unadjusted CIs and point out the possibly conservative limits due to familial dependence.

The left column of Table 3 shows colorectal adenoma RRs according to parental history of CRC and colorectal adenoma: it was increased among offspring of patients with colon cancer (RR = 2.59; 95% CI = 2.28–2.94), rectal cancer (RR = 2.59; 95% CI = 2.20–3.05), colon adenoma (RR = 4.43; 95% CI = 3.09–6.34), and rectal adenoma (RR = 2.62; 95% CI = 1.77–3.89). Corresponding risks with a sibling history of CRC and colorectal adenoma are displayed in the right column of Table 3, with particularly high risks when a sibling had colon (RR = 11.3; 95% CI = 8.15–15.7) or rectal adenoma (RR = 6.94; 95% CI = 4.42–10.9). Colorectal adenoma was higher for the offspring of individuals with colon adenoma (RR = 4.43) than those with colon cancer (RR = 2.59; P-value <0.01). It was also higher for those with a sibling with colon adenoma (RR = 11.3) than when a sibling had colon cancer (RR = 2.64; P-value <0.01). Colorectal adenoma risk was higher when a sibling had rectal adenoma (RR = 6.94), than when a sibling had rectal cancer (RR = 2.75; P-value <0.01).

The offspring risk of colorectal adenoma was higher when parents had multiple adenomas than when parents presented with single adenomas (RR = 21.6; 95% CI = 5.70–82.0). Sibling risk was also significantly higher for multiple than for single adenomas in any colorectal site (RR = 20.7; 95% CI = 3.48–123) (results not shown).

Table 4 shows colorectal adenoma RRs with a family history of malignancies other than CRC, but only for sites where at least 10 individuals with a family history of cancer had colorectal adenoma.

The risk was increased among the offspring of parents with leukaemia (RR = 1.34; 95% CI = 1.02–1.76). Among the 53 affected parents, 17 had chronic lymphoblastic, 14 acute myeloid, 5 acute lymphoblastic (ALL), 2 chronic myeloid leukaemias; 7 type unspecified; 8 polycythaemia vera. Colorectal adenoma risk was the highest among the offspring of the five patients with ALL (RR = 3.38; 95% CI = 1.41–8.14) in which the leukaemias were diagnosed at advanced ages (63–94 years). Risk was also increased among the offspring of parents with acute myeloid leukaemia (RR = 1.79; 95% CI = 1.06–3.02). It was also increased among individuals with a parental history of stomach (RR = 1.28; 95% CI = 0.77–2.13) (results not shown).
Table 4  Relative risk of colorectal adenoma for the offspring/siblings of individuals with invasive cancer

| Cancer site in parent/sibling | Offspring N | RR (95% CI) | Sibling N | RR (95% CI) |
|------------------------------|-------------|-------------|-----------|-------------|
| Tongue/mouth                 | 27          | 1.12 (0.76–1.63) | 5         | 0.79 (0.33–1.89) |
| Stomach                      | 100         | 1.28 (1.05–1.57) | 9         | 1.35 (0.70–2.59) |
| Liver                        | 56          | 1.22 (0.93–1.58) | 6         | 1.12 (0.50–2.49) |
| Pancreas                     | 51          | 1.12 (0.85–1.48) | 13        | 2.18 (1.27–3.77) |
| Lung                         | 108         | 1.13 (0.93–1.37) | 31        | 1.35 (0.95–1.92) |
| Breast                       | 151         | 1.04 (0.88–1.22) | 80        | 1.05 (0.84–1.31) |
| Cervix uteri                 | 22          | 0.81 (0.53–1.23) | 13        | 1.46 (0.85–2.51) |
| Endometrium                  | 51          | 1.45 (1.10–1.91) | 20        | 1.63 (1.05–2.54) |
| Ovary                        | 28          | 0.88 (0.60–1.27) | 11        | 0.93 (0.52–1.69) |
| Prostate                     | 233         | 1.17 (1.03–1.34) | 59        | 1.45 (1.12–1.88) |
| Kidney                       | 55          | 1.22 (0.93–1.59) | 4         | 3.25 (1.22–8.68) |
| Urinary organs               | 72          | 1.10 (0.87–1.39) | 12        | 0.87 (0.49–1.53) |
| Melanoma                     | 36          | 1.30 (0.94–1.81) | 28        | 1.34 (0.93–1.95) |
| Squamous cell skin           | 51          | 0.94 (0.71–1.24) | 13        | 1.67 (0.97–2.87) |
| Nervous system               | 37          | 1.06 (0.77–1.47) | 21        | 1.19 (0.77–1.83) |
| Endocrine glands             | 18          | 0.88 (0.55–1.40) | 13        | 1.36 (0.79–2.34) |
| Connective tissue            | 10          | 1.16 (0.62–2.15) |           |             |
| Non-Hodgkin lymphoma         | 39          | 1.04 (0.76–1.43) | 3         | 1.26 (0.41–3.91) |
| Multiple myeloma             | 21          | 0.93 (0.61–1.44) | 10        | 2.63 (1.42–4.90) |
| Leukaemia                    | 53          | 1.34 (1.02–1.76) | 9         | 0.95 (0.49–1.83) |
| Any cancer                   | 1446        | 1.50 (1.39–1.61) | 451       | 1.44 (1.30–1.59) |

Bold signifies P<0.05.
In conclusion, a family history of colorectal adenoma is a risk factor for colorectal adenoma particularly for first-degree relatives of patients with multiple adenomas. Unrelated to known CRC syndromes, we found increases among the offspring and siblings of patients with prostate cancer, and the offspring of patients with leukaemia. However, given the number of tests performed, chance may have operated in some of our findings. Our data may help to understand the adenoma–carcinoma sequence and to develop prevention strategies.

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Conflicts of interest

The authors state no conflicts of interest.

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