Mr Richard Perry

Colorectal Surgeon

Christchurch

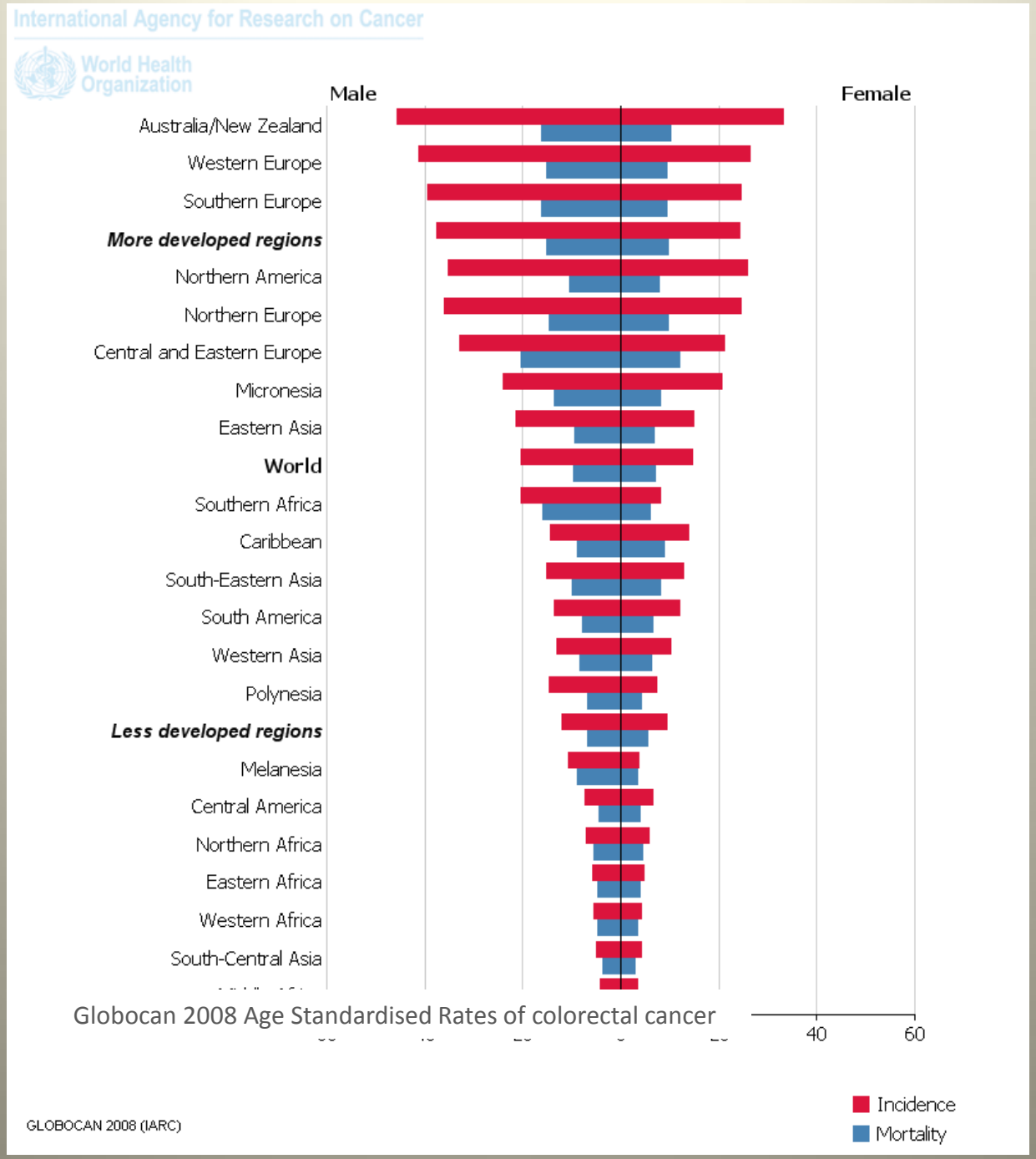
Pelvic Floor Dysfunction - Concurrent Workshop

Saturday, 17 August 2013 Start 4:30pm Duration: 60mins Monet

Colorectal Cancer

Richard Perry	Colorectal and General Surgeon
Ingo Kolossa	Colorectal Surgeon
Alison Ross	Gastroenterologist
Judith Collett	Gastroenterologist
Craig Lynch	Colorectal and General Surgeon

Intus Digestive and Colorectal Care
Christchurch and Queenstown



Globocan 2008 Age Standardised Rates of colorectal cancer

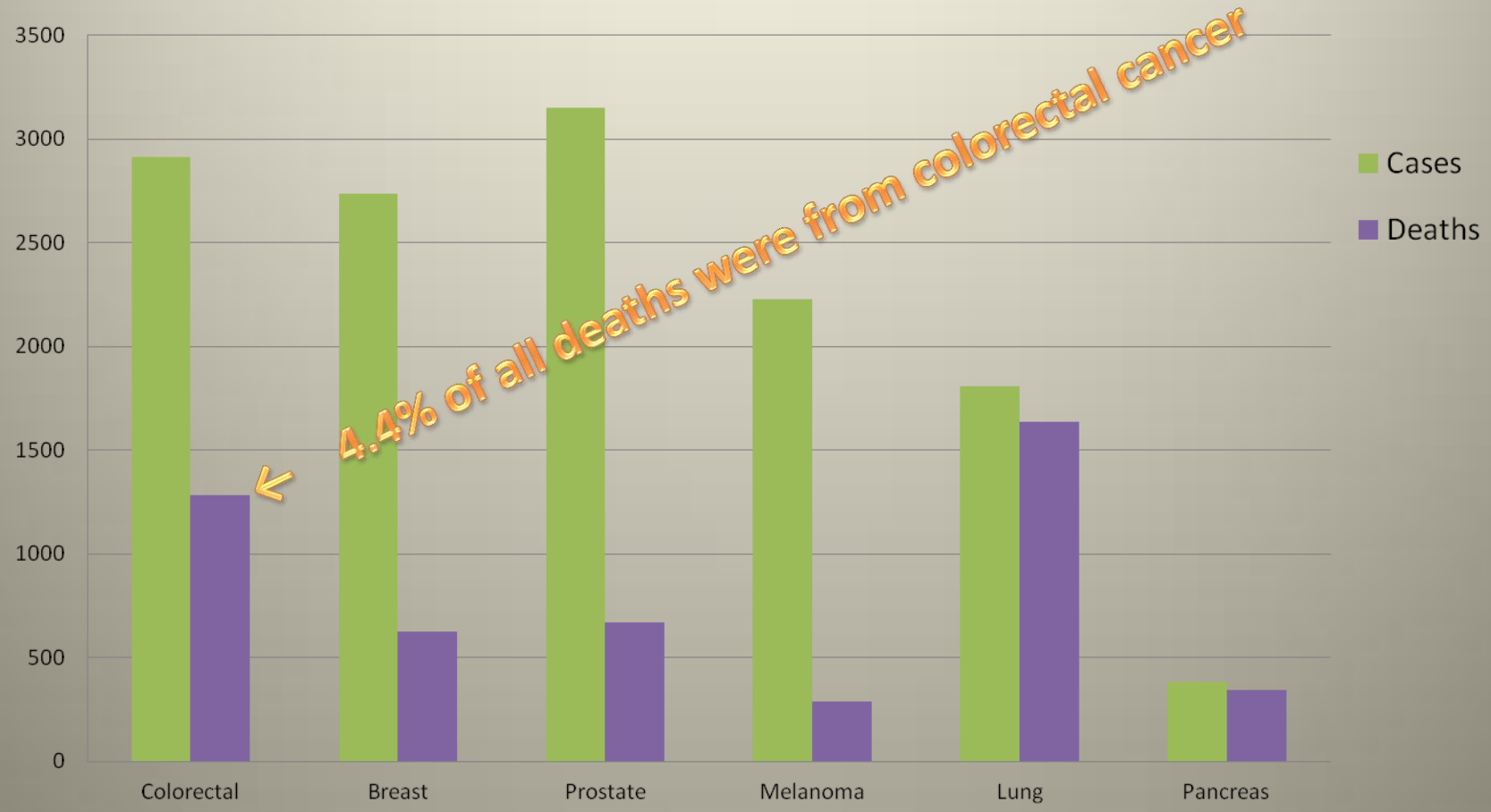
CRCa Incidence per 100,000

Country	cases	deaths
Ireland	48.7	26.4
Canada	56.8	22.4
USA	57.5	20.6
UK	60.4	28.9
Australia	62.8	24.9
NZ	**69.0**	**31.0**

Source: Globocan 2002 Database (Crude rates)

Cancer in New Zealand 2008

29,312 deaths 8,566 from cancer



Source: Globocan factsheet 2008

Colorectal Cancer in NZ

Every year…..

FOUR people die from colorectal cancer

for every: ONE who dies from an MVA

and TWO who die from breast cancer

1. NZHIS. Cancer: New registrations and deaths 2004. www.nzhis.govt.nz/moh.nsf/pagesns/493
2. LTSA NZ Road toll statistics. www.ltsa.govt.nz /research/toll.htm

Objectives

- What's new in aetiology
- Genetics of Colorectal cancer
- Epigenetic factors
- Screening

Diet and Colorectal Cancer

- Fibre ↔
- Fat ↔
- Red meat ↔
- Fruit 13% ↓
- Vegetables 40% ↓
- Aspirin 80mg 20% ↓ but 325mg ↔
- Selenium 50% ↓
- Calcium 15% ↓
- Alcohol 100% ↑

From Marshall JR. Prevention of Colorectal Cancer. Gastroenterol Clin N Am 2008;37:73-82

The Human Microbiome

- 90 % of cells in human are bacteria
- 10^{14} in gut, 10^{3} different species, most in colon
- initially derived from mother
- modified by infections, antibiotics, diet
- symbiotic, but some produce toxic and genotoxic metabolites
- strict anaerobes 1000x facultative anaerobes

CRCa – The role of infectious agents

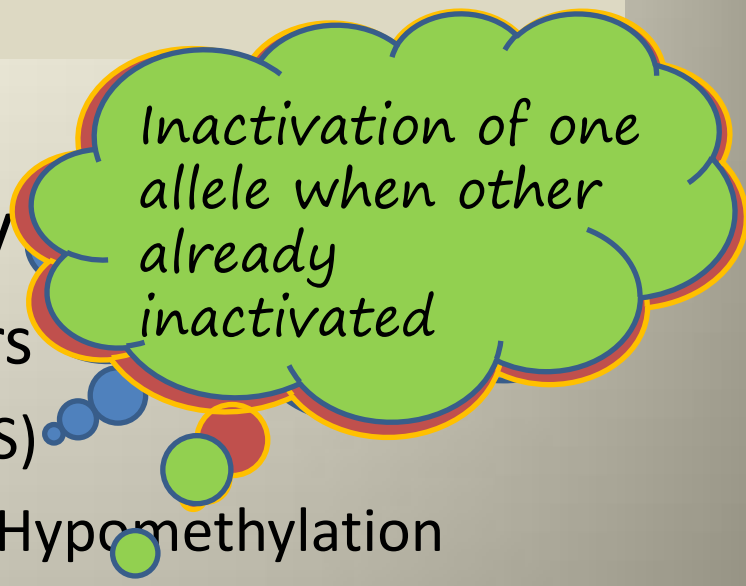
- HPV- SCC oesophagus, cervix, anus
- Helicobacter – Ca Stomach, ? GI lymphoma
- Role of microflora derived β-glucuronidase
  - ↓ by some types of dietary fibre & probiotics
- Fusobacterium Nucleatum implicated
  - Constituent of oral microbiota
  - Causes periodontitis and appendicitis

Genetic Pathways to CRCa

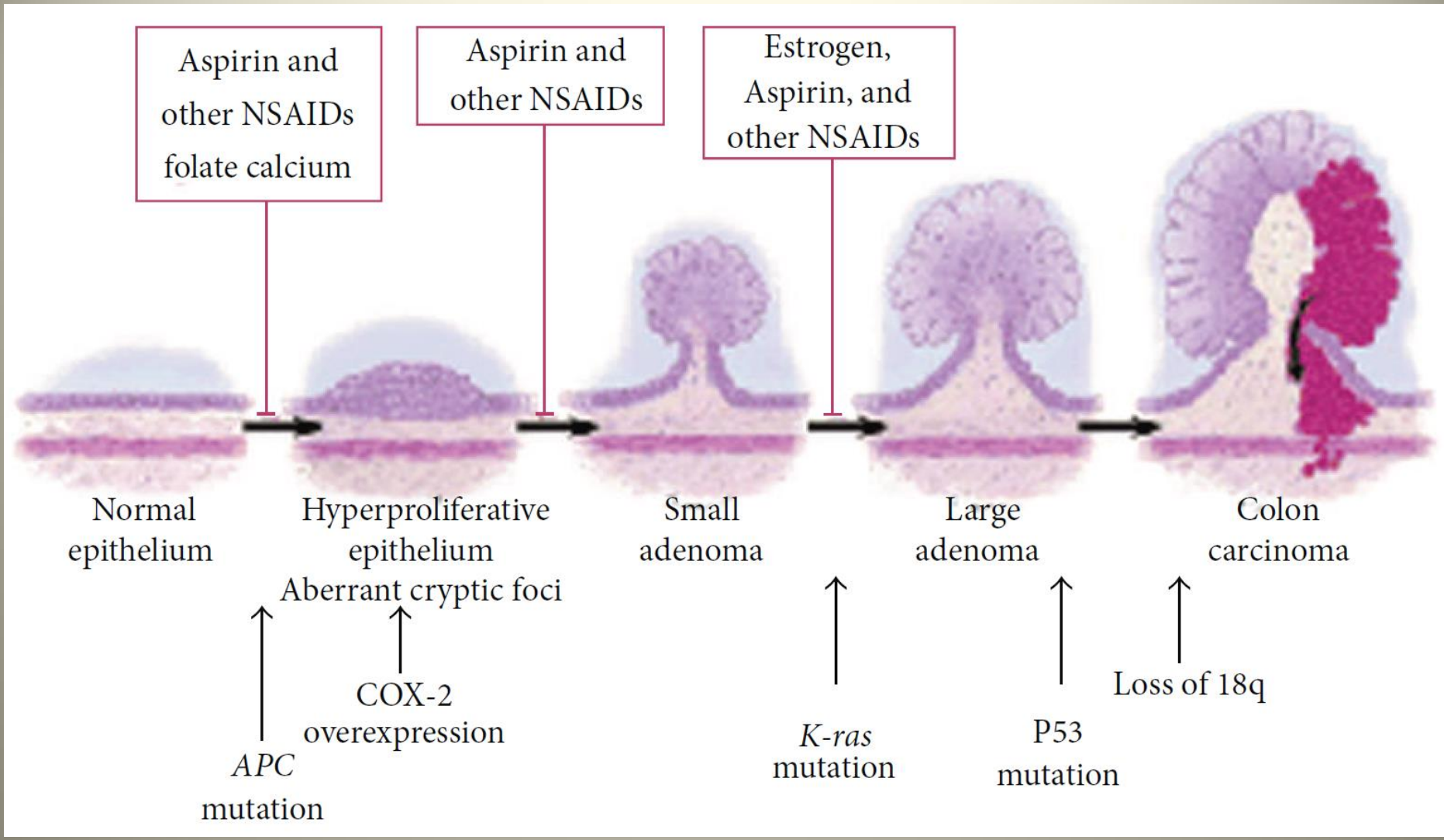
- Chromosomal Instability
- Mismatch Repair Deficiency
- CpG Island Methylation

Genetic Pathways to CRCa

1. Chromosomal Instability
   - 85% of Colorectal cancers
     - Microsatellite Stable (MSS)
     - Results from Global DNA Hypomethylation
     - Loss of heterozygosity (LOH)
     - Sequential mutations: adenoma→carcinoma



Matsubara N. Dis Colon Rectum 2012;55(1):96-104



APC loss → K-*ras* loss → 18q loss,? DCC mutations → TP53

Dysplastic aberrant crypt foci *Simple adenoma* *Advanced adenoma* *Invasive carcinoma*

Genetic Pathways to CR

Microsatellites: short sequences of repeating units of 1-6 base pairs

2. Microsatellite Instability (MIS)
   - Inherited (Lynch Syndrome) or sporadic (MSI-H)
   - Accumulation of mutations in Microsatellites
   - Due to MisMatch Repair (MMR) gene dysfunction
     - MLH1, MSH2, PMS1, PMS2, MSH6
       - E.g. silencing of MLH1 due to promoter methylation

Genetic Pathways to CRCa

3. Epigenetic CpG Island Methylation (CIMP)
   - 10-15% of sporadic CRCa
   - serrated adenomas / hyperplastic polyps
   - BRAF oncogene mutation

   CIMP +ve tumours:
   - older women
   - right colon
   - high grade, mucinous

Treatment implications of Genetics

- MSI tumours not 5-FU responsive
  - MMR failure impairs pyrimidine effect of 5-FU

...but ARE Irinotecan & Oxaliplatin responsive

- KRAS tumours not EGFR Mab responsive
- Future therapeutic possibilities
  - Pathway deregulation
    - Wnt, EGFR, TGR-β
    - ?MicroRNA (miR) role

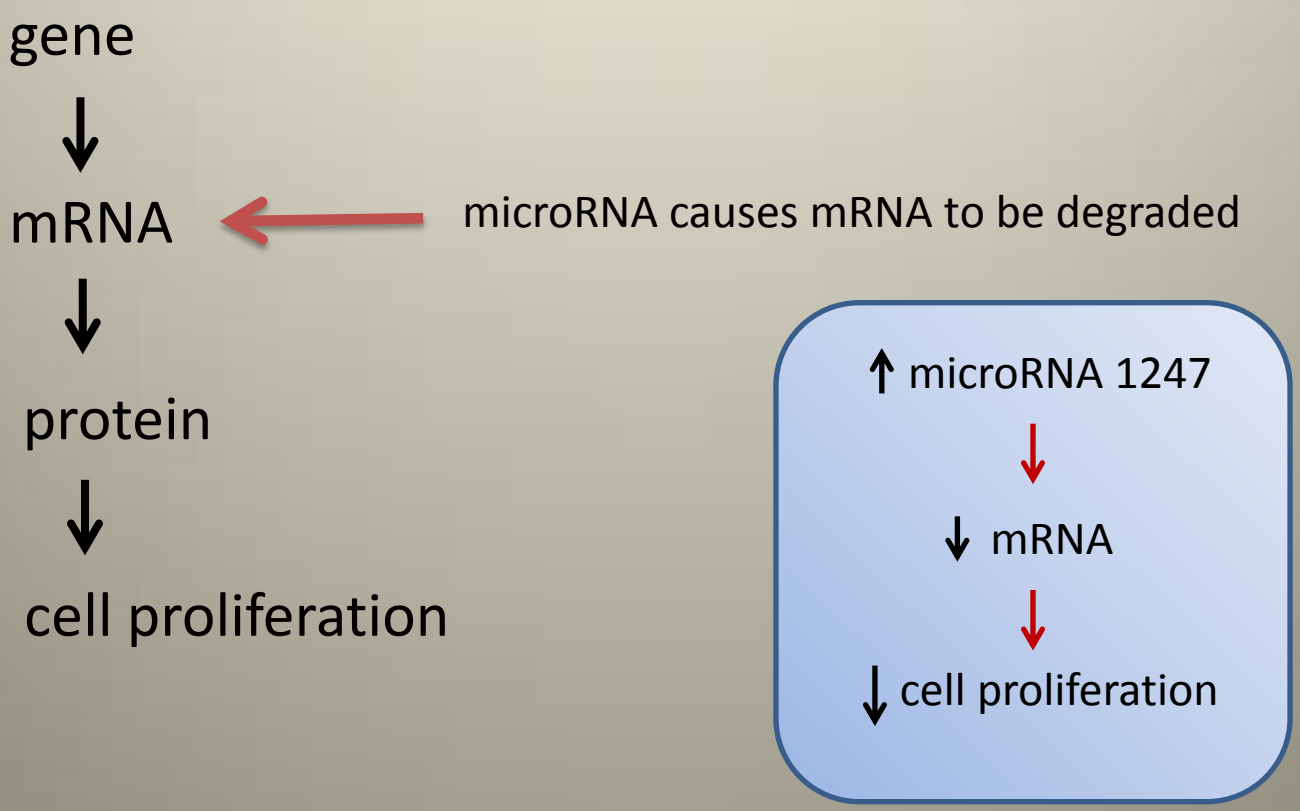
Epigenetic events in CRCa

- Heritable changes in gene expression
  - DNA methylation
  - Histone modification
  - Chromatin remodelling
  - microRNA
- CpG islands densely methylated in CRCa
  - silences transcription
  - microRNA switched on and off by CpG methylation
- Hundreds of epigenetic effects documented

Epigenetics and dietary prevention of CRCa

- Curcumin (turmeric)
  - Inhibits histone acetyl transferase
  - Inhibits mi-RNA-21 expression → ↓ proliferation
- Butyrate
  - Inhibits histone deacetylase → apoptosis
- Epigallocatechin gallate (EGCG) in green tea
  - Demethylates methylated DNA → reactivates silenced tumour suppressor genes
- Garlic, Broccoli, Selenium, Folate….etc

microRNA 1247 acts as tumour suppressor in CIMP type CRCa



Adenoma – Carcinoma sequence
an opportunity for prevention

Chen's model:

- 30% CRCa de novo, 70% from polyps
- Risk of transformation to carcinoma
  - Adenomas 6-10mm = 2.17x (*compared to <5mm)*
  - Adenomas >10mm = 4.25x
- Mean time to transition
  - Adenomas 6-10mm to >10mm = 7.75yrs
  - Adenomas >10mm to Cancer = 5.27yrs

Chen C-D et al. BrJCancer 2003;88(12):1866-73

Early detection and Prevention

- Faecal Occult Blood testing
  - Guaiac (gFOBT)
  - Faecal Immunochemical Testing (iFOBT)
- Flexible Sigmoidoscopy
- CT Colonography
- Colonoscopy

American Cancer Society Recommendations since 2001

Test	Interval from age 50	Comment
FOBT	Yearly	+ve tests → Colonoscopy
Flexible Sigmoidoscopy	5 yearly	+ve tests → Colonoscopy
Colonoscopy	10 yearly	

Why Faecal Occult Blood Testing?

4 prospective randomised trials[1]

- Funen, Nottingham, Minnesota, Goteborg
- 16% reduction in mortality from CRCa
  - after 10-18 years of annual gFOBT
  - Possibly 25% reduction in active participants

Participation in FOBT better: 34% vs 25% for Colonoscopic Screening programs[2]

There have been no PRTs of colonoscopic screening

1. Hewitson P et al Am J Gastro 2008; 103(6):1541-9 Cochrane Review
2. Quintero E et al NEJM 2012;366(8):697-706

Which Faecal Occult Blood Test?

- iFOBT (FIT) better than gFOBT (guaiac)

iFOBT vs gFOBT [1]	Sensitivity	Specificity	PPV
Carcinoma	70% vs 79%	94% vs 87%	5.0 vs 2.5
Ca or Polyp>1cm	67% vs 69%	95% vs 87%	20.5 vs 9.2

- NZ Waitemata pilot using iFOBT in 50-74yo pop^{n}
- Questions
  - cut-off values: 50ng Hb/ml – 200ng Hb/ml
  - Age to screen: 49% of CRCa patients <50 or >75 [2]

1. Allison JE et al NEJM 1996;334(3):155-9
2. Shellnut JK et al DisColonRectum 2012;53:5-8

Optimising compliance with Screening

- Compliance typically < 50% …..as low as 20%
- GP critical to success
  - Education / Awareness raising
  - Working through through social & cultural barriers[1]
  - Discussing too many options causes confusion

Confusion reduces compliance[2]

1. Reeder AI NZMJ 2011;124(1331):1-11
2. Jones RM et al Cancer Epidemiology, Biomarkers & Prevention 2010;19(11):2821-5

Concerns about FOBT screening

- PRCTs not powered to show ↓ total mortality
- 81-95% false +ves [1]
- Verification bias may overestimate sensitivity
  - False negative rates not ascertained
  - Sensitivity 0.36 (0.25-0.47) when -ve FOBTs verified vs 0.70 (0.60-0.80) if not[2]
- Higher sensitivity for Left vs Right sided CRCa[3]
- Only 25% of CRCas detected by screening
  - Remainder 'interval' Cancers or in non-compliers

1. Ekelund et al Int J Colorectal Dis 2010
2. Rosman AS & Korsten MA JGIM 2010 (Meta-analysis of verification bias)
3. Haug et al Expert RevMolDiagn 2011 (Meta-analysis)

Colonoscopy following +ve FOBT

- Expect 5-8% +ve iFOBTs
- ~90% compliance with colonoscopy?
- Cancer detection rate 4-6%
- Adenoma detection rate 40-60%
- Perforation rate <1%
- Bleeding rate <1%

Gupta S. Colorectal Disease 2012;14(2):166-73 (St Marks Bowel Cancer Screening Centre)
Parente F et al Br J Surg 2009;96(5):533-540 (Lecco, Italy)

A +ve iFOBT rate of 8%

would lead to same number of colonoscopies as one-off colonoscopy screening at 60

NZ Colorectal Cancer Screening Advisory Group Report 2006

Colonoscopy yield vs FOBT

- CRCa
  - Similar per invited person (0.1%)
  - Greater per screened person (0.5% vs 0.3%)
- Advanced adenomas
  - 1.9% vs 0.9% $p<0.001$
- Small adenomas
  - 4.2% vs 0.4% $p<0.001$

and….

Quintero E et al NEJM 2012;366(8):697-706 (Spanish PRT; Colonoscopy vs iFOBT screening due 2021)
Bretthauer M et al NEJM 2012;366(8):759-60

Patients who die from CRCa are less likely to have had a Colonoscopy

Ontario case-controlled study

- 10,292 CRCa patients matched 51,460 controls
- Case patients less likely to have had colonoscopy (OR 0.69: 0.63-0.74, $p<0.001$)
- Complete colonoscopy strongly associated with fewer deaths from Left sided CRCa (OR 0.33: 0.28-0.39)

Baxter NN et al Ann Int Med 2009

Flexible Sigmoidoscopy prevents CRCa

Prospective Multicentre Randomised Trial - UK

- Flex Sig (57,237 patients) vs Control (113,195 patients)
- Single examination age 55-64

- Outcome: incidence & death from CRCa
- median fu 11.2yrs

- Incidence distal CRCa ↓ 50%, All CRCa ↓ 23%
- Mortality from CRCa ↓ 43%

Atkin WS, Lancet 2010

Flexible Sigmoidoscopy prevents CRCa

Prospective Multicentre Randomised Trial - Italy

- Flex Sig (17,136 patients) vs Control (17,136 patients)
- Single examination age 55-64

- Outcome: incidence & death from CRCa
- median fu 10.5yrs

- Incidence CRCa ↓ 18% (intention to treat analysis)
- Mortality from CRCa ↓ 22%

Atkin WS, Lancet 2010

Colonoscopy prevents more colorectal cancer deaths

- 9112 patients without personal or FHx CRCa
- 2602 had adenomas removed
  - 12 died CRCa median fu 16yrs
- 25.4 expected deaths in general population
- Suggests 53% reduction in mortality
  - vs 18% from FOBT screening

Zauber AG et al, NEJM 2012;366(8):687-96 (National Polyp Study)

“ An appealing concept would be to use colonoscopy as a triage screening test, offering it once for everybody at 60 years of age and using the results to classify persons as having a low risk of colorectal cancer (no adenomas detected) or a high risk (adenomas detected, particularly advanced ones), with strict surveillance for the latter group but no further screening for the former.”

Dr Michael Bretthauer, Riks Hospital Oslo, in Editorial, NEJM 2012;366(8):759-60

Improving Colonoscopy Acceptability

- Preparation
  - Low volume, palatable, few side-effects
  - Fluid & Electrolyte support
- Social normalisation
  - Facilitative, supportive communications
  - Non-clinical examination environment
- Technical
  - Gentle technique; anticipate difficulties
  - Minimal Sedation, Patient engagement

Measuring the quality of Colonoscopy

"differences between endoscopists' polyp detection rates were significant p<0.001"[1]

- MNP: Mean number of polyps[2]
- Ileal intubation rate (>95%)
- Patient satisfaction vs Sedation
- Inspection / withdrawal time (>6 mins)
- Complication rates
  - Perforation <0.1% of biopsies, Bleeding <0.2%
  - Post-colonoscopy pain

1 Chen SC. Am J Gastroenterol 2007;102,856-861

2 Denis B et al. Gastrointestinal Endoscopy 2011; 74(6):1325-36

Conclusion

- Pick your pedigree
- Control the epigenetic phenomena
  - diet, probiotics, ?viral mediated Mi-RNA transfection….etc…watch this space
- Remove polyps
  - urgent need to expand resources for community colonoscopy