Colorectal Cancer in NZ: Stuck at the bottom of the world?

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Disclosures

• No financial conflicts of interest?
• Paid to research and treat CRC, public and private
Cancer is the leading cause of death in NZ

- Cancer
- Heart disease
- Cerebrovascular disease
- Lung disease
- Diabetes
- Road accidents
- Other
2010 NZ Cancer Registrations

Men 11 068

Women 10 167

- Prostate: 27%
- Colon & rectum: 14%
- Melanoma of skin: 11%
- Lung & bronchus: 10%
- Non-Hodgkin lymphoma: 4%
- Kidney: 3%
- Leukaemia: 3%
- Urinary bladder: 2%
- Stomach: 2%
- Head & Neck: 2%
- All Other Sites: 20%

- Breast: 28%
- Colon & rectum: 14%
- Melanoma of skin: 10%
- Lung & bronchus: 9%
- Uterine corpus: 4%
- Non-Hodgkin lymphoma: 3%
- Ovary: 3%
- Leukaemia: 3%
- Pancreas: 2%
- Kidney: 2%
- All Other Sites: 22%

*Excludes basal and squamous cell skin cancers.
Source: Cancer: New Registrations and Deaths. MOH 2013
Worldwide Variations in Colorectal Cancer

International Agency for Research on Cancer

World Health Organization

More developed regions
- Central and Eastern Europe
- Northern Europe
- Micronesia
- Eastern Asia

Less developed regions
- Southern Africa
- Polynesia
- Melanesia
- Central America
- Northern Africa
- Eastern Africa
- South-Central Asia
- Middle Africa
- Western Africa

Male
Female

Incidence
Mortality
## Dietary meat consumption by region

<table>
<thead>
<tr>
<th>Rank</th>
<th>BEEF AND VEAL</th>
<th>kg/person/yr</th>
<th>All meat</th>
<th>Kg/person/yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Argentina</td>
<td>70.2</td>
<td>Luxembourg</td>
<td>136.73</td>
</tr>
<tr>
<td>2</td>
<td>Uruguay</td>
<td>60.4</td>
<td>United States</td>
<td>122.79</td>
</tr>
<tr>
<td>3</td>
<td>United States</td>
<td>45.3</td>
<td>Australia</td>
<td>122.7</td>
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<tr>
<td>4</td>
<td>Australia</td>
<td>40.2</td>
<td>New Zealand</td>
<td>116.81</td>
</tr>
<tr>
<td>5</td>
<td>New Zealand</td>
<td>34.1</td>
<td>Spain</td>
<td>111.56</td>
</tr>
<tr>
<td>6</td>
<td>Brazil</td>
<td>32.3</td>
<td>French Polynesia</td>
<td>108.61</td>
</tr>
<tr>
<td>7</td>
<td>Canada</td>
<td>32.1</td>
<td>Austria</td>
<td>103.18</td>
</tr>
<tr>
<td>8</td>
<td>France</td>
<td>26.8</td>
<td>Cyprus</td>
<td>102.18</td>
</tr>
<tr>
<td>9</td>
<td>Italy</td>
<td>26.3</td>
<td>Israel</td>
<td>98.89</td>
</tr>
<tr>
<td>10</td>
<td>Czech Republic</td>
<td>24.5</td>
<td>Canada</td>
<td>98.83</td>
</tr>
</tbody>
</table>


Food and Agriculture Organization of the United Nations (FAO) 2010, Livestock and Fish Primary Equivalent, 02 June 2010, FAOSTAT on-line statistical service,

Risk factors

- Personal / Family history
- Ulcerative colitis
- Hyperinsulinism: RR 1.30
- Alcohol: > 2 pints/d, 4 glasses wine / d: RR 1.41
- Obesity: RR 1.5 if BMI > 25
- Vitamin B6 inversely related to colon cancer risk: RR 0.51
  - Unclear whether supplementation or diet important
- Exercise: RR 0.33-0.60
- Diet – Western Diet
- Red meat > 300g / week
- Smoking – modest increased risk
- Vitamin D, Calcium controversial

Association does not prove causation
Mortality CRC NZ and AUS

\[ y = 2E^{-0.05}x^4 - 0.0022x^3 + 0.0722x^2 - 0.6147x + 24.153 \]
\[ R^2 = 0.9168 \]

\[ y = -0.0002x^3 + 0.0094x^2 - 0.0854x + 20.898 \]
\[ R^2 = 0.982 \]

Teo, Sneyd, Jackson 2012, Unpublished data
CURRENT DIAGNOSIS & TREATMENT
Symptoms: non-specific

• Few symptom clusters specific
• Mostly age > 50
• Persistent change in BM > 6 weeks
• Particularly tendency to looser more frequent stool
• Bloating, gurgling
• Abdominal mass
• Tenesmus, narrow stool, bleeding, melena
• Anemia; r/o coeliac, IBD
• Family and personal history important, not well recorded
Investigations

- Family and personal history
- Rectal examination
- Bloods: Ferritin and coeliac screen
- CEA not helpful in early disease
- Imaging:
  - Barium enema misses 20%
  - FOBT: validated in asymptomatic people
    - Guaiac v IHC
  - CT Colonography
- Colonoscopy gold standard; access
CT Colonography

- Bowel prep still needed
- Detects lesions >1cm
- Abnormalities need colonoscopy: 8%
- Those with high risk or personal hx shd still get colonosc
- 7% incidental findings need further Ix

Kim et al NEJM 2007: 357;14:: 1403-1412
THE NEW ZEALAND PROBLEM

Why are we doing so badly?
Mortality

Incidence

Diagnosis

Treatment

Comorbidity

Ethnic inequities

Mortality
Cancer stage at diagnosis

Samson, O’Grady, Keating. NZMJ 2009
Colonoscopy access

• UK: Timeliness measures since 2000
• Aus: Medicare
• US: Carte Blanche

• Screening
• Private capacity
• Nurse endoscopy

Timeliness of care – first intervention

Time to first treatment – Auckland Rectal Cancer

Murray, Findlay NZMJ 2011
Health Care Systems: Complex “extracellular” signalling pathways

Laurent-Puig P et al. JCO 2012;30:1550-1552
Timeliness of care – adjuvant therapy

Colon cancer
- 2 to 4 weeks: 6%
- 4 to 6 weeks: 21%
- 6 to 8 weeks: 42%
- 8 to 12 weeks: 19%
- >12 weeks: 12%

Rectal cancer
- 0 to 2 weeks: 5%
- 4 to 6 weeks: 24%
- 6 to 8 weeks: 38%
- 8 to 12 weeks: 24%
- >12 weeks: 10%
## Components of delay to adjuvant treatment

<table>
<thead>
<tr>
<th>Component</th>
<th>Dunedin n=38</th>
<th>Invercargill n=25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical</td>
<td>20 days</td>
<td>32 days</td>
</tr>
<tr>
<td>Inpatient stay</td>
<td>8 (6-13)</td>
<td>6 (5-12)</td>
</tr>
<tr>
<td>Post-operative complications / readmission</td>
<td></td>
<td>17%</td>
</tr>
<tr>
<td>Clerical factors</td>
<td>5 (1-7)</td>
<td>14 (11-21.5)</td>
</tr>
<tr>
<td>Decision delay</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Oncological</td>
<td>36 (26-48)</td>
<td>28 (22-39)</td>
</tr>
<tr>
<td>FSA capacity delay</td>
<td>14 (11-20)</td>
<td>16.5 (13-21)</td>
</tr>
<tr>
<td>Treatment capacity delay</td>
<td>12.5 (7-25)</td>
<td>6 (5-12)</td>
</tr>
<tr>
<td>Overall time to adjuvant treatment</td>
<td>56 (47-69)</td>
<td>60 (44-68)</td>
</tr>
</tbody>
</table>

Jackson, Parkin et al – in preparation
Treatment factors

• National quality initiatives
  – EURECCA rectal cancer
• Drug access (minor)
• Aggressive surveillance?
• Aggressive management of recurrence?
Quality of follow-up

Timeliness of colonoscopy related to surgery, by age and tumour site

Ahmadi, Jackson NZAGS 2010
Comorbidity
Ethnic inequalities – quality indicators

- Lower lymph node harvest
- Higher peri-operative mortality
- Lower rates of adjuvant chemotherapy; longer wait to commence
- Higher rates of palliative bypass or stoma
- Less likely to receive treatment at Cancer Centre or Private facility
- “Lower quality of care”

Hill, Sarfati et al Cancer 2010
Political Factors

• Publically funded colonoscopy resource
  – Aus, US, Canada
• Wait time targets for investigation of cancer
  – Aus, UK, US
• Slower uptake of adjuvant drugs
  – Aus Oct 05; UK Apr 06; NZ Dec 07
• Fewer advanced disease drugs
• National screening programmes
  – Pilots: UK 2000; Aus 2004; NZ 2011
• Capturing outcomes
• Meaningful reporting of quality
Recent initiatives

- National Bowel Cancer Work Group
- Direct access colonoscopy
- Increase in CT Colonography
  - Reduction in Barium Enema
- Faster Cancer Treatment Indicators
- CRC Screening PILOT
- CRC Standards of service provision
- Sill lacks major investment
Issues for Primary Care

• Non-specific symptoms
  – The FOBT is not for the symptomatic patient (insufficient sensitivity and specificity in diagnostic context)

• Referral pathways
  – “High suspicion”
  – Don’t use barium enema

• Screening for family members
  – NZFGICS
  – NZ Guidelines Group

• Dietary advice

• Exercise advice

• Aspirin advice

• Alcohol advice

• Follow-up once diagnosed
WHAT YOU SHOULD KNOW ABOUT BOWEL CANCER

Don’t sit on your symptoms

Click here for a brochure

It could be the death of you!

Don’t sit on your symptoms

Beat Bowel Cancer

NOW

LATER

TOMORROW

NEXT YEAR

NEXT WEEK

SAME DAY
Colorectal Cancer: New Zealand's Cancer.
Chemoprevention: ASPIRIN

- COX-2 over expressed in 2/3 CRC
- JAMA 2009: 1279 pt nested cohort, 2ndry prevention, 12 year follow-up
  - Observational; 81-325mg
  - 4% reduction in recurrence and mortality in stage 1-3 pts.
  - NNT = 25; GI bleeds 1.4 per 1000 pt years
  - Only COX-2 over-expressing tumours
- Lancet 2010: Primary prevention of CVD, 4 randomised studies; analysis of CRC risk
  - Strong proportional reduction: 56% for right sided tumours; 2% absolute benefit
Lifestyle advice – diet

• JAMA 2007: Meyerhardt
• 1009 patients
• Dietary patterns and relapse rates
• Effect as strong as adjuvant chemotherapy; cumulative not exclusive
• US PPP trial as supportive evidence
  – Dietary intervention independent of obesity, T2DM
Lifestyle advice – exercise

- 668 patient cohort with stage 1-3 CRC
- Pre- and post-cancer exercise levels
- Highest MET level halves risk of CRC compared with lowest
- Brisk half hour walk = 3.3
- 10 min run = 10 MET

Lifestyle advice – general

- Hyperinsulinism: RR 1.30
- Obesity: RR 1.5 if BMI > 25
  ➔ Lose weight
- Alcohol: > 2 pints/d, 4 glasses wine / d: RR 1.41
  ➔ Drink less
- Vitamin B6 inversely related to colon cancer risk: RR 0.51
  ➔ Vitamin supplements? (or healthy diet)
Localised disease

- TEM
- Laparoscopic
- Pouch formation
- Definitive chemoradiation
TME Surgery

Conventional surgery

Local recurrence
25 - 40%

TME Surgery

Local recurrence
6 - 10%
Pre-operative radiotherapy
Chemotherapy improves survival

Stage 2-3: chemo vs none

Stage 4: chemo vs none

Scheithauer BMJ 1993
Potential toxicities of chemotherapy
Potential toxicities of chemotherapy
10 year survival following liver resection

Ablative techniques for metastatic disease
Incremental progress = big gains

- 5-FU/LV (Saltz)
- IFL (Saltz)
- 5-FU/LV (De Gramont)
- Oxaliplatin plus 5-FU/LV (De Gramont)
- IFL (Douillard)
- IrOx (Goldberg)
- FOLFOX4 (Goldberg)
- FOLFIRI then FOLFOX6 (Tournigand)
- IFL plus Bevacizumab (Hurwitz)
- FOLFOX4 plus Bevacizumab (Cassidy)
- XELOX plus Bevacizumab (Cassidy)
- FOLFOXIRI (Falcone)
- BRITE Registry (Kozloff)

“Personalised therapies” in Cancer

Oestrogen receptor identified in breast cancer in 1968
1973: lab experiments identify tamoxifen as antagonist to ER+ breast cancer
1982: Adjuvant tamoxifen in ER+ breast ca shown to reduce relapse
Cetuximab in CRC: unimpressive in unselected patients

Progression-free survival time (months)

PFS estimate

HR = 0.851; 95% CI = [0.726-0.998]
Stratified log-rank p-value = 0.0479

1-year PFS rate
23% vs 34%

Van Cutsem ASCO 2007
Cell growth, proliferation, invasion and metastases
Cell growth, proliferation, invasion and metastases
Cell growth, proliferation, invasion and metastases
Cetuximab facial rash
MoH initiatives

• National Bowel Cancer Work Group
• Faster Cancer Wait times
• National consistency for colonoscopy access
• National Tumour-specific standards
• HRC CRC initiative
SCREENING
Screening for cancer

1. An important health problem
2. Accepted treatment for the disease
3. Adequate facilities for diagnosis and treatment
4. Precursor stage
5. Suitable screening test
6. Screening test acceptable
7. Natural history of disease should be understood
8. An agreed policy on whom to treat as patients
9. Cost effective
10. Case-finding should be a continuing process and not a “once and for all” project.

Colorectal cancer screening
Interpreting degree of benefit

- Incidence / prevalence
- Sensitivity and specificity
  - False positives, false negatives
- Uptake and acceptability
- Age of commencing screening
- Frequency of screening
Screening - results

- 4 trials examining FOBT effect on CRC mortality
- Biennial testing; Age range 45-70
- FOBT → Colonoscopy
Flexible sigmoidoscopy

- Distal part of colon
- Those with polyps go to full screening
- Reduction in incidence and deaths from CRC
- Studies selected populations interested in screening (may inflate results)
### Table 2. Sensitivity of One-Time Colorectal-Cancer Screening Tests.

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cancer</td>
<td>Advanced Adenomas*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>percent</td>
</tr>
<tr>
<td><strong>Stool-based tests</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard guaiac fecal occult-blood</td>
<td>33–50</td>
<td>11</td>
</tr>
<tr>
<td>test (three stool samples)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitive guaiac fecal occult-blood</td>
<td>50–75</td>
<td>20–25</td>
</tr>
<tr>
<td>test (three stool samples)</td>
<td></td>
<td></td>
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<tr>
<td>Immunochemical fecal occult-blood</td>
<td>60–85</td>
<td>20–50</td>
</tr>
<tr>
<td>test (one–three stool samples)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Old stool DNA test (one stool sample)</td>
<td>51</td>
<td>18</td>
</tr>
<tr>
<td>New stool DNA test (one stool sample)</td>
<td>≥80</td>
<td>40</td>
</tr>
<tr>
<td><strong>Structural examinations of the colon</strong></td>
<td></td>
<td></td>
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<tr>
<td>CT colonography</td>
<td>Uncertain; probably &gt;90</td>
<td>90 (if ≥10 mm in diameter)</td>
</tr>
<tr>
<td>Sigmoidoscopy</td>
<td>&gt;95 (in the distal colon)</td>
<td>70†</td>
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<tr>
<td>Colonoscopy</td>
<td>&gt;95</td>
<td>88–98</td>
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</table>

References:
- Mandel et al., 13
- Hardcastle et al., 14
- Kronborg et al., 15
- Imperiale et al., 16
- Ahlquist et al., 17
- Levin et al., 2
- Whitlock et al., 4
- Ahlquist et al., 17
- Allison et al., 18
- Levin et al., 2
- Whitlock et al., 4
- Imperiale et al., 16
- Allison et al., 18
- Itzkowitz et al., 19
- Johnson et al., 20
- Selby et al., 21
- Lieberman et al., 22
- Lieberman et al., 22
- Imperiale et al., 23
- Schoenfeld et al., 24
- Lieberman et al., 25
- Pickhardt et al., 26
- Cotton et al., 27
- Rockey et al., 28
Screening

• UK NHS pilot commenced 2000
  – 478,250 invited; age 50-59; 56.8% uptake; 2% positive test
  – 552 cancers: 48% Dukes’ A, 1% distant spread
• National coverage end of 2009

• Australia pilot Nov 2002 – June 2004
  – 56,907 invited; 45.5% uptake; 9% positive test
  – 67 cancers, stage info not available
• National coverage commenced July 2008 (age 50-65)
Bowel cancer is the second most common cancer in New Zealand.

Bowel screening helps catch early signs of cancer.

If you are aged between 50 and 74 years and live in the Waitemata DHB area, you will be invited to check yourself out with our free BowelScreening programme. See your doctor NOW if you have any bowel symptoms that concern you.
Screening – opportunistic?

- Mole Mapping
- PSA testing
- CXR in smokers
- Mammography prior to National Programme
- Mammography < 50 years of age
- Cervical Cancer
WHAT TO DO?
Gaps in NZ research

• Exclusion of rectal cancer from previous work
• Data capture limited to categories
  – eg chemo: yes/no; surgery yes/no; stoma yes/no
• Focus on inputs and treatments rather than outcomes
  – eg local or distant recurrence; quality of follow-up; survival
• Nuanced quality aspects not examined
  – eg TME, local recurrence, follow-up, pre-operative evaluation
• Pilot work demonstrates significant gaps in quality
  – < 25% with complete colonoscopy within 12 months
  – < 40% with annual CT follow-up
• Network and Registry data contain gaps
HRC Partnership Programme: RFP

• Part of the Research Partnerships for New Zealand Health Delivery (RPNZHD) initiative
• Request for proposals in Bowel Cancer Research issued in Oct 2010
  – Examination of the bowel cancer pathway – including treatment outcomes
  – Identify variations across NZ
  – Investigate ethnic disparities (particularly in treatment and management)
  – Provide an evidence base for strengthening current services in NZ
  – Strongly encouraged national collaboration
The PIPER Project

Methods

• 3 year project
• National audit of patient notes and relevant regional databases for all patients diagnosed with CRC in 2007 & 2008
• Extended cohort of Maori and Pacific cases to include 2006, 2009, 2010 and 2011
• Expected number of cases is 6352
• Data will be collected regionally
• Data will be collected for each patient for a period of 3 years post diagnosis
• Summer studentship to assess quality of ethnicity data
The PIPER Project

Methods

• Proportions of patients meeting Key Performance Indicators considered best practice internationally will be calculated.
• Proportions will be compared between groups of urban/rural residence, ethnicity and socioeconomic status.
• Suggested recommendations for service changes will be developed by the research group with guidance from the advisory group.

Main outcome measure:
Progression-free survival at 3 years post diagnosis.
The PIPER Project

Key Performance Indicators

• Examples:
  – Staging process
    • method of diagnosis
    • synoptic pathological reporting
    • number of lymph nodes examined
    • incomplete colonoscopy follow-up
    • pre-op investigations (radiology + CEA)
  – Treatment
    • review at an MDM
    • participation in a clinical trial
    • Stage-specific KPIs e.g. % stage III offered adjuvant chemotherapy
The PIPER Project

Key Performance Indicators

• Examples:
  – Management
    • median time referral receipt to diagnosis
    • median time diagnosis to treatment
    • median time to initiation of adjuvant treatment
    • % <50 years old undergoing MSI testing
    • family history recorded at diagnosis
    • proportion receiving 3 follow-up CT scans over 3 years
    • proportion receiving at least one follow-up colonoscopy within 3 years
The Future

- Provides a comprehensive dataset of characteristics, treatment and outcome
- Validates data set for future recording (national prospective audit / database)
- Engagement with ethics around retrospective paraffin and correlative/translational studies
- Establishes national framework for prospective national collaboration including translational research
- Springboard for health services improvement and prospective treatment-based research
WHAT DO WE WANT?
EVIDENCE-BASED CHANGE
WHEN DO WE WANT IT?
AFTER PEER REVIEW