8th International Conference on Cancer Prevention International Society of Cancer Prevention (ISCaP)

Consensus Recommendations for CRC Prevention

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Houston, Texas, USA

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ISCaP GI Prevention Conference
June 24-25
Barcelona, Spain

40 international cancer prevention experts, GI cancer physicians and researchers gathered to develop a consensus statement focused on CRC prevention

Sessions:

1. CRC Tumorigenesis: State of the Science
2. Screening and early detection of CRC
3. GI Cancer Prevention Interventions:
4. Prevention of Upper GI cancers: esophageal and gastric
5. Development of Consensus Statement on CRC prevention

Colorectal Prevention

Goals of the ISCaP Conference:

1. To discuss the state-of-the-science pertaining to CRC carcinogenesis, screening, and preventive interventions

2. To develop a consensus statement describing current recommendations for CRC screening, genetic assessment, and cancer preventive interventions

3. To describe knowledge gaps to address to in future CRC prevention research

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What are the best strategies to prevent CRC ?

1. Screening:
   - Colonoscopy vs. FIT vs. DNA test vs. Blood test (sensitivity/specificity for polyps/CRCs, and compliance)
   - Population (general vs high-risk)
   - Frequency
2. Preventive interventions
   - Behavioral interventions (Diet, exercise, reduce obesity)
   - Preventive therapy (“chemoprevention”)
   - Vaccine therapy
3. Target Population
   - general population
   - high-risk markers (genetic syndromes, SNPs, polyps, CRC survivors)

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Screening Consensus Statements:

1. CRC screening recommendations and techniques differ across countries
   - Colonoscopy vs. FOBT/FIT vs. sigmoidoscopy
2. In all countries, uptake of CRC screening is too low (40-60% at highest)
3. Most importantly – some form of CRC screening should be strongly recommended (typically after age 50).
4. More emphasis should be on promoting screening to increase uptake

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Screening Consensus Statements: New Advances

1. **Biggest variable – operator and patient dependent**

- Bowel prep
- Endoscopist experience, time, success reaching cecum

2. **Discussion of novel colonoscopy techniques:**

- Water exchange colonoscopy
- Capsule colonoscopy

3. **New techniques show great promise:**

- DNA panel + FIT on stool samples (Cologuard)
- Blood-based tests for cDNA (epiPRO-COLON)
- microRNAs (mir29a+92a, mir19a+19b+15a)

Candidate Early Detection Biomakers

Feces

- Occult blood (new FITs)
- Secreted mucins or metalloproteinases
- Exfoliated:
  - DNA (mutations, methylation, long DNA)
  - RNA (mRNA, miRNAs)
  - Tumor-derived proteins

Blood

- Circulating tumor cells
- Circulating nucleic acids (plasma/serum/whole blood)
  - DNA
  - RNA (miRNAs)
- Circulating proteins (plasma/serum)

DeeP-C Study

Prospective, cross-sectional, average CRC risk screening study (FDA pivotal clinical study)

Asymptomatic, aged 50-84 years
(no. evaluable patients, ≈10,000)

↓

Cologuard® test vs. OC-FIT CHEK®
(both specimens taken from the same single stool)

↓

Screening colonoscopy
All patients within 90 days of enrollment

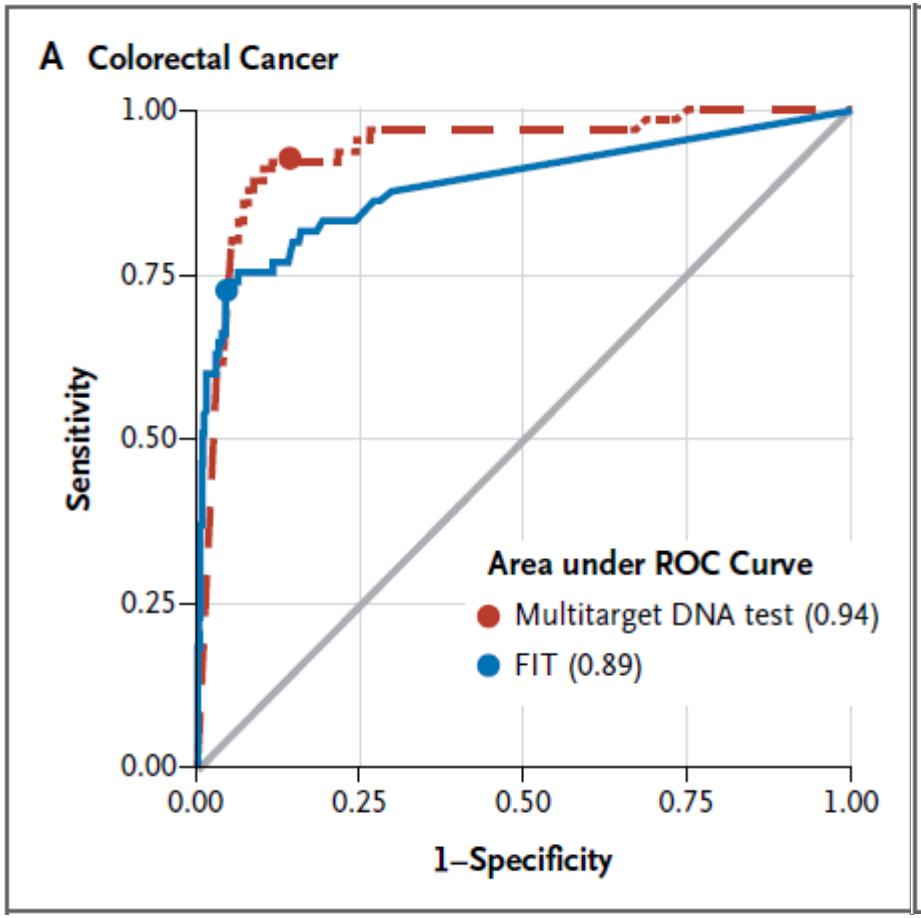
ClinicalTrials.gov NCT0139774

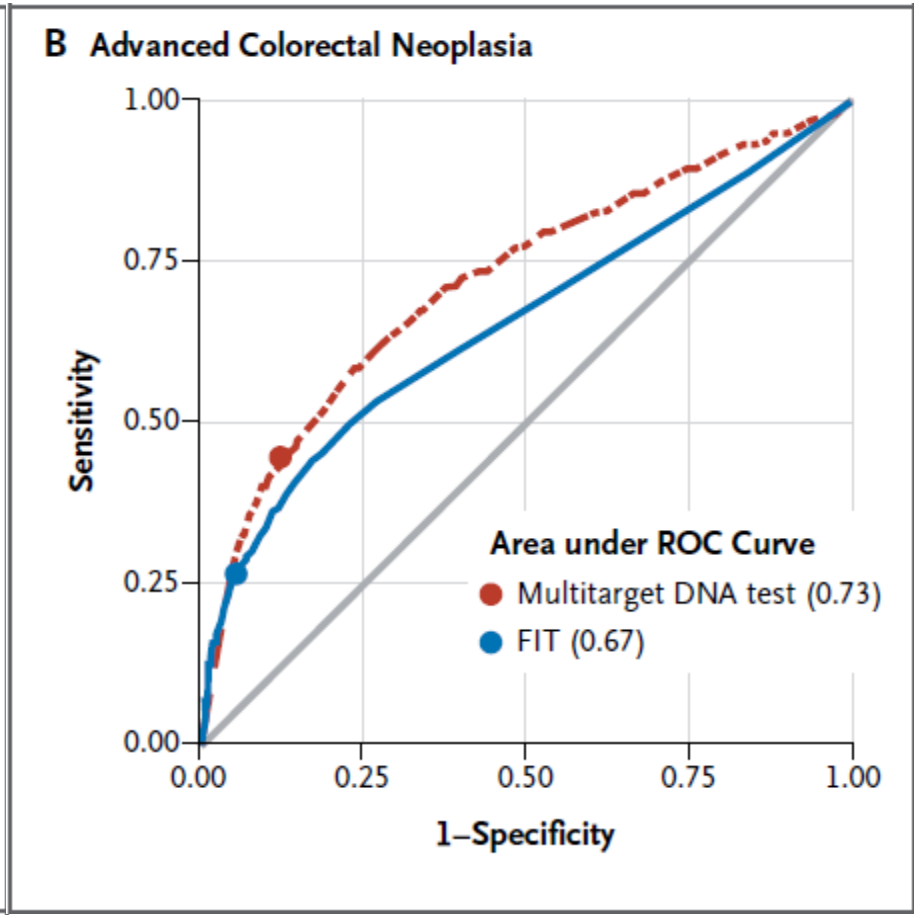
Cologuard® Test

- Detects pre-cancers and cancer
- Non-invasive
- No bowel preparation
- No diet or medication restrictions
- Unlimited access, can be mailed
- Affordable
- Fast results

Imperiale *et al*. NEJM 2014

ROC curves





Imperiale *et al*. NEJM 2014

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Prevention Intervention Statements: Behavioral

1. Strong evidence for exercise recommendation
   (30-45 minutes of vigorous exercise, 3-5 times per week; less aggressive exercise still shows benefit)
2. Epidemiologic data shows dietary factors affect risk
   (red meat increases risk; fruit, vegetables, high fiber decrease risk. Difficult to implement, RCTs have not shown benefit so far)
3. New e-Health technology may facilitate behavioral interventions (“i-FIT” wristbands, i-phone Aps).

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Prevention Intervention Statements: Aspirin

1. Strong evidence for use of aspirin to reduce CRC incidence and cancer-related mortality
   (Rothwell Lancet, 2010, 2011 (mortality), 2012 (incidence))
2. Delayed effect (seen after 5 years of starting) which lasts for at least 10 years (Rothwell, Lancet, 2011; Cook et al. Annals of Internal Med, 2012)
3. Optimal dose is not known (research question), but definitive evidence for benefit for 100mg daily or less.
4. Dose is being tested in Lynch Syndrome patients (CAPP3)
5. Risk of GI bleed is age dependent, and is slight in individuals aged 50-65.
6. Recommend aspirin use for CRC prevention in individuals aged 50-65, especially in patients with FH of CRC

December 11th
2008;359:2567-2578
CAPP2: 1009 Lynch syndrome recruits

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

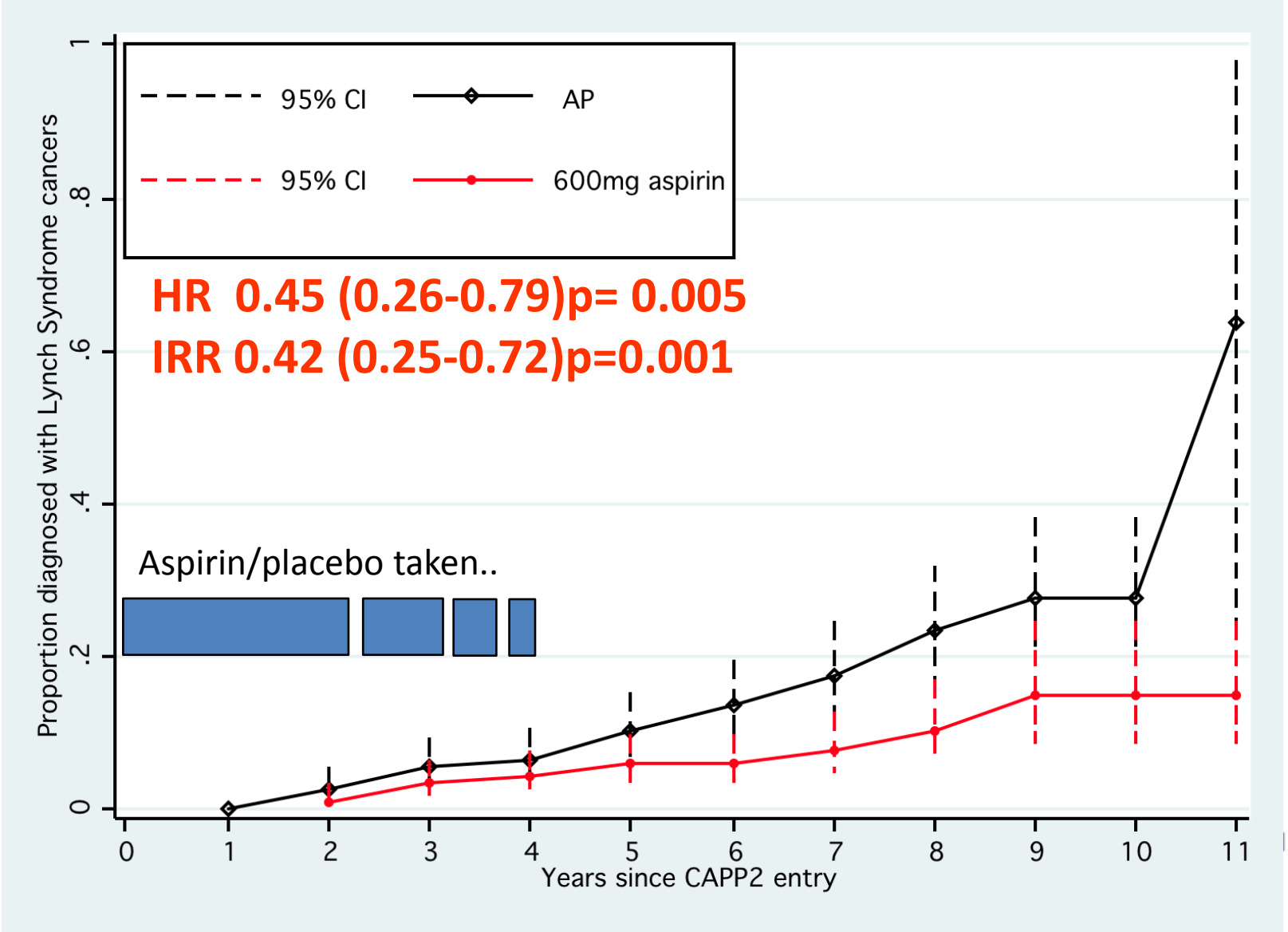
Effect of Aspirin or Resistant Starch on Colorectal Neoplasia in the Lynch Syndrome

John Burn, M.D., D. Timothy Bishop, Ph.D., Jukka-Pekka Mecklin, M.D., Finlay Macrae, M.D., Gabriela Möslein, M.D., Sylviane Olschwang, Ph.D., Marie-Luise Bisgaard, M.D., Raj Ramesar, Ph.D., Diana Eccles, M.D., Eamonn R. Maher, M.D., Lucio Bertario, M.D., Heikki J. Jarvinen, M.D., Annika Lindblom, M.D., D. Gareth Evans, M.D., Jan Lubinski, M.D., Patrick J. Morrison, M.D., Judy W.C. Ho, M.D., Hans F.A. Vasen, M.D., Lucy Side, M.D., Huw J.W. Thomas, M.D., Rodney J. Scott, Ph.D., Malcolm Dunlop, M.D., Gail Barker, B.A., Faye Elliott, M.Sc., Jeremy R. Jass, M.D., Ricardo Fodde, Ph.D., Henry T. Lynch, M.D., and John C. Mathers, Ph.D., for the CAPP2 Investigators*

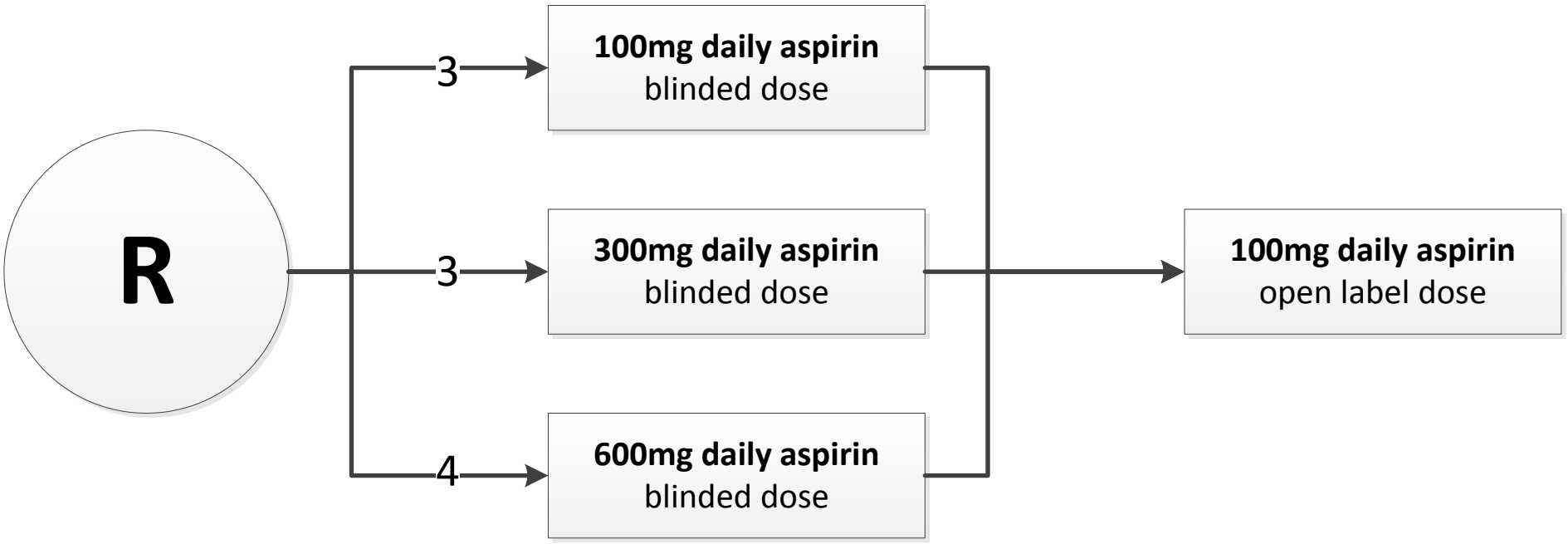
600mg aspirin for up to 4 yrs had no effect

But GI bleeds: Aspirin 11,placebo 9

CAPP2 per protocol analysis
All Lynch syndrome cancers



CaPP3: Dose non-inferiority randomised trial: Under Development (John Burns, UK)



CANCER RESEARCH UK

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Prevention Intervention Statement: New Agents

1. Cox-2 inhibitors limited by their cardiac side effects

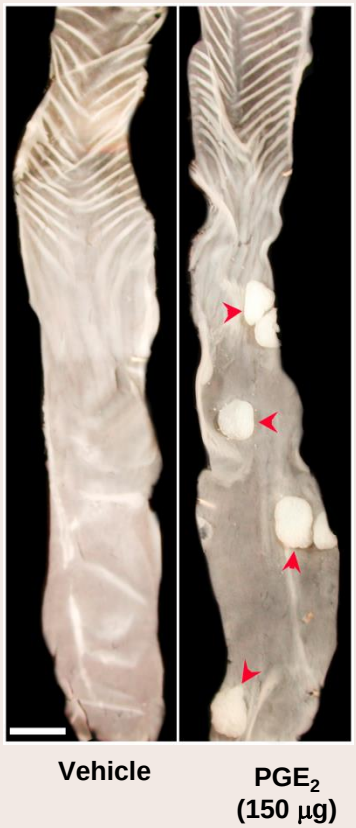
2. New ways to target the inflammatory pathways
(EP antagonists, CXCR2 antagonists, down-stream pathways)

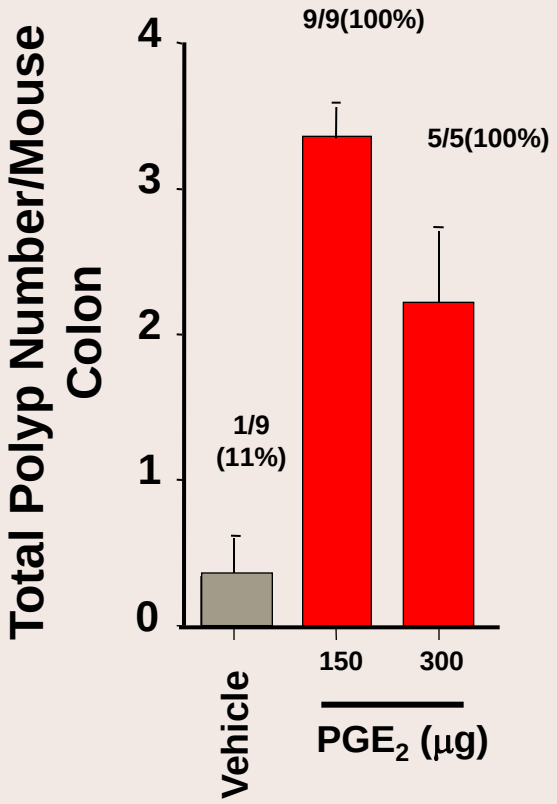
3. DMFO/sulindac is promising, possibly in young FAP patients before having colectomy

4. Peptide vaccines are very promising in individuals with Lynch and other mis-match repair syndromes

PGE_2 accelerates adenoma growth (Ray DuBois)

Treatment with PGE_2 increases tumor size and number

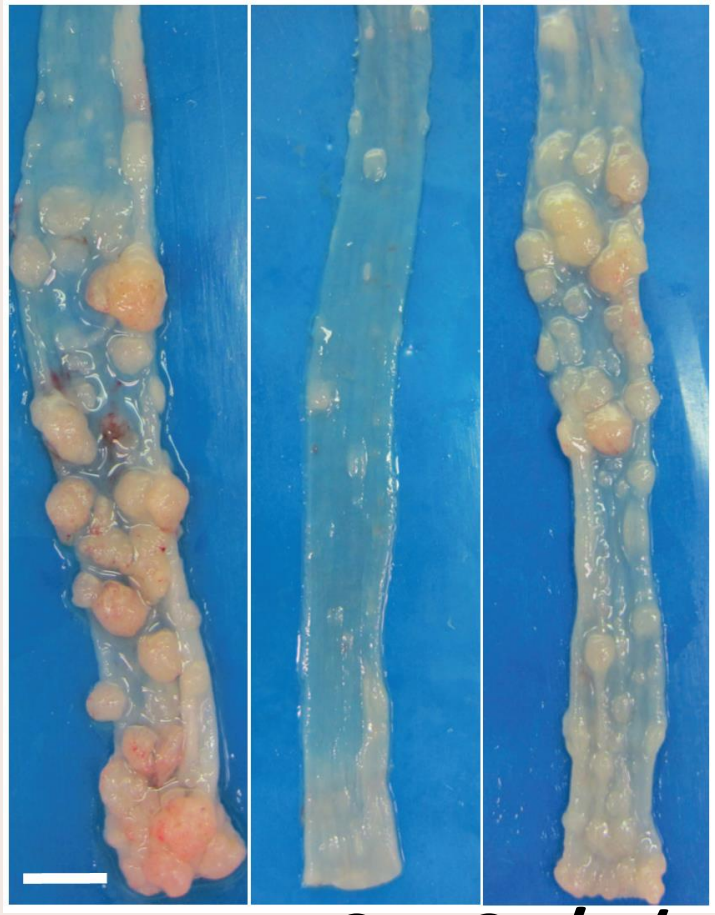




Wang et al. 2004 *Cancer Cell*; 6, 285-95

Transfer of WT and Cxcr2 -/- MDSC's (Ray DuBois)

Cxcr2 -/- WT (MDSC transplant)



WT Cxcr2 -/- (mice)

Conclusions

1. CRC prevention is possible with current strategies
2. Increasing uptake of CRC screening is most impactful and cost-effective
3. Major effort needs to be made to promote screening (using currently available techniques – FOBT, FIT, sigmoidoscopy, colonoscopy)
4. New screening approaches look promising (Cologuard, cDNA, microRNA)
5. Aspirin can prevent CRC incidence and mortality, and should be considered in individuals 50-65 if they have no contra-indications
6. Dose of aspirin not clear, but 100mg daily or lower is currently considered safe and effective
7. New preventive agents are being tested (DMFO/sulindac, novel peptide vaccines)

Questions ?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International Society of
Cancer Prevention