

REPRINTS AND REFLECTIONS

Colorectal cancer risk, chronic illnesses, operations and medications: case–control results from the Melbourne Colorectal Cancer Study[†]

Gabriel A Kune, Susan Kune and Lyndsey F Watson

The associations between colorectal cancer risk and several chronic illnesses, operations and various medications were examined in 715 colorectal cancer cases and 727 age- and sex-matched controls in data derived from a large, comprehensive population-based study of this cancer conducted in Melbourne, Australia. There was a statistically significant deficit among cases of hypertension, heart disease, stroke, chronic chest disease and chronic arthritis and a statistically significant excess of 'haemorrhoids' among cases, and all of these differences were consistent for both colon and rectal cancers and for both males and females. Although no statistically significant differences were found for other cancers, there were twice as many breast cancers among cases (16) than among controls (8) and also there were 9 uterine cancers among cases and only 2 among controls. There was a statistically significant deficit among cases in the use of aspirin-containing medication and vitamin supplements and this was consistent for both colon and rectal cancers and for both males and females. There was a statistically significant excess of large bowel polypectomy among cases. The modelling of these significant associations simultaneously in a logistic regression equation indicated that hypertension, heart disease, chronic arthritis and aspirin use were each independent effects and consistent for both colon and rectal cancers for both males and females and also that these effects were independent of dietary risk factors previously described in the Melbourne study. The possible relevance of these findings towards an understanding of colorectal cancer risk and aetiology is discussed.

Introduction

This article describes the associations found between colorectal cancer risk and several chronic illnesses, operations and medications. The data are drawn from the case–control substudy arm of a large, comprehensive population-based clinicopathological and epidemiological investigation of colorectal cancer, The Melbourne Colorectal Cancer Study.¹ The objectives for obtaining these data on illnesses, operations and medications were partly to examine some current hypotheses of colorectal cancer risk, partly to examine previously described associations between colorectal cancer and other cancers and

partly as an exploratory to stimulate the creation of new hypotheses of colorectal cancer aetiology.

Patients and methods

Definition of cases and controls

All histologically confirmed new cases of colorectal adenocarcinoma diagnosed in the 12-month period from April 1980 to April 1981, who were usual residents of Metropolitan Melbourne (population, 2.81 million) constituted the cases.^{1–3} Those with a past history of ulcerative colitis or familial polyposis coli (10 cases) were excluded. Community controls, who were age- and sex frequency matched with the cases, were randomly selected from the same geographic area from which the cases were chosen, according to a cluster sampling plan

[†] First published *Cancer Res* 1988;48:4399–404. Reprinted with permission. Department of Surgery, University of Melbourne, Repatriation General Hospital, Heidelberg 3081, Victoria, Australia.

Table 1 Distribution of chronic illnesses among cases and controls and relative risk estimates

Illness	Status	Males (cases, <i>n</i> = 388; controls, <i>n</i> = 398)				Females (cases, <i>n</i> = 326; controls, <i>n</i> = 329)				Total (cases, <i>n</i> = 714; controls, <i>n</i> = 727)			
		No. with illness	RR	95% CI	<i>P</i>	No. with illness	RR	95% CI	<i>P</i>	No. with illness	RR	95% CI	<i>P</i>
Hypertension	Case	113	0.69	0.51–0.93	0.02	114	0.78	0.57–1.08	0.15	227	0.73	0.59–0.91	0.005
	Control	149				134				283			
Stroke	Case	13	0.52	0.26–1.03	0.08	8	0.43	0.19–1.01	0.08	21	0.48	0.28–0.82	0.009
	Control	25				18				43			
Heart disease	Case	72	0.63	0.45–0.88	0.008	49	0.70	0.47–1.06	0.11	121	0.66	0.51–0.85	0.002
	Control	106				66				172			
Chest disease	Case	61	0.68	0.47–0.97	0.04	43	0.81	0.52–1.25	0.4	104	0.73	0.55–0.96	0.03
	Control	86				52				138			
Asthma	Case	28	0.95	0.56–1.63	0.99	20	0.79	0.43–1.47	0.6	48	0.89	0.60–1.33	0.6
	Control	30				25				55			
Arthritis	Case	118	0.56	0.42–0.75	<0.001	151	0.69	0.51–0.93	0.02	269	0.62	0.51–0.77	<0.001
	Control	175				183				358			
Diabetes	Case	21	1.28	0.67–2.47	0.6	12	0.75	0.35–1.61	0.6	33	1.02	0.62–1.67	0.99
	Control	17				16				33			
Indigestion or ulcer	Case	166	1.26	0.95–1.68	0.12	93	0.67	0.48–0.93	0.02	259	0.96	0.78–1.19	0.7
	Control	148				123				271			
Diverticulitis	Case	21	1.57	0.79–3.13	0.3	26	1.27	0.70–2.32	0.5	47	1.39	0.88–2.17	0.18
	Control	14				21				35			
Haemorrhoids	Case	138	1.39	1.03–1.88	0.04	114	2.23	1.56–3.23	<0.001	252	1.69	1.35–2.13	<0.001
	Control	113				64				177			
Nervousness or nervous breakdown	Case	63	1.05	0.72–1.54	0.9	88	1.34	0.93–1.92	0.12	151	1.20	0.93–1.56	0.19
	Control	62				71				133			
Allergies or hayfever	Case	110	0.78	0.58–1.06	0.12	128	0.88	0.65–1.20	0.5	238	0.83	0.67–1.03	0.10
	Control	134				139				273			

devised by the Australian Bureau of Statistics.^{1,2} There were 715 cases and 727 age- and sex frequency matched controls available for this analysis.

Data collection

Data were collected by two questionnaires, which were administered by personal interview, each on a separate occasion and by two different sets of interviewers. The first questionnaire included data on age, sex, country of birth and religion; current and past illnesses, operations and medications; bowel habit; biopsychosocial factors; number of children and family history data. The second interview was the dietary questionnaire, which included alcohol intake and tobacco use. The section of the interview that dealt with previous illnesses operations and medications was introduced uniformly by the interviewer as follows, 'I'd like to talk to you about your general health. I am now going to read through a list of operations, illnesses, and medications. Would you tell me if you have had any of these, and if so, when?' The responses were recorded as 'yes,' 'no' or 'don't know.' For operations, the actual year of the procedure was recorded. For the illnesses, the year of commencement and the year of termination of the illness was recorded. For

medications, the frequency was recorded as 'daily,' 'weekly' or 'don't know' and the duration was recorded from commencement year to termination year of medication. The data obtained were not verified by any other means, such as by checking physician or hospital records or by interviewing close relatives or friends. The chronic illnesses that were asked are listed in Table 1, the cancers (other than colorectal cancer) in Table 2, the medications in Table 3 and the operations in Table 4.

Data analysis

Data manipulations and cross-tabulations were made using SPSS-x.⁴ The analysis of the associations between the various illnesses, operations and medications and colorectal cancer was done using the GLIM⁵ statistical package to carry out unconditional logistic regression,⁶ which gives multiplicative models for the relative risk (RR) of being a case. Design constraints, namely age and sex (due to frequency matching between cases and controls), were adjusted for in all logistic regression models.

Preliminary assessment of these associations was done univariately for colon and rectal cancers as well as for colorectal cancer (colon and rectum combined). Possible sex differences

Table 2 Distribution of cancers, other than colorectal cancer, among cases and controls and their relative risk estimates

	Satus	Males (Cases, n = 388; controls, n = 398)					Females (cases, n = 327; controls, n = 329)					Total (cases, n = 715; controls, n = 727)				
		No.		RR	95% CI	P	No.		RR	95% CI	P	No.		RR	95% CI	P
		Yes	DK ^a				Yes	DK				Yes	DK			
Excision for skin cancer	Case	42	24	1.30	0.81–2.09	0.3	18	15	0.74	0.39–1.39	0.4	60	39	1.06	0.72–1.54	0.8
	Control	34	5				24	6				58	11			
Mastectomy for cancer	Case	1	0				15	0	1.93	0.81–4.61	0.2	16	0	2.06	0.87–4.84	0.14
	Control	0	0				8	0				8	0			
Hysterectomy for uterine cancer	Case						9	17	4.63	0.99–21.6	0.07					
	Control						2	8								
Prostatic surgery for cancer	Case	1	27	0.25		0.4										
	Control	4	3													
Cancer in other sites	Case											7	0	0.71	0.27–1.87	0.7
	Control											10	0			

^aDK, don't know. All 'don't know' responses considered for RR estimation to be non-malignant.

Table 3 Distribution of medication use among cases and controls and RR estimates

Medication	Satus	Males (cases, n = 388; controls, n = 398)				Females (cases, n = 325 ^a ; controls, n = 329)				Total (cases, n = 713; controls, n = 727)						
		No. using		RR	95% CI	P	No. using		RR	95% CI	P	No. using		RR	95% CI	P
		Yes	DK				Yes	DK				Yes	DK			
Aspirin and aspirin containing	Case	41	0.58	0.38–0.88	0.02	44	0.49	0.32–0.73	<0.001	85	0.53	0.40–0.71	<0.001			
	Control	67				80				147						
Non-steroid anti-inflammatories	Case	61	0.80	0.56–1.16	0.3	61	0.74	0.51–1.09	0.1	122	0.77	0.60–1.01	0.06			
	Control	75				78				153						
Steroids	Case	21	1.69	0.83–3.45	0.2	28	0.94	0.55–1.61	0.9	49	1.17	0.77–1.79	0.5			
	Control	13				30				43						
Oral contraceptives	Case					47	1.26	0.80–2.0	0.4							
	Control					39										
Tranquilizers and sedatives	Case	56	0.86	0.58–1.28	0.5	66	0.98	0.67–1.43	0.99	122	0.93	0.71–1.22	0.6			
	Control	65				68				133						
Sleeping pills	Case	44	0.96	0.62–1.47	0.9	57	0.72	0.49–1.06	0.1	101	0.82	0.61–1.09	0.2			
	Control	47				75				122						
Vitamin supplements Retinol	Case	8	0.28	0.13–0.63	0.02	4	0.16	0.05–0.46	<0.001	12	0.22	0.12–0.42	<0.001			
	Control	28				24				52						
Vitamin C	Case	20	0.42	0.24–0.72	0.02	12	0.24	0.12–0.45	<0.001	32	0.32	0.21–0.49	<0.001			
	Control	46				46				92						

^aTwo female cases with missing data excluded.

were also tested for. Simultaneous assessment of significant variables was then done and a multivariate model was developed and tested for consistency across site and sex and also with simultaneous adjustment for a dietary model of risk previously developed for this data set.⁷

Results

This analysis is of 715 cases (388 males and 327 females) and 727 controls (398 males and 329 females). There were 392 colon cancers and 323 rectal cancers among the cases.

Cases and controls were group matched for age and sex and the age- and sex distribution of the cases and controls was therefore similar, with a mean age of 65 years (SD of 10 for males and 12 for females).

Univariate analyses of associations

Illnesses

Table 1 summarizes the chronic illnesses findings. There was a statistically significant deficit among cases of hypertension, stroke, heart disease, chronic chest disease and chronic arthritis and these deficits were consistent in both colon and rectal

Table 4 Distribution of previous operations, excluding cancer operations, among cases and controls and RR estimates

Operation	Status	Males (cases, <i>n</i> = 388; controls, <i>n</i> = 398)				Females (cases, <i>n</i> = 327; controls, <i>n</i> = 329)				Total (cases, <i>n</i> = 715; controls, <i>n</i> = 727)			
		No. with previous operation	RR	95% CI	<i>P</i>	No. with previous operation	RR	95% CI	<i>P</i>	No. with previous operation	RR	95% CI	<i>P</i>
Tonsillectomy	Case	140	0.93	0.70–1.25	0.7	117	0.92	0.67–1.27	0.6	257	0.93	0.75–1.15	0.5
	Control	150				124				274			
Appendectomy	Case	81	0.99	0.70–1.39	0.99	88	1.23	0.68–1.75	0.3	169	1.10	0.85–1.41	0.5
	Control	84				76				160			
Haemorrhoidectomy	Case	41	1.35	0.83–2.17	0.3	12	0.93	0.42–2.04	0.99	53	1.21	0.81–1.82	0.4
	Control	32				13				45			
Cholecystectomy	Case	17	1.26	0.61–2.56	0.7	42	0.98	0.62–1.54	0.99	59	1.06	0.72–1.54	0.8
	Control	14				43				57			
Hernia repair	Case	87	1.13	0.81–1.59	0.5	13	0.93	0.43–2.00	0.99	100	1.08	0.80–1.47	0.7
	Control	81				14				95			
Hiatus hernia repair	Case	1	1.03			2	0.67			3	0.76		
	Control	1				3				4			
Peptic ulcer surgery	Case	9	0.76	0.32–1.82	0.7	2	0.40	0.08–2.08	0.5	11	0.65	0.30–1.41	0.4
	Control	12				5				17			
Bowel polypectomy ^a	Case	10	5.24	1.14–25	0.04	14	7.31	1.64–33	0.005	24	6.28	6.28–20	<0.001
	Control	2				2				4			
Uterine curettage	Case					74	0.68	0.48–0.96	0.04				
	Control					99							
Hysterectomy for non-malignant lesion	Case					97	0.80	0.57–1.11	0.11				
	Control					119							
Breast lumpectomy	Case					14	0.62	0.31–1.25	0.2				
	Control					22							
Prostatic surgery for non-malignant lesion	Case	30	0.75	0.46–1.23	0.3								
	Control	40											

^aFour male cases and 12 female cases with 'don't know' responses excluded.

cancers and in both males and females. Among cases, there was a statistically significant excess of 'haemorrhoids' in both colon and rectal cancers. There was a statistically significant deficit of 'indigestion or ulcer' reported by female cases and this was similar for both colon and rectal cancers. No differences were found for asthma, diabetes, diverticular disease, 'extreme nervousness and nervous breakdowns' and allergies.

A past history of cancers other than colorectal cancer was seen in 85 cases and 75 controls, there being 92 instances in cases and 82 in controls (Table 2). Note that a past history of colorectal cancer was an exclusion for controls. For operations, all the 'don't know' responses were in relation to malignant or pre-malignant conditions and were distributed as follows: bowel polypectomy, 16 cases and no controls; gastric cancer surgery, 2 cases and no controls; prostatic cancer surgery, 27 cases and 3 controls; uterine cancer surgery, 17 cases and 8 controls and skin cancer surgery, 39 cases and 11 controls. Thus, the 123 'don't know' answers were distributed among cases in 101 instances and among controls in 22 instances. The distribution of cancer sites among cases and controls is described in Table 2 and in this table, for RR estimates, all 'don't know' responses were considered to be

non-malignant. There were no statistically significant differences either in the total number of other cancers or in any one site and the rates were similar for colon and rectal cancers. It is noteworthy that there were twice as many breast cancers among cases than among controls. The difference for uterine cancer was approaching statistical significance at the 5% level ($P=0.07$; Table 2). Note that in the question on hysterectomy for uterine cancer, no distinction was made in the questionnaire between endometrial cancer and cervical cancer.

Medications

With past medications (Table 3) there was a statistically significant deficit among cases consuming aspirin and aspirin-containing medications, retinol supplements and vitamin C supplements and these deficits were consistent for males and females. The statistically significant lower consumption of aspirin and aspirin-containing medications among cases remained after adjustment was made for those with arthritis, who may be supposed to be frequent users of aspirin-containing compounds [RR=0.63; 95% confidence interval (CI), 0.50–0.78; $P<0.001$]. The use of non-steroidal anti-inflammatory agents, steroids, oral contraceptives,

Table 5 Model of illnesses and aspirin use, by site and sex, and with simultaneous adjustment for model of dietary risk

	Hypertension			Heart disease			Chronic arthritis			Aspirin use		
	RR	95% CI	P	RR	95% CI	P	RR	95% CI	P	RR	95% CI	P
Colorectal cancer												
Males + females	0.80	0.63–1.01	0.05	0.73	0.55–0.97	0.03	0.66	0.53–0.83	<0.001	0.60	0.44–0.82	<0.001
Males	0.76	0.55–1.04	0.08	0.70	0.49–1.00	0.05	0.60	0.44–0.82	<0.001	0.72	0.46–1.12	0.13
Females	0.84	0.60–1.19	0.3	0.78	0.50–1.21	0.26	0.74	0.53–1.03	0.06	0.52	0.34–0.80	0.00
After adjustment for diet factors	0.79	0.62–1.02	0.06	0.76	0.56–1.03	0.07	0.71	0.56–0.90	0.004	0.57	0.41–0.79	<0.001
Colon cancer												
Males + females	0.74	0.56–0.98	0.03	0.73	0.52–1.03	0.06	0.57	0.43–0.75	<0.001	0.57	0.39–0.83	0.003
Males	0.71	0.48–1.06	0.09	0.72	0.46–1.12	0.14	0.46	0.31–0.68	<0.001	0.61	0.34–1.10	0.09
Females	0.76	0.51–1.14	0.17	0.75	0.44–1.26	0.27	0.70	0.48–1.03	0.06	0.55	0.33–0.91	0.02
After adjustment for diet factors	0.75	0.55–1.02	0.06	0.72	0.50–1.03	0.07	0.63	0.47–0.85	0.001	0.53	0.35–0.80	0.001
Rectal cancer												
Males + females	0.89	0.66–1.20	0.4	0.73	0.51–1.06	0.09	0.78	0.58–1.03	0.08	0.64	0.43–0.95	0.02
Males	0.82	0.55–1.23	0.3	0.68	0.43–1.09	0.10	0.78	0.53–1.14	0.19	0.83	0.48–1.42	0.5
Females	0.97	0.62–1.51	0.9	0.81	0.45–1.45	0.5	0.76	0.49–1.18	0.21	0.49	0.27–0.87	0.01
After adjustment for diet factors	0.87	0.63–1.20	0.4	0.76	0.52–1.13	0.16	0.78	0.57–1.06	0.10	0.59	0.39–0.91	0.01

sedatives, tranquilizers and sleeping pills was similar for cases and controls and consistent for males and females, colon and rectal cancers combined (Table 3). When these groups of medications were analysed by site (colon cancer and rectal cancer), the above-mentioned effects were unaltered with the exception of non-steroidal anti-inflammatory agents, where a deficit was noted for colon cancer cases (RR=0.66; 95% CI, 0.47–0.92; $P=0.001$) and this was consistent for both males and females.

Operations

A history of a previous bowel polypectomy showed a statistically significant excess in cases and there was also a statistically significant deficit of cases who had uterine curettage (Table 4). The rates of tonsillectomy, appendectomy, haemorrhoidectomy, cholecystectomy, hernia repair, hiatus hernia repair, peptic ulcer surgery, hysterectomy for non-malignant lesions, breast lumpectomy and prostatic surgery for non-malignant lesions showed no statistically significant differences between cases and controls, colon and rectal cancers combined (Table 4).

When these operations were analysed by site (colon cancer and rectal cancers) the above-mentioned effects were unaltered, with the exception of breast lumpectomy, where the deficit was seen only in colon cancer cases (RR=0.22; 95% CI, 0.06–0.78; $P=0.02$). The numbers in this last subset were very small (3 cases and 14 controls).

Multivariate modelling of significant associations

The illnesses and medications that were consistently statistically significantly associated with the risk of colorectal cancer in the univariate analysis were considered simultaneously in a logistic regression equation. The illnesses considered in this

equation were hypertension, stroke, heart disease, chronic chest disease and chronic arthritis and aspirin use. Although 'haemorrhoids' were associated with the risk of colorectal cancer, this variable was not included because of the consideration that 'haemorrhoid symptomatology' is likely to be confounded with that of colorectal cancer. Also, vitamin supplements were not included in the modelling because they form part of the dietary risk model described below.

Chronic chest disease was removed from this equation because the P -value associated with its inclusion was only 0.13. The resulting equation showed that both hypertension and stroke were only marginally significant ($P=0.07$ and $P=0.06$, respectively). The number reporting stroke was small (Table 1) and its effect compared with that of hypertension was considered to have less power; therefore, stroke was excluded from the model at this stage. The model then included hypertension, heart disease, chronic arthritis and aspirin use and was considered to be an adequate explanation of the associations found. These results were consistent across sex and site (colon and rectum) although less statistically powerful in the rectum (Table 5).

In the dietary part of the Melbourne study, a model of dietary risk factors was created. The dietary factors were highly statistically significantly associated with colorectal cancer risk⁷ (deviance change approximated by $\chi_{11}^2=212$, $P<0.001$). These risk factors were low intake of dietary fibre vegetables, cruciferous vegetables, dietary vitamin C, pork, fish, 'other meats' (as defined in the study), vitamin supplements, low or high intake of milk drinks and high intake of fat, and, for males only, high intake of beef. These factors were fitted as possible confounders and did not explain the case-control differences found for hypertension, heart disease, chronic arthritis and aspirin use. Similar effects were found when the data were analysed by colon cancer and rectal cancer (Table 5).

Discussion

In the univariate analysis, the statistically significant deficit of hypertension, stroke, chronic chest disease, chronic arthritis and aspirin use noted for cases is an interesting finding that challenges the cancer epidemiologist to generate new hypotheses of colorectal cancer aetiology and risk. When all these factors were examined together in a logistic regression equation, the effects of stroke and chronic chest disease were very much reduced and were therefore removed from the consequent etiological model. The authors had no a priori hypotheses regarding colorectal cancer and these factors.

Subsequent to these findings, diet was postulated to be the factor explaining the case-control differences found with hypertension, heart disease, chronic arthritis and aspirin use. This was tested by fitting into a logistic regression model, simultaneously, the dietary risk factors (found in the Melbourne study⁷ and described earlier under Results) and the above illnesses and aspirin use. It was seen that the estimation of all these effects was unchanged and then it was concluded that the diet risk factors were independent of the above-mentioned illnesses and aspirin use.

The highly statistically significant deficit of chronic arthritis among cases applied to both males and females separately and was not explained by dietary differences. It may be that the control group was more active throughout their life and have developed degenerative arthritis related to sport or physical activity more often than the colorectal cancer cases. It has been found that physical activity, as seen both in occupational physical activity⁸ and in avocational physical activity,⁹ is protective for colorectal cancer. It may be that with the greater physical activity, the controls are more prone to degenerative arthritis.

A previous history of 'haemorrhoids' was statistically significantly more common in the cases than in controls and this applied to both males and females. The interpretation of these findings is problematic partly because the presence or absence of haemorrhoids was not verified in any other way apart from its being reported at the interview and partly because the word 'haemorrhoids' is very loosely used among lay people for a variety of anorectal conditions other than internal haemorrhoids. Although for the cases, the illnesses were recorded prior to the onset of the symptoms of colorectal cancer, it is possible that for some of the cases, what was taken by them to be a symptom of 'haemorrhoids' was in fact part of the symptomatology of their colorectal cancer. In spite of these serious problems of interpretation, this difference is interesting and is consistent with Burkitt's suggestion that there is an overlapping aetiology between those who have colorectal cancer and haemorrhoids, in as much as both groups have a low intake of dietary fibre.¹⁰ Against this finding on haemorrhoids is that there were no differences in other illnesses postulated by Burkitt to have overlapping aetiologies, namely appendicitis and diverticulitis.¹⁰

An examination of the distribution of cancers other than colorectal cancer among cases and controls showed no statistically significant differences (Table 2). Based partly on inter-population comparisons, it has been suggested that breast cancer and cancer of the endometrium are more frequent in colorectal cancer than others,¹¹ and the Melbourne data are

consistent with this view (Table 2). Of interest was the observation that in questions that relate to previous surgery that may have been done for a cancer, most of the 'don't know' answers were distributed among the cases (Table 2), perhaps indicating differences in recall, or possibly differences in the personalities of the two groups. If the hypothesis that those who develop cancer are often personalities who are passive, who internalize and repress their emotions and who lack self-expression is accepted,^{12,13} then the very high number of 'don't know' answers among the cases may be interpreted as 'don't want to know'.

There was a statistically significant deficit of the use of aspirin and aspirin-containing compounds among cases and these differences remained statistically significant after adjustment for hypertension, heart disease, chronic arthritis and diet in both males and females (Table 5). This finding, whatever the mechanism may be, has potential significance in colorectal cancer chemoprevention and merits early confirmation. Aspirin is now widely used in the chemoprophylaxis of cardiovascular disease and may also be useful in a similar way in the prevention of colorectal cancer and perhaps also of other cancers. There was no statistically significant difference between cases and controls in the previous use of oral contraceptives and this was also the finding in two other case-control studies^{14,15} and one cohort study,⁹ although in one of these there was a trend for protection against colon cancer¹⁴ and in another a trend for risk of rectal cancer¹⁵ with oral contraceptive use. The use of tranquilizers, sedatives and sleeping pills was equally distributed among cases and controls and this was also found in another study on breast cancer and controls.¹² This is in keeping with the finding that extreme nervousness or having had a nervous breakdown is similar among cases and controls (Table 1) and indicates that in the development of colorectal cancer, nervous tension and anxiety are not risk or etiological factors.¹²

With the exception of uterine curettage and bowel polypectomy, the distribution of all other operations was similar between cases and controls (Table 4). There was a statistically significant deficit among cases of uterine curettage. The authors have no hypotheses about this finding. The finding of a 6-fold risk for colorectal cancer in those with a history of previous colorectal polypectomy is consistent with the view that those with adenomatous colorectal polyps require regular surveillance of their large bowel as a screening measure for colorectal cancer.¹⁶ There was no statistically significant association between previous cholecystectomy and colorectal cancer risk in this study (Table 4). While there was some evidence from earlier studies of an association between previous cholecystectomy and right colon cancer in females, this association has probably resulted from a bias due to confounding symptomatology and on current evidence, it seems most unlikely that previous cholecystectomy is a risk for colorectal cancer.^{17,18}

Acknowledgements

This part of the Melbourne Colorectal Cancer Study was generously supported by the 'Nicholas and Elizabeth Slezak Cancer Research Fund' of the University of Melbourne.

Conflicts of interest: None declared.

References

- ¹ Kune GA, Kune S. *The Melbourne Colorectal Cancer Study. A Description of the Investigation*. Melbourne, Australia: University of Melbourne, Department of Surgery Publication, 1986. pp. 1–31.
- ² Kune S. An epidemiological study of colorectal cancer. PhD dissertation. University of Melbourne, 1985; pp. 1–378. No. 8608980, pp. 1–407, Ann Arbor, MI: University Microfilms International, 1986 (copyright).
- ³ Kune S, Kune GA, Watson L. The Melbourne colorectal cancer study: incidence data on age, sex, site, migrants and religion. *Int J Epidemiol* 1986;**15**:483–93.
- ⁴ *SPSS-x User's Guide*. New York: McGraw-Hill Book Co., 1983.
- ⁵ Baker RJ, Nelder JA. *The GLIM System. Release 3*. Oxford, England: Numerical Algorithm Group, 1978.
- ⁶ Adena MA, Wilson SR. *Generalized Linear Models in Epidemiological Research: Case Control Studies*. Sydney, Australia: INTSTAT Foundation, 1982.
- ⁷ Kune S, Kune GA, Watson LF. Case-control study of dietary etiological factors: the Melbourne colorectal cancer study. *Nutr Cancer* 1987;**9**:21–42.
- ⁸ Garabrant DH, Peters JM, Mack TM, Bernstein L. Job activity and colon cancer risk. *Am J Epidemiol* 1984;**119**:1005–14.
- ⁹ Wu AH, Paganini-Hill A, Ross RK, Henderson SBE. Alcohol, physical activity and other risk factors for colorectal cancer: a prospective study. *Br J Cancer* 1987;**55**:687–94.
- ¹⁰ Burkitt DP. Non-infective disease of the large bowel. *Br Med Bull* 1984;**40**:387–89.
- ¹¹ Correa P, Haenszel W. The epidemiology of large bowel cancer. *Adv Cancer Res* 1978;**26**:1–141.
- ¹² Kune GA, Bremond A, Bahnson CB. Personality and psychosocial factors in breast cancer patients. In: Dennerstein L, Fraser I (eds). *Hormones and Behaviour*. Amsterdam: Elsevier/North-Holland Biomedical Press, 1986. pp. 585–89.
- ¹³ Cooper CL, Cooper RFD, Faragher EB. A prospective study of the relationship between breast cancer and life events, type A behaviour, social support and coping skills. *Stress Med* 1986;**2**:271–77.
- ¹⁴ Potter JD, McMichael AJ. Large bowel cancer in women in relation to reproductive and hormonal factors: a case control study. *J Natl Cancer Inst* 1983;**71**:703–9.
- ¹⁵ Weiss NS, Daling JR, Chow WH. Incidence of cancer of the large bowel in women in relation to reproductive and hormonal factors. *J Natl Cancer Inst* 1981;**76**:57–60.
- ¹⁶ Kune GA, Kune S, Watson LF. History of colorectal polypectomy and risk of subsequent colorectal cancer. *Br J Surg* 1987;**75**:1064–65.
- ¹⁷ Friedman GD, Goldhaber MK, Quesenberry CP Jr. Cholecystectomy and large bowel cancer. *Lancet* 1987;**1**:906–8.
- ¹⁸ Kune GA, Kune S, Watson LF. Large bowel cancer after cholecystectomy. *Am J Surg* 1988. (in press).

Commentary: Aspirin and cancer prevention

Gabriel Kune

Accepted 24 August 2007

In research the horizon recedes as we advance.

And research is always incomplete

Mark Pattison 1813–84

English Educationist

Isaac Casaubon (1875) Chapter 10

The risk of colorectal cancer in relation to several chronic illnesses, previous operations and medication use was investigated as a part of a large population-based study on colorectal cancer incidence, aetiology and survival, *The Melbourne Colorectal Cancer Study*, and the results were reported in 1988.¹ We had no specific hypotheses regarding any of the medication groups, which were aspirin, non-aspirin, non-steroidal anti-inflammatories, steroids, oral contraceptives, tranquillizers and sleeping

pills, and these groups were included as a general category of exposures to be tested in this comprehensive case-control study. There were several findings of interest; however, the focus of this commentary is on the statistically significant protective effect among regular aspirin users for both colon and rectal cancer in both men and women, this being the first report of this association. The paper 'Colorectal cancer, chronic illnesses, operations and medications. Case control results from the Melbourne Colorectal Cancer Study' was also the first report of a similar but less consistent protective effect of non-aspirin, non-steroidal, anti-inflammatory drugs in use at that time. The aspirin finding was independent of the other risk factors found in our study up to that time and especially so for the various dietary risks. We wrote in 1988: '...this finding, whatever the mechanism may be, has potential significance in colorectal cancer chemoprevention and merits early confirmation. Aspirin is now widely used in the