FIT thresholds based on sex

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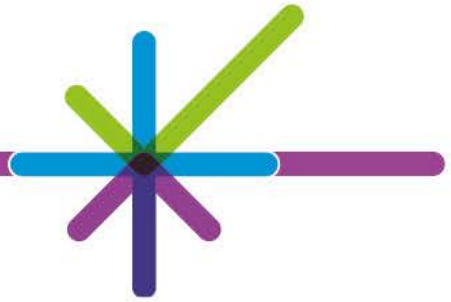
Background

- CRC screening implemented using gFOBT in Scotland:
  - Piloted from 2000 (three screening rounds in three NHS Regions)
  - National roll-out began in 2007, completed 2009

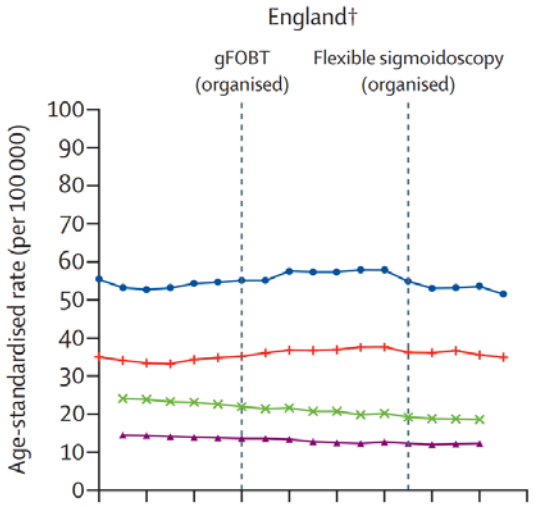
- Implemented on the basis of RCT evidence of a reduction in CRC mortality

- There is evidence that this reduction is not uniform between women and men…



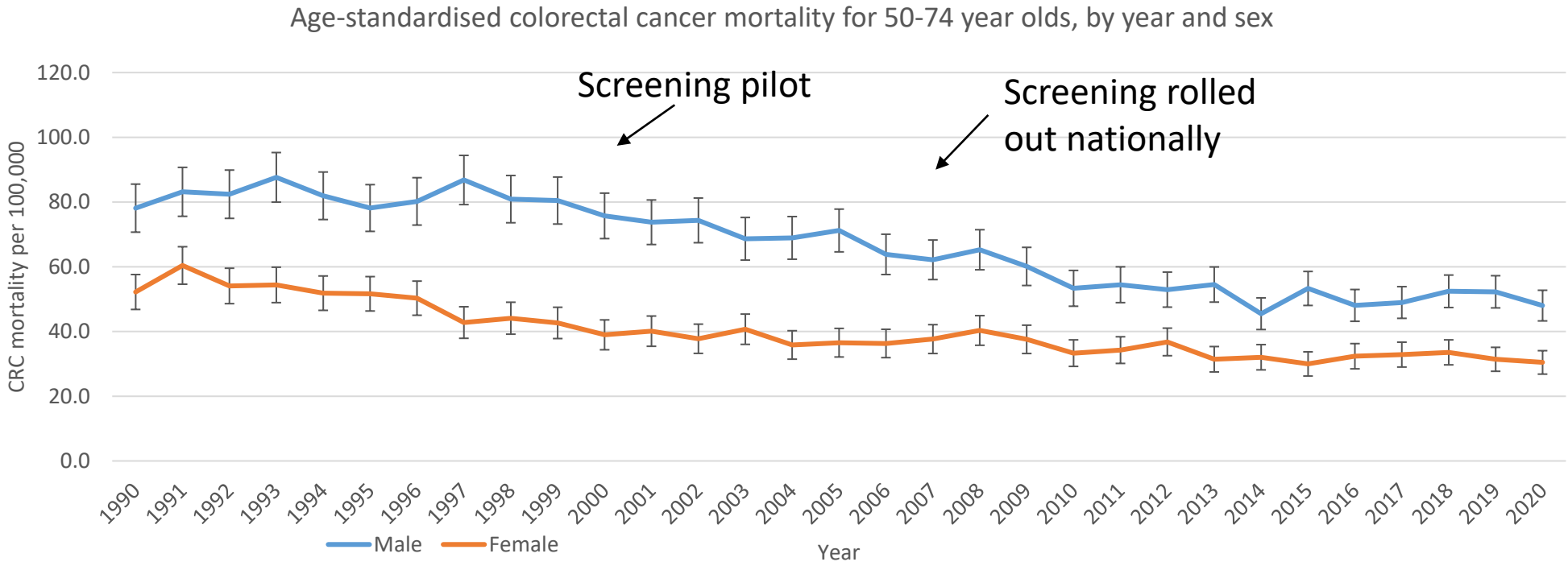
CRC mortality England and Wales

- Mortality data from England and Wales provided as part of European study
- Calculated average annual percentage change (AAPC) in CRC mortality from 2000-2017
- Found a greater reduction in mortality for all age-groups in men (-1.8%, 95% CI: -2.0 to 1.7%) than in women (-1.3%, -1.5 to -1.1%) in the period

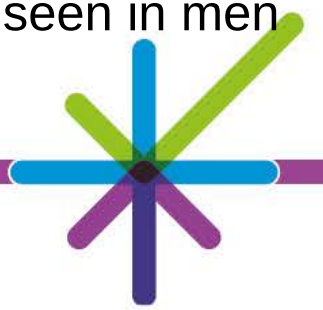


Colorectal cancer incidence, mortality, and stage distribution in European countries in the colorectal cancer screening era: an international population-based study

CRC mortality in Scotland in screening age range



- AAPC for 2000-2020 for 50- to 74-year-olds:
  - **All: -1.9%, Women: -1.3%, Men: -2.4%**
  - But increases in mortality also seen in women under 50 years, not seen in men



Sex variation in colorectal cancer mortality: trends and implications for screening

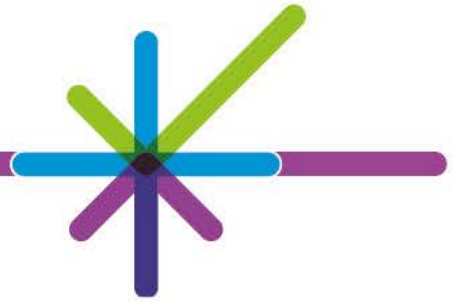
Gavin R.C. Clark [1], Callum G. Fraser [2], Judith A. Strachan [3], Robert J.C. Steele [2]

CRC mortality and sex – RCT evidence

- Nottingham RCT showed similar reductions for women and men after 20 years follow-up (Hardcastle, 2012)

- Minnesota RCT showed smaller (statistically non-significant) mortality reduction for women (8%) than for men (37%) for biennial screening after 30 years follow-up (Shaukat, 2013).
  - Pooled analysis of **compliers** in Danish and Minnesota RCT showed reduction of 25% in men, 9% in women, with the latter value non-significant (Shaukat, 2020)

- Finnish gFOBT trial showed mortality reduction in men only (Pitkäniemi, 2015), median follow-up of 4.5 years



Why - test sensitivity?

- Gies et al. (2021) evaluated the performance of nine FIT in those undergoing screening colonoscopy
- Lower sensitivity for advanced neoplasia was seen in women than men for all of the nine different manufacturers
- Consistent with prior findings from Brenner (2010) and van Turenhout (2014)

Table 2. Sensitivity and specificity for detection of advanced neoplasia by sex.

FIT Brand	Sensitivity (%)				Specificity (%)			
	Female	Male	Diff.	*p*	Female	Male	Diff.	*p*
At original thresholds recommended by the manufacturers								
IDK Hb ELISA	40.5	49.3	−8.8	0.22	90.3	80.7	+9.6	**0.02**
QuantOn Hem	36.5	48.6	−12.1	0.09	89.0	82.1	+6.9	0.09
immoCARE-C	33.8	41.1	−7.3	0.29	92.9	86.9	+6.0	0.09
CAREprime	28.4	38.0	−9.6	0.16	95.5	86.9	+8.6	**0.01**
RIDASCREEN Hb	32.4	43.0	−10.6	0.13	94.8	86.2	+8.6	**0.01**
Eurolyser FOB test	17.6	25.4	−7.8	0.20	98.7	95.2	+3.5	0.09
OC-Sensor	17.6	23.9	−6.3	0.28	99.4	95.9	+3.5	0.08
QuikRead go iFOBT	14.9	25.4	−10.5	0.08	98.7	94.5	+4.2	0.06
SENTiFIT-FOB Gold	17.6	23.9	−6.3	0.28	98.7	93.8	+4.9	**0.04**
GEE-Model	25.7	34.6	−8.9	0.12	96.2	90.8	+5.4	**0.005**

Why? Interval cancers and faecal haemoglobin

- Interval cancers – a cancer diagnosed in the interval following a “negative” screening examination but before the next examination
  - More likely late stage and so poorer outcomes than screen-detected

- In those who participate, a higher proportion of cancers are diagnosed as interval in women than in men (Wieten, 2018)

- Reasons unclear although could relate to:
  - Sex differences in cancer site
  - Type of lesion (sessile serrated lesions)
  - Women in the screening population have lower f-Hb on average, therefore lower positivity and lower cancer detection rate

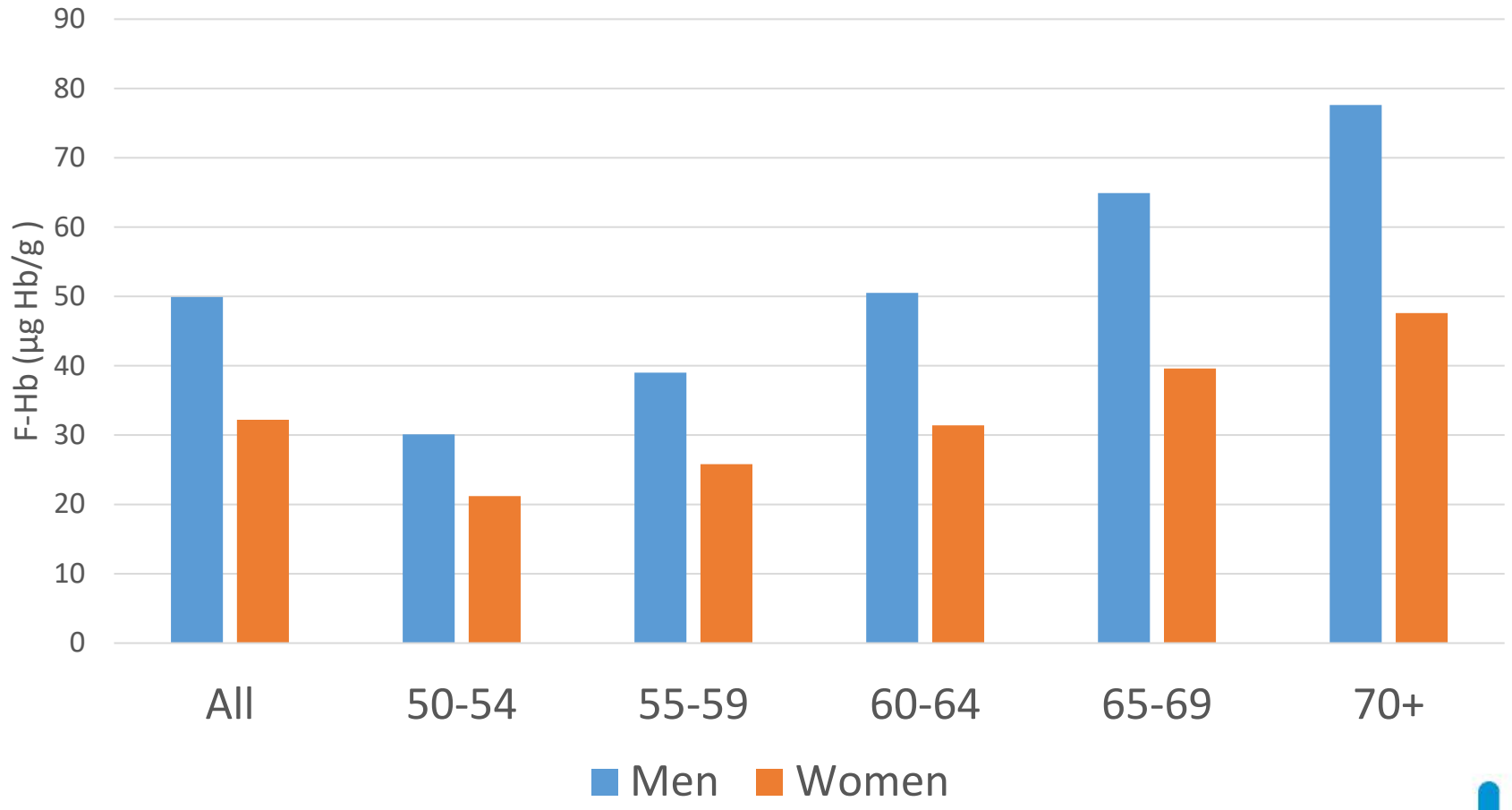
FIT introduction in Scotland

- Evidence for the evolution to Faecal Immunochemical Tests (FIT) was accumulating in 2000s, with advantages including:

  - Improved uptake (one sample rather than two from each of three)
  - Quantitative result (rather than colour change)
  - Customisable faecal haemoglobin concentration threshold
  - Greater sensitivity for CRC and large polyps (threshold-dependent)
  - Similar specificity at same level of test positivity

- Piloted in Scotland 2010 - replaced gFOBT in 2017 at a threshold of ≥80 µg Hb/g faeces

f-Hb in screening participants by age and sex

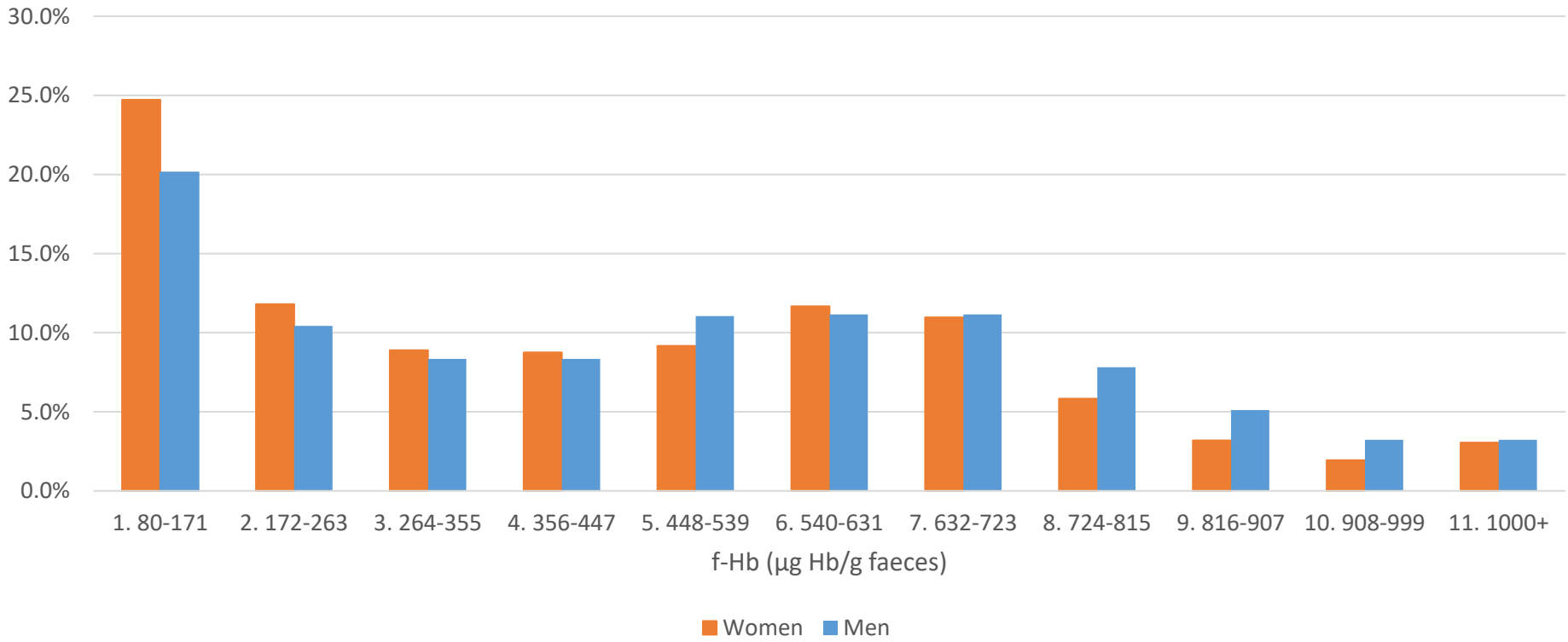


f-Hb in screen-detected CRC


Original Article

Faecal haemoglobin concentrations in women and men diagnosed with colorectal cancer in a national screening programme

Gavin RC Clark[1], Jayne Digby[2], Callum G Fraser[3], Judith A Strachan[3] and Robert JC Steele[3]



- f-Hb lower in women (median = 408 µg Hb/g faeces) than men (473 µg Hb/g faeces) with screen-detected cancer (p = 0.004)
- Holds even when comparing across CRC site and stage

FIT vs. gFOBT – possible solution

- Evidence for the evolution to Faecal Immunochemical Tests (FIT) was accumulating in 2000s, with advantages including:
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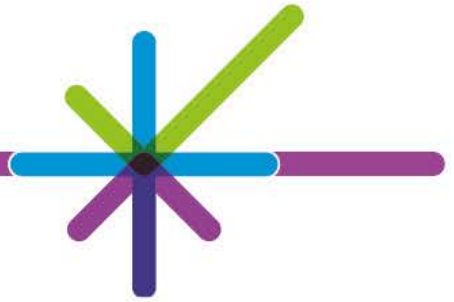
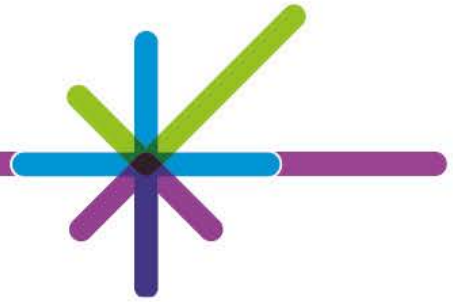
How do interval cancer proportions vary by sex and threshold?

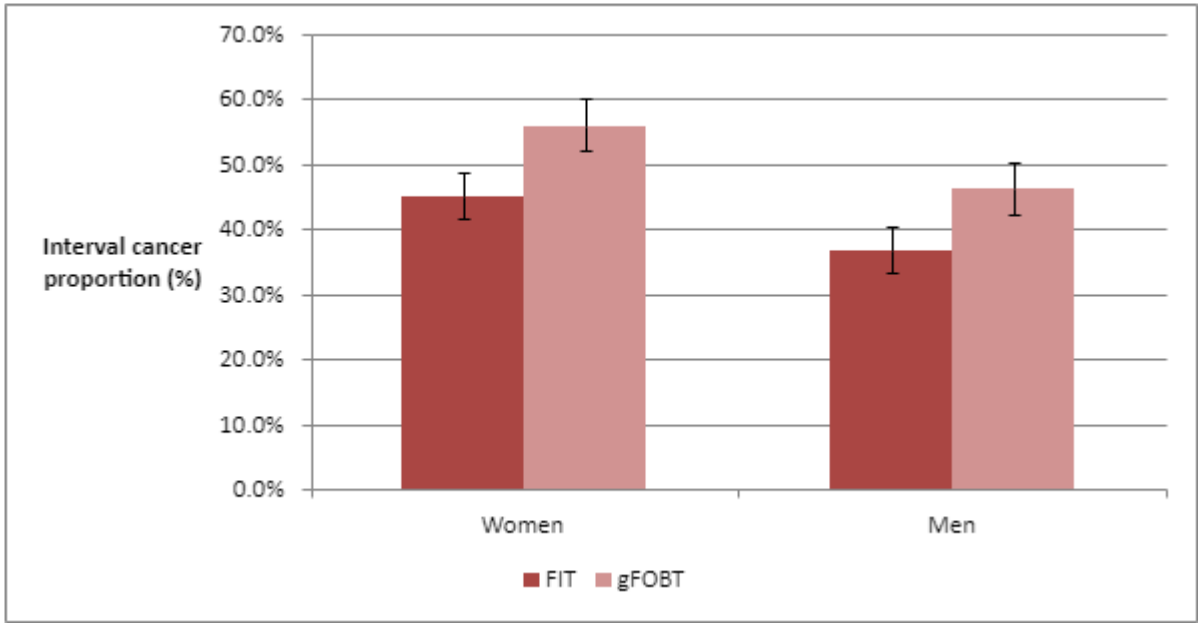


Methods

- Scottish Bowel Screening Database collects data nationally on participation and numerical f-Hb concentration
- Scottish Cancer Registry collect information on all colorectal cancers diagnosed
- Linkage with SBSD allowed identification of interval cancers: those diagnosed after a negative FIT result, before the next screening round invite
  - Cohort was those invited from Nov-17 to Oct-18
- Calculated interval cancer proportion: interval cancers as a proportion of all colorectal cancers in participants (i.e. screening and interval cancers combined)

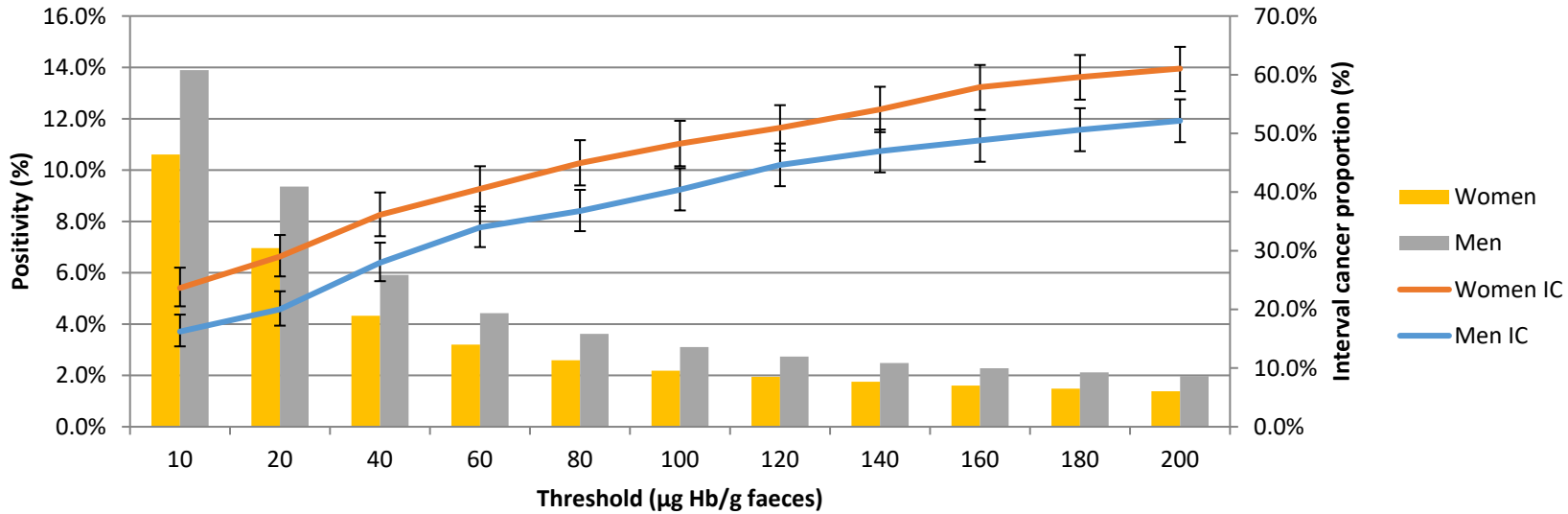


Results



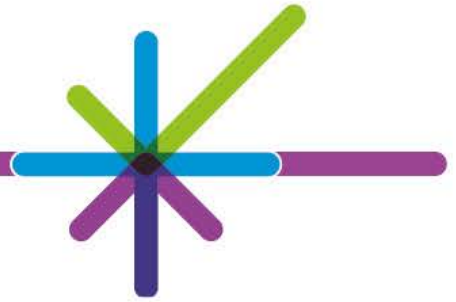
- 1,349 CRC in participants (screening and interval)
- 548 interval cancers, giving ICP of 40.6% with FIT
- ICP was greater in women (45.0%, 95 CI:41.1 to 48.8%) than men (36.8%, 33.3 to 40.4%)

Interval cancer proportion by f-Hb threshold and sex



- Interval cancer proportion is higher for women than men, at every threshold
- Equivalent IC proportion achieved by threshold of ca. 40 µg Hb/g faeces for women while maintaining current ≥80 µg Hb/g faeces for men
- But positivity increase of ~65% for women - increased colonoscopy demand

Conclusions



Conclusions

- Scottish data provide further evidence for poorer sensitivity and higher interval cancer proportions in women

- FIT afford the opportunity to address this inequity in ICP/test sensitivity by reducing f-Hb threshold for women to ≥40 µg/g

- However, colonoscopy resource constrained in Scotland

- Furthermore, increase in false positives and complications, reduction in PPV

Experience in other countries

- Sweden and Finland have lower f-Hb thresholds in women than men

- Sweden have f-Hb thresholds of ≥40 µg Hb/g faeces in women and ≥80 µg Hb/g faeces in men, with similar sensitivity between the two groups (Wilen, 2023)

- Finland have thresholds of ≥25 µg Hb/g faeces in women and ≥70 µg Hb/g faeces in men, though no published IC data
  - Similar CRC PPV in women (8.8%) and men (9.0%)
  - Lower advanced adenoma PPV in women (21.3%) than men (34.8%)

Other possible variables

- Alternatives to interval cancer proportion/sensitivity when setting threshold could include:
  - Positivity
  - Positive predictive value
  - Cancer detection rate
  - Risk

- Cost-effectiveness – 2018 ScHARR report suggested that ≥20 µg Hb/g faeces is optimal threshold

Acknowledgements

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Questions?