The Melbourne Colorectal Cancer Study: reflections on a 30-year experience

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In 1978, I began designing a comprehensive epidemiological and clinicopathological study of colorectal cancer (CRC) incidence, risk and survival, as a single dataset — the Melbourne Colorectal Cancer Study. I was joined by Susan Kune (now Susan Bannerman) as co-investigator, who was chiefly responsible for the dietary, alcohol, smoking and psychosocial aspects; she left a decade later to begin practice as a clinical psychologist. Lyndsey Watson joined as statistician, and continued in this capacity throughout the study.

Here, I present an overview of the study design, the preliminary research, the major results with brief updates, and my views of their possible impact on the understanding of CRC risk, causation and prevention.

Box 1 sets the scene for what can reasonably be regarded as common knowledge about CRC when we commenced the study.

Preliminary consultation and research

Preliminary work commenced in 1978–1980, and involved consulting over 120 Australian and international authorities on the study design, the questionnaires, all aspects of methodology of the principal variables, methods of testing for potential biases, and computer technologies and statistical analyses.[1]

I spent 6 months personally contacting 168 Melbourne surgeons and colonoscopists, 26 pathology groups reporting on colorectal tumour pathology, and the administrations and ethics committees of 59 hospitals, obtaining an unprecedented 100% cooperation rate. Over a year was spent performing pilot studies on almost 400 participants, comprising 160 patients with incident CRC cases, 159 non-cancer hospital control patients (used in part to test for some potential biases) and 80 community control subjects, used for testing and honing the two study questionnaires, training the interviewers, testing the feasibility of interviewing CRC patients after their surgery, and testing the feasibility of the random sampling plan devised by the Australian Bureau of Statistics for the community control subjects. No data from the pilot studies were used in the

ABSTRACT

- This article reflects on 30 years of conducting the Melbourne Colorectal Cancer Study, a comprehensive, population-based investigation of colorectal cancer (CRC).

- The study had an incidence arm, a case–control arm and a survival arm, and contributed considerable knowledge about CRC risk, aetiology, prevention and screening.

- The incidence arm: confirmed high rates of CRC in Australia and the prevalent view that rates rise in first-generation immigrants from countries with low rates of CRC; and enabled the first report of high rates of colon cancer among Australian Jewish people and the first report of high rectal cancer rates anywhere.

- The case–control arm elicited: the contribution of family history, antecedent colorectal polypectomy and multiple antecedent stressful life events to CRC risk; the risk of rectal cancer in habitual beer drinkers; the first dietary risk score (emphasising the importance of a diet pursued over adult life that is high in foods of plant origin and fish, and low in fat and red meat); and the highly protective effect of regular aspirin use (stimulating much research globally, with the possibility of aspirin becoming an important preventive agent).

- The survival arm: found an adjusted CRC-specific 5-year survival rate of 42% among patients with CRC and 85% among matched control subjects; confirmed cancer stage as the most important single determinant of survival; and found that the survival rate among people with the earliest stage of CRC was only marginally lower than that of matched community control subjects, underlining the importance of early detection.

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main analyses. In my view, this preliminary research and consultation was crucial in obtaining reliable high-quality data.

The definitive study

All patients with histologically confirmed incident cases of colorectal adenocarcinoma in metropolitan Melbourne (population 2.81 million) during the 12 months from April 1980 to April 1981 were included.[1] Patients with cancers associated with familial adenomatous polyposis and ulcerative colitis were excluded.

The study had three arms: the incidence study of 1150 incident cases of CRC; the case–control study of 715 cases derived from the 1150 incident cases and 727 community control subjects frequency-matched for age and sex; and the survival study of the 1150 incident cases and the 727 community control subjects. The principal variables examined are shown in Box 2.

The data were obtained by two consecutive face-to-face interviews. The first was conducted by university-qualified science graduates who gathered all relevant data, with the exception of

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1 Common knowledge about ordinary colorectal cancer in the late 1970s

- There was a high incidence in developed countries, such as Australia
- Colorectal polyps were recognised as important precancerous lesions
- History of colorectal cancer in near-relatives was suspected as a risk factor
- Low dietary fibre intake, high fat intake and high alcohol consumption were suspected as risk factors
- Overall 5-year survival of patients with colorectal cancer was about 50%
- The chance of 5-year survival was mainly dependent on the stage of the cancer ◆

2 Variables examined in the three arms of the Melbourne Colorectal Cancer Study

	Incidence arm	Case–control arm	Survival arm	
Cases	1150	715	1150	—
Controls	—	727	—	727
Variables	Age	Family history of colorectal cancer	Age	Survival or death
	Sex	Past colorectal polypectomy	Sex	Cause of death
	Site and subsite of colorectal cancer	Diet	Site of colorectal cancer	
	Country of birth	Alcohol consumption	Cancer stage	
	Religion	Smoking	Other clinicopathological factors†	
	Occupation	Bowel habit		
		Parity factors		
		Past medications		
		Stressful life events		
		Other factors*		

* Such as past surgery, personality factors, etc. † Such as cancer cell differentiation, cell mucin content, bowel obstruction, etc. ◆

past diet, alcohol consumption and smoking status. These data were the subject of the second interview, which was conducted by university-qualified nutritionists. Pathology reports of all incident cases were obtained, as was information from surgeons whenever data such as cancer stage were not available.

Results and updates

The significant findings, both original and confirmatory, of the study are summarised in Box 3.

Incidence study[2]

Incidence rates: The median age of patients with CRC was 67 years, and most were aged 60–79 years. Age-standardised incidence rates per 100 000 population for CRC were high (male colon, 21.0; female colon, 17.7; male rectum, 19.3; female rectum, 12.1). The rectal cancer rates were one of the highest in the world, perhaps in part because of high levels of beer consumption in Australia. These rates were similar to those obtained later by the Victorian Cancer Registry, which first came into full operation after our data were obtained (Graham Giles, Director, Victorian Cancer Registry, personal communication).

Migrants: Our data on first-generation migrants to Australia generally supported the view held at that time that with migration from countries with a low risk of CRC to those with a high risk, such as Australia, there is a transition of rates towards the risk levels of the new country, suggesting that environmental factors are responsible. A new finding was that these rates among migrants were closest to Australian rates for cancers in the distal large bowel, suggesting an increasing role for environmental factors with distance down the bowel.

Jewish people: The Melbourne Jewish population (comprising mainly Ashkenazi Jews) had rates nearly double those of the Melbourne general population for both colon and rectal cancer, and this was a hitherto unreported finding in Australia. Ashkenazim had previously been reported to have elevated rates of colon cancer, but not rectal cancer, in the United States, South Africa and Israel. Non-Ashkenazi Jews living in Israel have low rates of CRC.[3] Significant progress was made in this regard when the first genetic abnormality

in Ashkenazim was found — the I1307K adenomatous polyposis coli gene variant, for which screening is now possible.[4]

Case–control study

Family history of CRC:[5] A positive family history of CRC conferred a twofold, statistically significant and apparently independent risk, and this was higher when more than one relative had a history of CRC. For those aged 50 years or younger, a positive family history of CRC was present seven times more often among patients with CRC than among control subjects. Ten per cent of control subjects and 18% of patients with CRC had a positive family history of CRC. This arm of the study produced the first report from a population-based controlled study, and the data were almost identical to those reported 5 years later in the Nurses' Health Study[6] and the Health Professionals Follow-up Study,[6] and to several other studies reported subsequently.[3] We estimated the risk attributable to inherited factors in ordinary CRC to be 10%,[7] an important indication for screening.

Colorectal polypectomy:[8] There was a sixfold statistically significant risk of CRC with a history of previous colorectal polypectomy. We were therefore early advocates of regular screening with such an antecedent; regular screening is now standard practice.

Diet:[9,10] A fully quantitative dietary history of all foods eaten during the most representative period of adult life was obtained through face-to-face interviews by specially trained nutritionists; this dietary period was always before symptoms developed in patients with CRC. Extensive and unprecedented measures were taken to assess the reliability and validity of the methods relating to the dietary data, and of major potential biases inherent in case–control studies, and it was concluded that no substantial bias was present in the dietary data.[9]

A diet with a high proportion of vegetables when combined with a high-fibre diet was protective; diets with a high intake of cruciferous vegetables were particularly protective, as were vitamin C-rich foods.[10] Dietary fibre alone was not protective, even at the highest consumption level. Fish was highly protective. A diet with a high total proportion of fat was a risk factor, as was a high red meat intake, especially in men. Moderate milk consumption was protective, but very low and very high levels of milk consumption

were risk factors.[10] There was no evidence of overestimation or underestimation of intake when cases were compared with controls.[9] As each of these dietary factors made only a very modest contribution to the risk of CRC, a dietary model — the first of its kind — was elaborated, based on the argument that it is the dietary pattern over many years, rather than individual foods or nutrients, that is important in determining the risk of CRC associated with diet. The previous diet of patients with CRC was very different from that of the controls, with the dietary risk score showing a 200-fold statistically significant difference between what we called a high-risk diet versus a protective diet.[10] With the development of food tables not previously available, we later found that several micronutrients involved in DNA methylation, synthesis and repair, particularly vitamins B_6 and B_{12} and, less consistently, folate-rich foods and some with antioxidant properties (especially vitamins C and E and selenium-rich foods), all had protective effects.[11] Nutritional supplements were not involved in these calculations.

New dietary information has emerged since our publications, which I will summarise briefly. The protective role of fibre has been further de-emphasised, as have, to some extent, foods of plant origin. Fats have been classified, and the CRC risk is believed to lie mainly with saturated fat. Low-fat and non-fat dairy foods have been developed, and calcium intake has been emphasised as being protective. High energy intake and obesity have come to be regarded as risk factors for CRC. However, a diet high in plant foods (ie, vegetables, fruit, nuts and whole grains) as well as fish, low-fat or fat-free dairy foods, a low intake of saturated fat and red meat, a low energy intake and weight control remain important.

Alcohol consumption:[12] Lifetime alcohol consumption conferred a twofold independent, statistically significant risk for rectal cancer among beer drinkers, with a significant dose–response effect. A high intake of vitamin C-rich foods annulled this risk. Foods rich in vitamin E and lycopene and, to a smaller extent, vitamins B_6 and B_{12} and folate-rich foods, also had an ameliorating effect (data to be published). These ameliorating dietary factors raise the possibility that there may be relatively simple dietary means of counteracting the risk of CRC in habitual beer drinkers, and these deserve further investigation.

Parity factors:[13] A statistically significant, independent protective effect for CRC was found for patients with one or more children compared with those who had no children, and there was also an increasing risk with increasing age at the birth of the first child. An intriguing finding was that these risks were not statistically different for men — a finding that cannot be verified for lack of other data. There was a null finding for colon cancer in previous users of oral contraceptives (OCs), and a twofold statistically significant risk of rectal cancer among previous users of OCs; this risk was particularly high among those with rectal cancer who were also beer drinkers.[14]

Null results: There were several null results (ie, associated with neither an increased nor decreased risk of CRC), which included chronic constipation, diarrhoea and laxative use,[15,16] previous surgery (including cholecystectomy),[17] and previous use of medications, with the exception of aspirin, discussed below. The effect of smoking was also largely null, except among a subgroup of men who smoked heavily, who showed a modest risk of colon cancer.[18] Physical activity, now regarded a likely protective factor, was unfortunately poorly measured in our study, and for a limited period only, with a null result.[19]

Religiosity:[20] Perceived self-reported "religiousness" was a statistically significant, independent protective factor, reducing the risk of CRC by 30%.[20] This is intriguing, but no comparable data are available.

Stressful life events: Major illness or death of a family member, major family problems and major work problems over the 5 years preceding diagnosis were significantly more common among patients with CRC than control subjects, and patients with CRC reported being significantly more upset with these life changes than did control subjects; these findings were independent of other risk factors found in the study.[21] As events in the distant past

were not risk factors, this temporal relationship caused us to hypothesise that recent events acted in some unknown way as a "proliferative stimulus" for the multiplication of precancer and cancer cells. Subsequently, an excellent case–control study from Sweden reported very similar results.[22]

Aspirin: A statistically highly significant protective effect of a 40% reduction in the risk of both colon and rectal cancer was found in both men and women who were regular aspirin users when compared with non-users; this effect was independent of other risk factors found in the study.[23,24] This world-first report in 1988 was followed by much research globally, confirming our data and establishing a causal relationship between aspirin and CRC prevention.[25] New lines of research indicate (i) that there may be subgroups in whom aspirin may be more effective for colorectal tumour chemoprevention, such as overweight or obese people, or those with, for example, variants of the UGT1A6 genotype; or (ii) that modified forms of aspirin, such as nitric oxide-donating aspirin, may be more effective than regular aspirin.[25]

However, several concerns have emerged that, at present, prohibit a role for aspirin in general chemoprevention of CRC. These concerns include a determination of the appropriate chemopreventive dose, the duration of aspirin administration, a precise delineation of the groups for whom such chemoprevention might be valuable, and the minimisation of adverse effects, particularly gastrointestinal bleeding.[25] Research is proceeding to answer these questions. My prediction is that aspirin will find a place in colorectal tumour prevention, most likely for individuals at increased risk (eg, those with previously removed adenomas or early cancers, or those with an inherited predisposition). Indeed, a recent report of a randomised trial indicates a protective effect of aspirin among those with hereditary non-polyposis CRC.[26]

Survival study

Five-year survival data were obtained for 97% of the 1150 patients with incident CRC cases and 96% of the 727 community control subjects. The adjusted 5-year CRC-specific survival rate was 42% among the cases and 85% in the age- and sex-matched control subjects.[3,27] The death rate from causes other than CRC was similar in the two groups, confirming the expectation that CRC patients die prematurely as a result of their cancer.[3]

The extent of the cancer as determined by clinicopathological staging was the most important single discriminatory factor ($P < 0.001$), confirming the findings of several previous reports.[27] Importantly, survival in the earliest stage of the disease (cancer confined to the bowel wall) was only marginally worse than that of the age- and sex-matched control population, highlighting the importance of early detection.[3] When adjusted for cancer stage, survival was better among women than men, better among those with cancer of the colon than cancer of the rectum, better for younger patients (except for incurable cases), and better with a high degree of cancer cell differentiation. Survival was not affected by the CRC being the first or a single tumour, multiple or synchronous primary tumours or a metachronous tumour. Survival was also not influenced by a positive family history of CRC, nor by parity factors.[27,28]

Survival rates have improved since we conducted our study, possibly because of the impact of screening, including with new techniques that detect more early cancers, and modern chemotherapy being used for advanced cancers.

Conclusions

The extensive 2-year preliminary consultation and research process was arduous, but it gave us some confidence about the accuracy and quality of the data ultimately obtained, and I strongly endorse it for similar studies. An early major challenge for me was to obtain the necessary funding, as the usual funding sources provided only 5% of the monies, presumably because the study design was untested.

The three arms of this population-based comprehensive study were within a single dataset, which allowed for extensive internal statistical manipulation, as well as external comparison. This design may be useful in aetiological and early-detection studies of other common cancers, such as breast and prostate cancer.

Some important likely risk factors slipped under our radar and were omitted, such as a whole-life measurement of physical activity and total calcium intake, and I take responsibility for these omissions. On the other hand, it was gratifying to publish some important world or Australian "firsts", or at least to publish one of the early reports that led to much more research, and some progress in the prevention and early detection of CRC. This includes the elevated rates in the Jewish population (screening), family history of CRC (screening), previous colorectal polypectomy (screening), a quantifiable model of dietary risk (prevention), and the highly protective effect of regular aspirin use (prevention). Much progress has been achieved in the prevention and early detection of CRC over the past 30 years, and much more still needs to be done. Although it was arduous at times, it has been a joy to be a small part of this progress.

Competing interests

None identified.

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