

The Canterbury Inflammatory Bowel Disease (IBD) Study

What have we found out three years later?

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Introduction

Specialists working in Canterbury have noticed that there has been an increase in the number of people being diagnosed with IBD in Canterbury over recent years. IBD comprises **Crohn's disease (CD)** and **ulcerative colitis (UC)**. This led to Dr Richard Gearry undertaking a PhD over three years to gain more knowledge of IBD in the Canterbury region. The Canterbury IBD Study began in 2003. The aims of the study were to determine:

- How common IBD is in Canterbury
- The pattern of disease in Canterbury (eg age, sex, race)
- Patterns of drug treatment and surgery amongst people with IBD in Canterbury
- The role of specific genes in IBD in Canterbury
- The role of environmental factors in IBD
- The effect of IBD on people's lives in Canterbury.

Researchers have done similar studies in other parts of the world, but this study had a very important difference. We wanted the study to be population-based, in other words, to include all people with IBD living in Canterbury regardless of age, sex or severity of disease. Almost all other studies have come from specialist centres and, therefore, often only have people with more severe IBD.

These studies have taken place over the last three years and the results are now available to participants in the study. This report summarises results of this research.

Methods

Over a two year period, 1420 Cantabrians with IBD gave informed consent to take part in this study. Each of these people gave a blood sample for DNA (genetic information), completed a questionnaire regarding environmental factors and gave permission for the researchers to check their medical records. The information was stored in secure computer databases. People without IBD (controls) also gave blood for genetic studies, or completed questionnaires to allow comparisons to be made between those with and those without IBD. Finally, statistical analysis was carried out on the data.

Results

The results of the Canterbury IBD Study will be divided into several sections and presented with the results of other studies performed in other parts of the world.

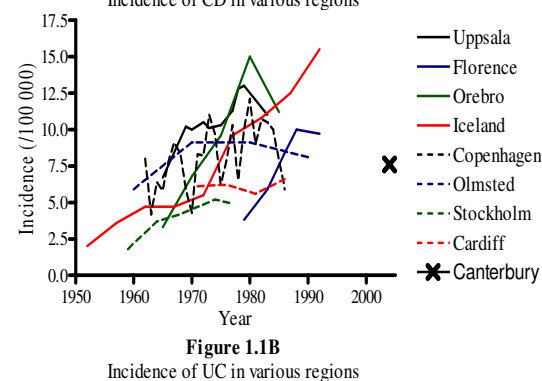
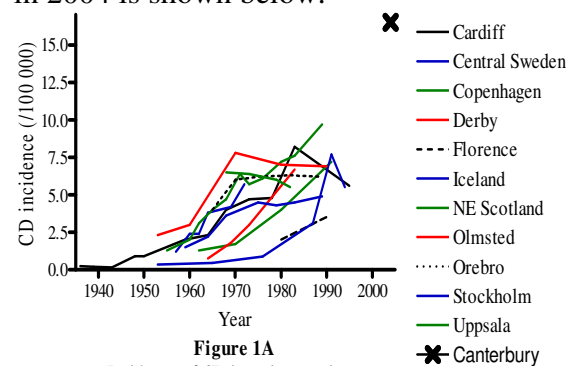
How common is IBD in Canterbury?

This question can be answered in two ways. Firstly, it is important to

know how many new cases are diagnosed each year (**incidence**). Secondly, it is also useful to know how many people have IBD in our community (**prevalence**)

Incidence

The IBD incidence in Canterbury in 2004 is shown below.



Figures 1A and 1B show that in 2004, Canterbury had the highest ever recorded incidence of CD. Previous studies from NZ (1962, 1982, 1984) suggested that CD was

less common here than in other countries but our results don't support this. As with a number of other countries, CD is now diagnosed more often than UC. The incidence of UC is comparable to that of other countries.

Prevalence

Canterbury has the second highest prevalence of CD ever recorded (155/100,000 people) compared with the highest from Manitoba in Canada (199/100,000). In our study, we estimate that over 91% of people with IBD living in Canterbury were included, so in fact the true number may be slightly higher. The prevalence of UC was similar to that from other regions (145/100,000). This is the first study to show more people with CD than UC in a given population.

Who is getting IBD?

Figures 2A and 2B show the sex and age distributions (at diagnosis) for people in Canterbury with IBD. More females than males are diagnosed with CD after the age of 15 years, although the reverse is true before this age.

Both CD and UC are most likely to be diagnosed between 15 and 35 years, although there has been a recent increase in the number of people diagnosed with CD after 45 years of age.

In Canterbury, both CD and UC are uncommon in Maori people and no people of Pacific Island descent were identified.

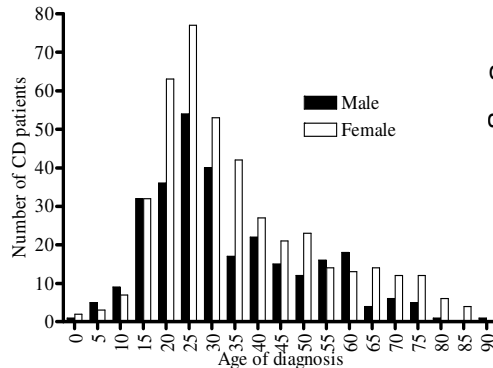


Figure 2A (Crohn's disease)

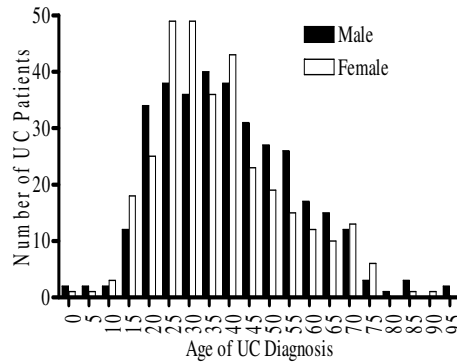


Figure 2B (ulcerative colitis)

What is IBD like in Canterbury?

For UC, the extent of colonic inflammation differs between individuals and can be classified as proctitis (affecting the rectum), left-sided disease (affecting the bowel from the anus to the splenic flexure) or pancolitis (affecting the entire colon) – see Figure 3A.

Figure 3B shows the distribution of inflammation for people in Canterbury with UC, compared with other large studies.

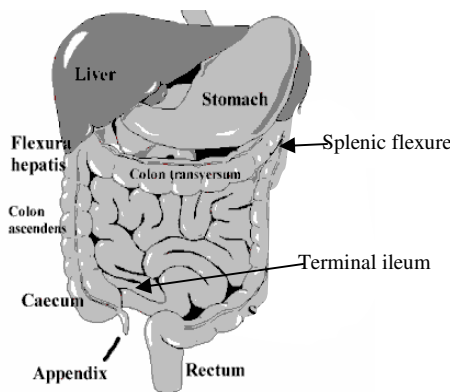


Figure 3A

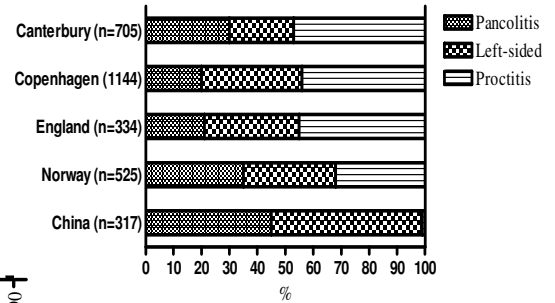


Figure 3B

The extent of disease also varies in CD. It is usually divided into ileal disease, colonic disease, ileocolonic disease and upper gastrointestinal disease. It may also be divided according to the way it behaves, including stricturing disease (narrowing of the bowel), penetrating disease (abscesses or fistulae) or inflammatory disease. These aspects are shown in Figures 3C and 3D respectively.

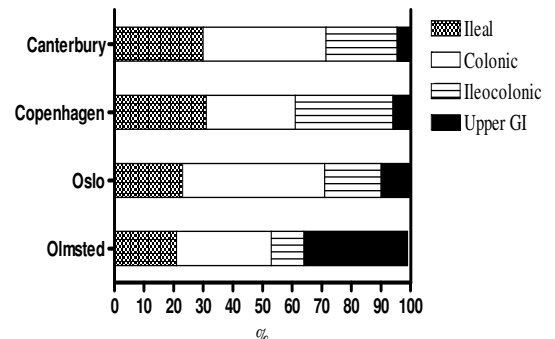


Figure 3C

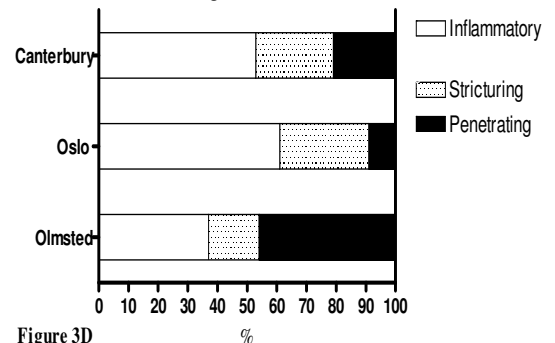


Figure 3D

Sometimes IBD can affect other parts of the body such as the liver, skin, joints or eyes. In Canterbury this was the case for 17.2% of patients.

How are people in Canterbury with IBD being treated?

The medical treatment of IBD usually includes the use of drugs and sometimes surgery. We were interested in how people in Canterbury were being treated for IBD.

Medications

Complementary and alternative medicine (CAM) use was assessed amongst those with IBD and controls. There was no difference in the overall rate of CAM use between those with and without IBD. However, some CAMs were used more frequently in those with IBD, notably slippery elm, omega3, fish oils and probiotics. Minerals were less commonly taken by those with IBD, possibly because they had been prescribed them by their doctor, rather than purchasing them independently. Those most likely to use CAM were females, of younger age, lower socio-economic status and coming from a middle class background. Interestingly, IBD severity and duration were not linked to high CAM use.

The most commonly prescribed drugs for IBD were 5-ASAs such as sulphasalazine, Asacol and Pentasa, with 72% of CD and 67% of UC patients using these drugs at the time of the study. Overall, 52% of CD and 23% of UC patients have ever been prescribed an immune system modulator such as azathioprine, methotrexate or infliximab. 16.7% of people with IBD in Canterbury were currently taking no prescribed medication for IBD (including those who had previously had surgery).

Surgery

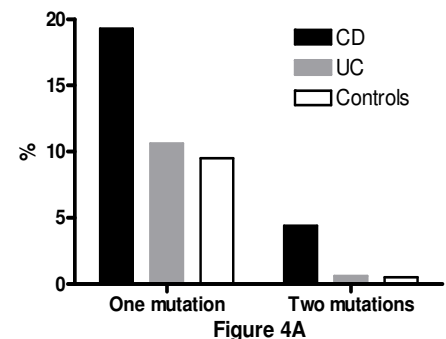
With regard to surgery, 33.6% of people with CD, and 16.3% with UC have required a bowel resection. CD patients tend to have bowel resections earlier in the course of their disease than those with UC. On average, CD patients have bowel resections earlier in the course of their disease than UC patients (2.2 years versus 7.8 years from diagnosis). On occasion, patients require permanent stomas following bowel resection. This occurred in 5.5% of CD patients and 6.3% of UC patients. CD patients may also require surgery for perianal disease. This was the case in 18.3% of patients, with 5.4% requiring greater than three perianal operations.

Are genes important in IBD?

It has long been recognized that the strongest risk factor for IBD is a family history of IBD. In 2001, mutations in the *CARD15* gene were found to be associated with CD in a number of populations around the world. These populations were from referral centres, which tend to have more sick patients. Therefore we looked at how common these mutations were in the whole Canterbury IBD population. Figure 4A shows the percentage of people without IBD, with CD and with UC who have either one or two mutations in the *CARD15* gene.

The first important fact is that less than 25% of Canterbury people with CD have a mutation in the *CARD15* gene. This is lower than in many other studies. Secondly, having one mutation doubles the risk of developing CD, while two mutations is associated with a ten-

fold increased risk. These risks are lower than those seen in studies from referral centres. There is no association between UC and *CARD15* mutations.



Some types of CD are more often associated with mutations in this gene. CD patients with inflammation of the ileum were 3x more likely than other CD patients to have a *CARD15* mutation, those with stricturing disease behaviour were 2x more likely, those who have had a bowel resection 4x more likely, those diagnosed before 17 years of age 2x as likely and those with a first degree relative with IBD 1.5x as likely.

Studies from referral centres tend to have more of these sorts of patients in their studies which may explain the high rate of *CARD15* mutations in other studies.

At this stage, *CARD15* genotyping is not performed routinely and has no clinical value, although information from this study will be helpful in defining clinical uses in the future.

What environmental factors are associated with IBD?

The questionnaire that was completed by participants in the Canterbury IBD Study was used to determine whether there were differences between environmental

factors that people with and without IBD have been exposed to.

Complex statistical analysis was used to control for confounding factors and produce a “multivariate logistical regression model.” A summary of many of the key positive findings can be seen in Table 5A and 5B. The results do not prove that an environmental factor causes IBD, rather that it is associated with IBD and the two could be linked.

Tables 5A and 5B demonstrate odds ratios for each of the risk factors. These are an estimate of the relative risk of having CD or UC if one has been exposed to the risk factor. Eg. OR=10 means that people with IBD are 10x more likely than people without IBD to have been exposed to the factor (ten-fold increased risk). OR=0.5 means that people without IBD are twice as likely as people with IBD to have been exposed to the factor (two-fold risk reduction). 95% confidence intervals are also given. These are a measure of how significant a result is. If the number 1 lies within the interval then it is unlikely that there is a significant association. Over 70 individual factors were assessed in the questionnaire, but only a small number of these are included in this report.

For both CD and UC, a family history of IBD is the strongest risk factor. Smoking is associated with an increased risk of CD but a reduced risk of UC. Being an ex-smoker is a risk factor for UC. Urban living is more common in those with CD than controls, as is contraceptive pill use amongst females with CD.

| Risk Factor | OR | 95%CI |
|-----------------------------------|-----|---------|
| One relative with IBD | 3.0 | 2.2-4.1 |
| Two relatives with IBD | 7.0 | 3.3-15 |
| Smoker at diagnosis | 2.0 | 1.5-2.7 |
| Maternal smoking in pregnancy | 1.7 | 1.2-2.3 |
| Appendicectomy | 1.7 | 1.2-2.0 |
| Tonsillectomy | 1.5 | 1.1-2.0 |
| Breastfed as infant | 0.5 | 0.4-0.7 |
| Oral Contraceptive Pill use | 1.8 | 1.1-3.1 |
| High antibiotic use (adolescence) | 2.1 | 1.3-3.3 |
| Urban living | 1.5 | 1.1-2.1 |
| Childhood vegetable garden | 0.5 | 0.4-0.7 |
| High childhood SES | 1.6 | 1.1-2.2 |
| High recruitment SES | 0.5 | 0.3-0.7 |

Table 5A Environmental factors and CD

| Risk Factor | OR | 95%CI |
|-----------------------------------|-----|---------|
| One relative IBD | 2.5 | 1.8-3.5 |
| Two relatives IBD | 6.8 | 3.2-15 |
| Smoker at diagnosis | 0.7 | 0.5-0.9 |
| Ex-smoker at diagnosis | 1.8 | 1.4-2.4 |
| Appendicectomy | 0.4 | 0.3-0.7 |
| Breastfed as infant | 0.7 | 0.5-0.9 |
| High antibiotic use (adolescence) | 1.7 | 1.1-2.8 |
| Childhood vege garden | 0.6 | 0.4-0.9 |
| Childhood SES | 1.7 | 1.2-2.4 |

Table 5B Environmental factors and UC

Appendicectomy is associated with an increased risk of CD (probably due to misdiagnosis of CD as appendicectomy) but a reduced risk of UC. These findings are the same as in other studies.

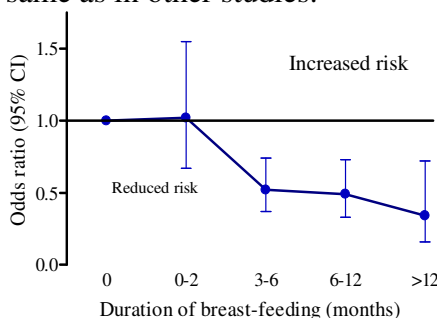


Figure 5C. CD/duration of breast-feeding

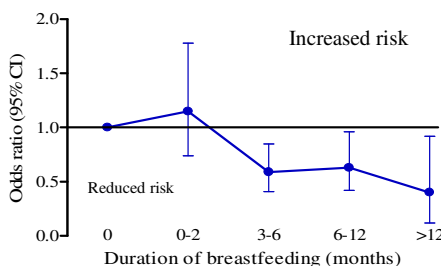


Figure 5D. UC/duration of breast-feeding

Breast-feeding is protective for the later development of both CD and

UC. In fact, this study is the first to show a duration-response effect, whereby the risk is only reduced after at least three months of breast-feeding (Figure 5C & 5D). Other interesting findings include the increased risk of CD in those with high antibiotic use in adolescence and those who have had a previous tonsillectomy. This may suggest that hygiene-related factors or infection may play a role in the subsequent development of CD. A surprising finding was that having a vegetable garden in one’s property in childhood was associated with a reduced risk of developing CD or UC. It is unclear how this association manifests itself, but it may reflect dietary differences between IBD cases and population controls.

How does IBD affect people?

Illness can have many effects on a person’s ability to function normally. This can be measured in a number of ways. For this study, we elected to use absenteeism from work, and questions that had previously been used in the 2001 New Zealand Census. Figure 6A and 6B show the effect of IBD on absenteeism from work.

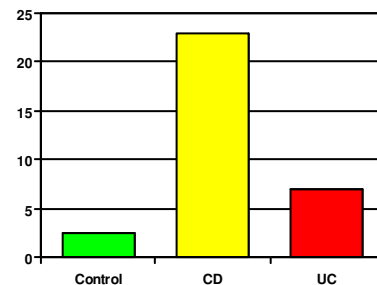


Figure 6A Number of days off work/year

Interestingly, people with IBD are no more likely than controls to have greater than one day away from usual activities. However, if

days off are taken, the number is considerably greater for patients with CD, than for UC or controls.

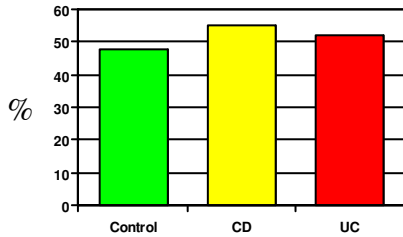


Figure 6B % >1 day away from usual activities

Figures 6C and 6D show the responses to the questions from the census concerning disability and activities of daily living.

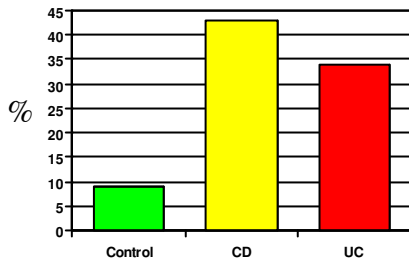


Figure 6C Does a health problem or condition you have cause you difficulty with or stop you doing everyday activities that people your age can usually do?

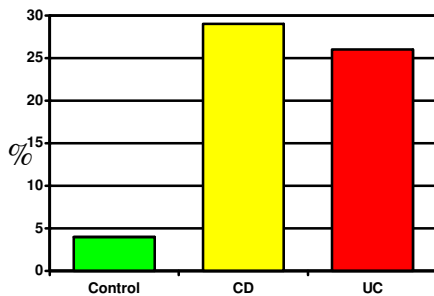


Figure 6D. Does a health problem or condition you have (>6 months) cause you difficulty with or stop doing communicating, mixing with others or socialising?

Figures 6C and D demonstrate that people with IBD may have times when they are not able to function as they usually would. This underlines the importance of further research into the causes of IBD and to improve treatment.

Conclusions

- IBD, particularly CD, is much more common in NZ than previously thought - we have the highest reported rate of CD.
- The pattern of IBD in Canterbury is similar to that seen in other populations.
- Complementary and alternative medicine use is no greater in people with IBD.
- Most CD patients have been prescribed an immune system modulator drug and most IBD patients are taking a 5-ASA drug.
- 16.7% of patients are currently on no medical treatment for IBD.
- One third of CD and one sixth of UC patients have had a bowel resection. 5% of IBD patients have a permanent stoma. Almost 20% of CD patients have required perianal surgery.
- *CARD15* gene mutations are associated with CD but are found less commonly in the Canterbury IBD population. Other genetic studies are planned for the future.
- Environmental factors are important in the development of IBD, specifically:

| | |
|--------------|----------------|
| smoking | appendicectomy |
| OCP use | tonsillectomy |
| urban living | antibiotic use |
- Breast-feeding for at least 3 months shows a protective effect for both CD and UC.
- People with IBD are no more likely to have time away from usual activities but if they do, it is for longer periods of time.
- IBD is associated with a reduction in everyday activities for some people.

Future directions for the Canterbury IBD Study

The work performed up until now represents the start of an ongoing research programme into IBD in Canterbury. The information that has been collated and analysed represents the first population-based IBD research resource of its type anywhere in the world. We aim to continue to perform ongoing studies into the causes of IBD and attempt to develop improved strategies for treating this condition.

Highlights this year include the following:

- A public lecture to present the results of this study and to increase public awareness of IBD and gastrointestinal health.
- Presentation of four papers from this study at Digestive Diseases Week in the USA (the largest and most prestigious annual gastroenterology conference in the world).
- Presentation of this research at other international meetings to be held in NZ, Australia and further afield.
- Publication of several papers relating to this research in international medical and scientific journals.
- Publication of Richard Geary's thesis "Aspects of IBD epidemiology and aetiology in Canterbury, New Zealand."
- Collaboration with other researchers in NZ and abroad in studies of IBD genetics, pharmacogenetics and potential microbial triggers of IBD.

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- Ongoing clinical trials of new therapies in IBD through the Gastroenterology Department, Christchurch Hospital.

Acknowledgements

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The Canterbury IBD Study has been a large collaborative project that began in 2003. As Principal Investigator, I would like to thank the other investigators Murray Barclay, Michael Burt, Bruce Chapman, Judith Collett, Chris Frampton, Martin Kennedy, Ann Richardson and Rebecca Roberts for their dedication to and support throughout this project. As a group, the investigators would like to specifically thank the following people:

Participants in the study

1420 people with IBD gave their time and a blood sample to help with the study. Without their help this research would not have taken place. We would specifically like to thank the Crohn's and Colitis Support Group and the Canterbury Ostomates Society for their support.

600 people agreed to complete a questionnaire to act as a control group for this research. Again, this was vital to the success of the project.

Research assistants

Andrew Dodgshun, Pip Shirley, Megan Reilly, Ramez Ailabouni, Cindy Chang, Charlotte Duncan and David Tan are medical students who all worked hard to recruit control participants, enter and analyse data. Judy Hoar, Rhonda Brown and Heather Brunton all worked tirelessly to enter data and post out forms to patients. Allison Miller, Nick Bockett, James Yeo and Melanie Allington worked tremendously hard on the genetics side of the project.

Health professionals

Physicians, paediatricians, general practitioners, general and colorectal surgeons throughout Canterbury allowed access to patient records and we are grateful to both the doctors and their nursing and administrative staff for their help in both the public and private sector. I would specifically like to thank the Department of Gastroenterology and Outpatient Department, Christchurch Hospital for their patience and support of this project.