Studies of the aetiology of oesophageal adenocarcinoma

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Trends Oesophageal Cancer

- WMCIU covers 10% England
- 1977-2004:
  - 15,138 OC
  - 5,517 Oesophageal adenocarcinoma (OAC)
  - 6,314 Oesophageal squamous cell carcinoma (OSCC)
  - 3,307 other/unknown morphology
  - n=4,252 validated
Incidence of Oesophageal Squamous Cell Carcinoma

Males
Females

Dashed lines indicate 95% confidence intervals

Dashed lines indicate 95% confidence intervals
## Age at diagnosis OAC

<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>Median</td>
<td>65</td>
<td>72.5</td>
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<tr>
<td>Mean</td>
<td>64.5</td>
<td>70.4</td>
</tr>
<tr>
<td>Interquartile Range</td>
<td>51-71.8</td>
<td>63.3-78</td>
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</tbody>
</table>
Incidence of Oesophageal Cancer in Men by Ethnic Group

1998-2004 Directly Age Standardised Rate (European Standard Population) (per 100,000)

Error bars indicate 95% confidence intervals
Incidence of Oesophageal Cancer in Women by Ethnic Group

1998-2004 Directly Age Standardised Rate
European Standard Population
(per 100,000)

Error bars indicate 95% confidence intervals

Ethnic Group
- White
- Asian
- Black

Adenocarcinoma
Squamous Cell Carcinoma
Influence of socioeconomic status

Influence of socioeconomic status
Risk factors for the development of oesophageal adenocarcinoma: a United Kingdom primary care case-control study

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Materials and methods

• Three control groups were identified: Barrett’s oesophagus (1:4), reflux oesophagitis (1:4) and community controls (1:10)

• Control subjects were matched by age (within 5 years), gender, geographical location (by GP practice) and time of diagnosis of OAC

• Logistic regression analysis generated odds ratios with 95% confidence intervals for association of these risk factors with the development of oesophageal cancer
Table 1: Demographics

<table>
<thead>
<tr>
<th></th>
<th>Oesophageal adenocarcinoma</th>
<th>Barrett's oesophagus</th>
<th>Reflux oesophagitis</th>
<th>Community subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>468</td>
<td>1636</td>
<td>1644</td>
<td>4652</td>
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<tr>
<td>Median age (IQR) years</td>
<td>69 (59-77) years</td>
<td>69 (59-77) years</td>
<td>69.5 (59.5-76.5) years</td>
<td>69.5 (59.5-77.5) years</td>
</tr>
<tr>
<td>Gender</td>
<td>82% men</td>
<td>81% men</td>
<td>81% men</td>
<td>82% men</td>
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<tr>
<td></td>
<td>OAC vs Barrett’s oesophagus</td>
<td>OAC vs reflux oesophagitis</td>
<td>OAC vs community subjects</td>
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<tr>
<td>Height (dm)</td>
<td>1.53 (1.28-1.84) p&lt;0.0001</td>
<td>1.3 (1.1-1.54) p=0.002</td>
<td>1.06 (0.99-1.12) p=NS</td>
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<tr>
<td>BMI</td>
<td>1.04 (1.01-1.07) p=0.025</td>
<td>1.05 (1.01-1.08) p=0.005</td>
<td>1.05 (1.02-1.08) p=0.003</td>
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<tr>
<td>Aspirin</td>
<td>0.78 (0.59-1.03) p=NS</td>
<td>0.62 (0.47-0.81) p=0.001</td>
<td>0.88 (0.68-1.12) p=NS</td>
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<tr>
<td>NSAIDs</td>
<td>0.74 (0.59-0.93) p=0.009</td>
<td>0.53 (0.42-0.66) p&lt;0.0001</td>
<td>0.86 (0.7-1.06) p=NS</td>
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<tr>
<td>PPI</td>
<td>0.42 (0.32-0.54) p&lt;0.0001</td>
<td>0.26 (0.2-0.33) p&lt;0.0001</td>
<td>1.33 (1.03-1.71) p=0.028</td>
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<tr>
<td></td>
<td>OAC vs Barrett's oesophagus</td>
<td>OAC vs reflux oesophagitis</td>
<td>OAC vs community subjects</td>
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<tr>
<td><strong>Smoking (ever vs never)</strong></td>
<td>1.44 (1.01-2.06) p=0.047</td>
<td>1.26 (0.88-1.79) p=NS</td>
<td>1.43 (1.02-2.01) p=0.036</td>
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<tr>
<td><strong>Ex-smoker</strong></td>
<td>1.2 (0.8-1.79) p=NS</td>
<td>1.09 (0.77-1.63) p=NS</td>
<td>1.42 (0.97-2.08) p=NS</td>
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<tr>
<td><strong>Current smoker</strong></td>
<td>1.71 (1.15-2.53) p=0.008</td>
<td>1.43 (0.97-2.12) p=NS</td>
<td>1.45 (1.00-2.09) p=0.047</td>
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</table>
Discussion

• Increasing height associated with OAC
• Also associated with increased gastric acid production
• BMI
• Promising results for effect of NSAIDs and aspirin
• PPI use merely a reflection of symptoms???
• Smoking
Midlands OeSophageal adenocarcinoma Epidemiology Study
(MOSES)

Cooper SC¹, Prew S¹, Podmore L¹, Nightingale P²,
Trudgill NJ¹

Department of Gastroenterology, Sandwell General Hospital¹, and
Wolfson Computer Laboratory, University Hospital Birmingham³
MOSES

- 3 year prospective case-control study examining potential aetiological factors for oesophageal adenocarcinoma
- 208 OAC pts from 12 Midlands NHS Trusts
- 3 control arms: community controls, reflux oesophagitis and Barrett’s oesophagus
- All controls age-, gender-, ethnically and geographically-matched
Methods

• All subjects interviewed in their own home/GP surgery or local hospital
• Blood taken for H. pylori and cagA serology
• Buffy coat stored
• 1 full time researcher, 2 part-time research nurses for 1 and 2 years of project
• Analysis by logistic regression modelling to generate OR with 95%CI
All investigated 1 and 10 years prior to diagnosis of OAC

- Duration, frequency and nocturnal symptoms of heartburn and acid regurgitation
- Duration of smoking, body mass index (BMI) and waist circumference (trouser size) were separated into quintiles, whilst quantity smoked into tertiles
- Frequency of ingestion (days per week) and weekly portion consumption of key dietary components (vegetables, potatoes, fruit, fruit juice, red and white meat, fish, tea and coffee) were separated into quintiles
Results

• 207 OAC patients were recruited: 177 men, median (inter-quartile range) age 68 (60-75) years
• 283 community control subjects (CC) were matched and recruited: 236 men, age 67 (60-74) years
• Symptoms of heartburn were associated with OAC vs CC
• Symptoms of acid regurgitation were also associated with OAC vs CC
• Duration of either symptom exhibited no associations
Discussion (Reflux)

• Subjects with GORD symptoms are at increased risk of developing OAC

• The increased risk of developing OAC is most marked in those in whom symptoms are occurring daily or greater

• Severity of symptoms, as shown by nocturnal waking and need for antacids, are also associated with OAC
Discussion (Smoking and alcohol)

• Smoking is associated with the development of OAC in comparison with community control subjects

• A clear dose-response relationship is observed with smoking and development of OAC as identified by quantity smoked 1- and 10-years prior to interview, although duration of smoking had no statistically significant relationship

• A negative association of consuming alcohol was supported by a similar negative association with duration, but not quantity of consumption

• In contrast to oesophageal squamous cell carcinoma, alcohol has negative associations

• Smoking has more of an impact than historically thought
Discussion BMI/waist circumference

- Increasing BMI, an indicator of obesity, is associated with development of OAC at all time frames.

- Increasing waist circumference was only significantly associated with OAC when compared against reflux oesophagitis patients, however the trend was also seen in comparison with community control subjects.

- The combination associations with BMI and waist circumference with the development of OAC indicates the role of abdominal adiposity (male pattern obesity) is likely to be significant. This may be by inducing/worsening gastro-oesophageal reflux, or the increased low-grade inflammation driven by abdominal adiposity.

- BMI and waist circumference are modifiable factors that are associated with OAC.
Discussion (diet)

- Vegetables, and more strikingly fruit were negatively associated with oesophageal adenocarcinoma

- Phytoprotectants in fruit and vegetables provide an explanation for the apparent protective effect

- Greater consumption of red meat and tea were positively associated with oesophageal adenocarcinoma

- Association of red meat with cancer may be due to high iron content, nitrosamine content or amine formation
Comparison with other epidemiological studies

- Swedish and US studies confirm high anti-oxidant intake inversely associated with development of OAC
- Diets high in fibre similarly, in keeping with anti-oxidant, and thus fruit and veg
- Dietary fat, cholesterol and protein linked with OAC (ref diets high in meat)
Fruit and vegetables

- Anthocyanins (polyphenols) provide distinct pigmentation to fruit and vegetables (red $\rightarrow$ black)
- Rapidly absorbed via the stomach
- Phenolic ring and hydroxyl groups provide anti-oxidant properties
- No convincing studies linking reduced incidence of cancer and serum concentrations of anthocyanins
- Lycopene (tomato based) in meta-analysis is protective against prostate, lung and stomach cancer, but not consistently in studies of OAC
Fruit and vegetables

- Isothiocyanates and Indole-3-carbinols found in cruciferous vegetables (e.g., broccoli, cabbage, sprouts)
- Multi-action (apoptosis, cell cycle arrest, inhibition of inflammation and signal pathways)

- Allyl sulphurs (garlic, onion, leek, chives)
- Observational evidence for protective effect in gastric, colorectal, prostate, laryngeal and breast cancer
- Food content may not equate to plasma level and cellular effect: preparation, cooking, absorption and metabolism
Vitamin D

- **Sources:**
  - 90% sunlight (UV-B)
  - Oily fish (wild>>farmed)

- Increasing incidence/awareness

- Inversely associated with many cancers but not OAC

- Among its’ effects, it reduces epithelial hyperplasia
Red meat

- High iron content: greater density of iron receptors demonstrated in OAC tissue, and may, in part, explain the gender ‘gap’ in OAC
- Saturated fat leading to obesity
- Heterocyclic amines formed from high temperature or open flame (BBQ)
- Processed meat high in nitrosamines
Nitrosative stress

• Nitrosamines from processed meat and increased use in fertilisers (20 fold since WW2)
• Entero-salivary circulation of nitric oxide
• Nitric oxide converted to reactive nitrogen species upon contact with gastric acid
• Those with GORD have greatest nitrosative stress in the lower oesophagus
Nitrosative stress (2)

• H. pylori infection negatively associated with OAC
• H. pylori induces achlorhydria
• By reducing gastric acid, does this in effect reduce nitrogen free radical creation?
Fish

- No association of fish consumption with OAC in MOSES
- No differentiation during interview between white and oily fish (n-3 fatty acids) in MOSES
- *In-vitro* evidence of reduced COX-2 synthesis, potentially offering protective effects
- N-3 and poly-unsaturated fatty acids inversely associated with Barrett’s oesophagus
- Very little evidence currently with influence of n-3 fatty acids upon the aetiology of OAC
Tea

• Caffeine in tea is recognised to lead to lower-oesophageal sphincter relaxation, predisposing to gastro-oesophageal reflux, thus Barrett’s oesophagus and risk of carcinogenesis.

• Whilst a similar trend with coffee consumption was not observed, tea is the predominant hot drink consumed by the age range of individuals in the UK.
Patient demographics

- As there is no impact of socio-economic status (SES) upon the aetiology of OAC, does dietary implications of SES?
- Good diets in the more affluent vs H.pylori in the deprived may balance this equation
- Ethnicity not a factor
Conclusion

• Rapidly rising incidence of OAC
• Modifiable factors include smoking, waist circumference, BMI and diet
• Diets high in fruit and vegetables may offer protective advantage
• Avoid diets high in red meat and tea
• It’s OK to have the occasional drink!