New Frontiers in Prevention & Early Detection of Cancer at the Population Level

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DISCLOSURE

- Advisory board for EXACT Sciences
- Funding from NCI (CRCHD, DCP); NIMHD
- AACR Board Member
Opportunities for Cancer Prevention
The Cancer Continuum

<table>
<thead>
<tr>
<th>PREVENTION</th>
<th>INTERCEPTION</th>
<th>DIAGNOSIS</th>
<th>TREATMENT</th>
<th>SURVIVOR</th>
</tr>
</thead>
</table>

- **Exposures**
  - Obesity/Diabetes
  - Heredity
  - Microbiome

- **Normal**
  - Premalignancy
  - Early Stage Cancers
  - Advanced Disease
  - Recurrence

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AT THE FOREFRONT
UCHealth Medicine
Comprehensive Cancer Center

NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute
Chemoprevention

“Use of pharmacologic or nutrient agents to prevent, reverse, or inhibit the process of carcinogenesis”
The Colorectal Adenoma/carcinoma Prevention Program (CAPP)

1071 participants allocated randomisation number

- 62 judged ineligible
- 72 eligible, but withdrew consent before intervention commenced
- 937 eligible commenced intervention and subject to analysis

76 requested randomisation to RS or RSP only

434 allocated aspirin placebo

- 434 analysed
  - 105 on-trial information only (3 CRC diagnoses)
  - 329 longer follow-up (27 CRC diagnoses)

427 allocated aspirin (600 mg)

- 427 analysed
  - 85 on-trial information only (5 CRC diagnoses)
  - 342 longer follow-up (13 CRC diagnoses)

Decreased Risk of Lynch-Cancers Among ASA Users

One-Third to One-Half of Cancer Deaths are Preventable in Western Populations

The Promise of Prevention

One-third to one-half of cancer deaths are preventable in western populations. Effective cancer prevention is applied in two domains across the lifespan:

- **Evidence-based personal actions**
  - Diet
  - Lack of exercise
  - Occupation
  - Viruses
  - Family history
  - Alcohol
  - UV & ionizing radiation
  - Prescription drugs
  - Reproductive factors
  - Pollution
  - Unknown

- **Effective cancer prevention**
  - Excess weight and obesity
  - Tobacco

- **Evidence-based population actions**
  - Particularly by “reaching” the less fortunate & underserved sectors of our population

- **Public policy**
- **Public & professional education**
- **Delivery of community-based clinical services**

- Maintain a healthy weight throughout life
- Know your family history
- Avoid tobacco & alcohol
- Follow a cancer-screening program
- Eat a healthy diet
- Use preventive meds & vaccines
- Be physically active
- Avoid excessive UV exposure

Obesity and Cancer Risk

- 12 Excess Body Fat related cancers
  - determined to be causally related with excess body weight by the International Agency for Research on Cancer (IARC)

- Approximately 19% (123,300 cases) of these cancers are attributed to excess body weight

- Physical activity is postulated to counteract some of the harmful metabolic and inflammatory effects of obesity
Does Physical Activity Reduces Cancer Risk across all BMI Levels?
Additive Effect of BMI & Physical Activity on EBF-Cancer Risk

Maret Maliniak AACR 2019

- To determine whether physical activity mitigates any of the association with high BMI
  - Evaluated **62,043 men** and **65,585 post-menopausal women** cancer-free at baseline (1992/1993) in the Cancer Prevention Study (CPS)-II Nutrition Cohort

Follow-up Nutrition Cohort Surveys

Baseline
~1.2 Million

Nutrition Cohort
~184,000


Deaths/Study end
Physical activity decreases EBF-Related Cancers

Men

Women

*Statistically significant additive interaction
World Health Organization

Classifies Processed Meat as Being Cancer Causing
Meat Consumption and Colorectal Cancer Risk

- **Red meat** is a probable carcinogen for CRC (WHO class 2A)
- **Processed meat** is a WHO Group I carcinogen
- **Meat-derived mutagens** may account for red and processed meat carcinogenicity

Bouvard et al The Lancet Oncology 2015
WCRF/AICR. Continuous Update Project Expert Report 2018
Tennessee Colorectal Polyp Study

- Large case-control study of colorectal polyps between 2003 and 2010
- Includes nearly 7,000 participants between 40-75
  - ~2,000 adenoma cases and ~4,000 polyp-free controls
  - No personal history of adenoma, cancer, IBD, or familial CRC syndrome
- Examine the association between meat consumption and Sessile Serrated Polyps

Dominique Mosley Am J Clin Nutr 2020
Outcome - Sessile Serrated Polyp Incidence
Total red and processed meat intake was associated with risk for SSP

<table>
<thead>
<tr>
<th>Meat Intake</th>
<th>SSPs vs controls</th>
<th>SSPs vs HPs</th>
<th>SSPs vs ADs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)(^a)</td>
<td>OR (95% CI)(^a)</td>
<td>OR (95% CI)(^a)</td>
</tr>
<tr>
<td><strong>Red Meat</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 (Low)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>Q2</td>
<td>1.17 (0.7, 1.96)</td>
<td>0.92 (0.51, 1.63)</td>
<td>0.98 (0.57, 1.66)</td>
</tr>
<tr>
<td>Q3</td>
<td>1.71 (1.05, 2.78)</td>
<td>1.25 (0.72, 2.17)</td>
<td>1.50 (0.91, 2.47)</td>
</tr>
<tr>
<td>Q4 (High)</td>
<td><strong>2.38 (1.45, 3.91)</strong></td>
<td><strong>1.69 (0.97, 2.98)</strong></td>
<td><strong>1.72 (1.03, 2.87)</strong></td>
</tr>
<tr>
<td>(P_{\text{trend}})</td>
<td>&lt;0.0001</td>
<td>0.02</td>
<td>0.009</td>
</tr>
<tr>
<td><strong>Processed Meat</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 (Low)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>Q2</td>
<td>1.11 (0.69, 1.78)</td>
<td>0.87 (0.51, 1.48)</td>
<td>1.0 (0.62, 1.63)</td>
</tr>
<tr>
<td>Q3</td>
<td>1.23 (0.78, 1.91)</td>
<td>1.05 (0.64, 1.73)</td>
<td>1.19 (0.75, 1.88)</td>
</tr>
<tr>
<td>Q4 (High)</td>
<td><strong>1.83 (1.18, 2.83)</strong></td>
<td><strong>1.59 (0.97, 2.61)</strong></td>
<td><strong>1.67 (1.06, 2.61)</strong></td>
</tr>
<tr>
<td>(P_{\text{trend}})</td>
<td>0.006</td>
<td>0.04</td>
<td>0.02</td>
</tr>
</tbody>
</table>

\(^a\) Adjusted for age, sex, educational attainment, study site, colonoscopy indication, race, cigarette smoking status, body mass index, regular NSAID use, physical activity, alcohol drinking status, and total daily intake of energy.

Dominique Mosley Am J Clin Nutr 2020
Dietary Patterns and Colorectal Adenomas in Lynch Syndrome

Akke Botma, PhD1; Hans F. A. Vasen, PhD, MD2; Fränzel J. B. van Duijnhoven, PhD1,3; Jan H. Kleibeuker, PhD, MD4; Fokko M. Nagengast, PhD, MD5; and Ellen Kampman, PhD1,6

☑ 486 LS cohort from Netherlands; followed for 20 months
☑ Outcome = development of adenomas (58 adenomas)

<table>
<thead>
<tr>
<th>Diet Type</th>
<th>OR (95% CI)</th>
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<tbody>
<tr>
<td>Prudent</td>
<td>0.73 (0.32 -1.66)</td>
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<tr>
<td>Meat</td>
<td>2.48 (1.26-5.02)</td>
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<tr>
<td>Snack</td>
<td>2.16 (1.03-4.49)</td>
</tr>
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Omega-3 PUFA

University of Kansas Center
NCT 03831698
Open Label Study (Single Arm)

• Intervention - Omega-3 PUFA 2 gm/day x 12 months

• Aim – to examine the effects of PUFA on molecular and intestinal microbiota in Lynch Syndrome
Early Detection – The Holy Grail

- Detection of Tumor DNA, exosomes and other vesicles
- Detection of analytes in serum, plasma, urine, saliva, sputum, etc.
- Number of analytes: cDNA, proteins, metabolites, miRNA, etc.
Osteopontin, Macrophage Migration Inhibitory Factor, and Anti-Interleukin-8 Early Stage Ovarian Cancer

• Evaluated more than 100 biomarkers, including HE4, CA72.4 and TP53, HE4/CA72.4 auto antibodies

• A panel of 4 biomarkers- CA125, osteopontin, macrophage migration inhibitory factor, anti-interleukin (IL)-8 autoantibody proved optimal

Guo et al. Cancer 2019;11:1386
Improved Diagnostic Accuracy for Detection of Early Onset Ovarian Cancer

82% vs. 65% Sensitivity

ROC of validation set

p Value of AUC is significant (p < 0.001)

Guo et al. Cancer 2019;11:1386
Vaccines in Cancer Prevention
RCT of a preventative MUC1 vaccine in patients with incidence advanced adenomas

Olivera J. Finn, AACR 2019

1990: Vogelstein Model of Colon Cancer Development

APC mutation   RAS mutation   p53 mutation   more mutations

Normal Epithelium → Small Adenoma → Large Adenoma → Carcinoma → Metastasis

Abnormal MUC1

Overall Kinetics & Response to MUC-1 Vaccine

Olivera J. Finn, AACR 2020

- MUC1 vaccine adenoma recurrence was observed in 27/48 (56.3%) vs. 31/47 (66.0%) receiving placebo (P=0.22)
- Among immune responders (49%) adenoma recurrence rate was 38% lower (p=0.002)
RCT 1:1 for Chromo vs. White Light HD
246 patients

Outcomes:
Polyps 27% vs 30%
OR: 1.23 (0.69-2.2)
Summary and Future Directions

- **Risk behavior modification** with increases in exercise, decrease in animal protein requires implementation and policy efforts
- **Chemoprevention** agents – anti-EGFR, NSAIDs, DFMO, bioflavinoids
- **Blood based** screening, early detection and surveillance methods including liquid biopsy continue to evolve
- **Immuno prevention** is rapidly evolving within pre-clinical and clinical models and promises to intercept the natural history of cancer
- Where is the magic pill? *Maybe is the magic vaccine!*
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