PostScript

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Diabetes mellitus, family history, and colorectal cancer

A population based, cross sectional study from East Anglia showed a relative risk of colorectal cancer of 2.9 in subjects with history of type II diabetes. The association was similar in men and women, but apparently stronger in subjects with family history of colorectal cancer.[1] This confirms previous data indicating that insulin—and its structural homologue insulin-like growth factor-I (IGF-I)—may promote colorectal carcinogenesis,[2–4] although the issue, and any related risk quantification, remain open to discussion.

To provide further information on the issue, we considered data from a case-control study conducted in the Swiss Canton of Vaud. Briefly, between 1992 and 2000 trained interviewers collected information on 286 cases (174 men, 112 women) with incident, histologically confirmed colon or rectal cancer (age range: 26–74; median age 65 years) who had been admitted to the University Hospital of Lausanne, Switzerland.

Controls were 550 subjects (269 men, 281 women) aged <75 years (range, 27 to 74 years; median age 59 years) residing in the same geographical area. They were admitted to the University Hospital of Lausanne for a wide spectrum of acute non-neoplastic conditions unrelated to long term diet modifications, including traumas (33%, mostly sprains and fractures), non-traumatic orthopaedic conditions (31%, mostly low back pain and disk disorders), surgical conditions (19%, mostly abdominal, such as acute appendicitis, kidney stones or strangulated hernia), and miscellaneous other disorders (17%, including acute medical, eye, nose and throat, and skin diseases).

All interviews were conducted in hospital during the admission diagnosis. Sixteen per cent of subjects (16% cases; 15% controls) approached for interview refused. The structured questionnaire included information on sociodemographic characteristics and lifestyle habits (for example, smoking, alcohol consumption, and physical exercise[5]), anthropometric factors, and a food frequency dietary section. A problem oriented medical history was also elicited, including a specific question on diabetes, and age at diagnosis.

Odds ratios (OR), and the corresponding 95% confidence intervals (CI), were derived from multiple logistic regression equations, including terms for sex, age, education, smoking, alcohol drinking, and family history of colorectal cancer.

Table 1 considers history of diabetes mellitus and family history. Twenty eight cases and 23 controls reported ever history of diabetes. The corresponding multivariate OR was 1.8 (95% CI 1.0 to 3.2). The OR was 1.3 (95% CI 0.6 to 2.7) in men and 3.6 (95% CI 1.0 to 12.1) in women. Family history of colorectal cancer in first degree relatives was reported by 18 cases and 12 controls, corresponding to an overall OR of 3.2 (95% CI 1.5 to 7.1); the OR was 2.1 (95% CI 0.8 to 5.9) for men and 4.9 (95% CI, 1.5 to 16.7) for women. None of the subjects with diabetes reported family history of the disease.

This study further confirms and quantifies that subjects with family history of colorectal cancer in first degree relatives have an about threefold excess risk, and that diabetes mellitus is a correlate of colorectal cancer risk, and can explain about 3% of cases in this population. The observation that the OR was persistently increased in subjects who had been diagnosed with diabetes for five or more years (OR=4.1, 95%CI 1.6 to 10.8) weighs against surveillance bias—that is, more careful ascertainment of intestinal neoplasms in the few years around the diagnosis of diabetes. Although we had no information on type of diabetes, only two cases and two controls were diagnosed with diabetes below age 45. Thus, the inference applies essentially to type II, insulin independent diabetes.

The hospital based design represents an optimal framework for assessing comparability of medical histories, which were satisfactorily reproducible, thus making information bias unlikely. With reference to confounding, the association was not appreciably modified by several potential distorting factors, including body weight and physical activity, which may indeed be steps in the causal pathways of both diabetes and colorectal cancer. This study was also unable to show a substantial modifying effect of family history on diabetes risk, possibly on account of its limited power to analyse interactions.

Besides providing clues to our understanding colorectal carcinogenesis, the confirmed association of an excess colorectal cancer risk in subjects with history of diabetes may have relevant implications for the management of diabetics.

Table 1 Odds ratios (OR) of colorectal cancer (and corresponding 95% confidence intervals (95% CI)) for history of diabetes mellitus and family history of colorectal cancer among 286 cases and 550 controls. Vaud, Switzerland, 1992–2000

	Sex	Nunber of cases: number of controls	Multivariate OR* (95% CI)
History of diabetes†			
No	M	153:251	1.0‡
Yes		21:18	1.30 (0.63 to 2.68)
No	F	105:276	1.0‡
Yes		7:5	3.56 (1.05 to 12.11)
No	Total§	258:527	1.0‡
Yes		28:23	1.75 (0.95 to 3.24)
Family history¶			
No	M	163:262	1.0‡
Yes		11:7	2.12 (0.76 to 5.90)
No	F	105:276	1.0‡
Yes		7:5	4.91 (1.45 to 16.69)
No	Total§	268:538	1.0‡
Yes		18:12	3.23 (1.47 to 7.09)

*Adjusted for age, smoking status, BMI, education, and alcohol consumption; †adjusted for family history of colorectal cancer; ‡reference category; §adjusted for sex; ¶adjusted for history of diabetes.

Acknowledgements

Funding: this work was partly supported by the Swiss National Science Foundation (grant no 32–31330.91) and by the Swiss Cancer Research Fund (KFS, Contract AKT no 72 and 700–8).

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Authors' reply

We thank Dr Levi and colleagues for their contribution to our previous report relating to type II diabetes, family history, and colorectal cancer. Their study indicates that both type II diabetes and family history are risk factors for this cancer, confirming previous analyses of these associations.[1] The authors did not, however, find an excess risk in people with both diabetes and family history of colorectal cancer. As Dr Levi and colleagues indicate, their failure to show this effect may be attributable to power limitations and sampling variation as a result of the small size of the study. Further large scale analyses may help clarify the risk of colorectal cancer associated with both family history of disease and type II diabetes.

None the less, in combination with other observational investigations and experimental studies,[1 2] these data provide an insight into the biological processes that may underlie the development of colorectal carcinoma. Clearly, carcinogenesis is a multifactorial and multistep process that involves an accumulation of genetic mutations. Throughout life, these mutations occur spontaneously and may be increased by exogenous mutagens and genetic predisposition.[2] Indeed, familial aggregation may reflect both epigenetic processes and genomic factors that may increase the occurrence of mutations and risk of cancer.

Metabolic changes associated with the development of type II diabetes may also increase the risk of colorectal cancer. With increasing glucose intolerance and in early type II diabetes, hyperinsulinaemia is a compensatory response to maintain glucose homeostasis in people who become resistant to insulin action. It is characterised by raised fasting plasma insulin and an exaggerated insulin response to an oral glucose load.[3] Recently, prospective observational studies have shown that high insulin levels and its metabolic correlates are associated with an increased risk of colorectal cancer.[4 5] As a result, it has been suggested that insulin may directly promote colorectal carcinogenesis via activation of either its own receptor, or those of insulin-like growth factor-I (IGF-I).[6] An alternative model proposes that consumption of excess dietary energy may result in the development of insulin resistance with increased circulating levels of insulin, triglycerides, and non-esterified fatty acids. These circulating factors may, in turn, initiate a general proliferative response from colonic epithelial cells and hence promote colorectal carcinogenesis.[7]

Because of the strong interrelation between insulin and the growth hormone (GH)/IGF-I axis, chronic hyperinsulinaemia may also indirectly promote colorectal carcinogenesis by inducing pathophysiological changes to circulating concentrations of IGF-I and its binding proteins. Specifically, as a result of insulin associated changes in IGF-I binding protein concentrations, increased levels of blood insulin may lead to increases in the bioavailability of IGF-I.[5] For many cell types, IGF-I is a potent anti-apoptotic factor and the hyperinsulinaemia induced increase in IGF-I bioavailability may promote the survival of transformed and mutated cells that would normally undergo apoptosis.[8]

The association between nutrition and growth is partly mediated via a complex biological interaction among insulin, GH, IGF-I, and its binding proteins.[9] Consequently, the interrelation between insulin and the GH/IGF-I axis may also provide one of several potential mechanisms through which previously identified environmental factors, such as diets, anthropometry, and associated lifestyles, may operate to increase the risk of colorectal cancer.[1 2 5 6 9]

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BOOK REVIEW

Manual of childhood infections, 2nd edn

E G Davies, *et al*. W B Saunders, 2001. (Pp 514; £24.95). ISBN 0-720-2626-3.

After all the books covering different aspects on childhood infections, it may come as a surprise as to the actual usefulness of this second edition of *Manual of childhood infections*. It could not have been easy to include such a lot of information in only 514 pages.

This book has two main virtues. Firstly, it is practical, as we can see in sections about emerging and re-emerging infections, common presenting symptoms or types of conditions, specific information on each individual infection, public health actions, essential web sites, antibiotic doses, refugees and internationally adopted children, laboratory diagnosis, ancillary and exactly needed tables, and so forth. Secondly, it includes clear written data, issues and descriptions as are only found in classic books.

For people working in the clinical field, it is a great aid to have this revised and updated companion book on the table or in the pocket (although may be it is too wide for that).

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