Of 134 faecal DNA samples analysed, 17 were found to have BAT26 alterations. Examples of the results from this assay are shown in the figure. All 17 faecal DNA samples yielding a positive BAT26 test were subsequently found to have been derived from patients with colorectal cancer (table).

Among the cancer patients with proximal lesions, the clinical sensitivity of the BAT26 faecal DNA test was 37% (17 of 46 [95% CI 23–52]), with no positives among 69 individuals with normal colonicoscopies or among 19 individuals with adenomas. The specificity was therefore 100% (95% CI 95–100). None of the patients in our cohort had variants of BAT26 alleles in their germ line.

To determine the concordance of BAT26 alterations between faecal DNA and tumours, we microdissected neoplastic lesions from paraffin-embedded specimens of all 65 tumours (46 cancers plus 19 adenomas). DNA of adequate quality was recovered from 57 lesions, and 18 cases with BAT26 alterations were seen, all among cancers. 17 of these 18 cases corresponded to those with positive faecal tests, and in each of these cases, the size of the BAT26 alteration in tumour and faecal DNA was identical (figure).

The results recorded above have several important implications for faecal DNA testing. First, they provide compelling evidence that mutations in faeces can be used to identify patients with cancer. The fact that 17 of the 18 cases with BAT26 mutations in their tumours gave rise to a positive faecal DNA test, coupled with the zero false-positive rate, was of particular note. Second, the results show that as proximal cancers do not represent a barrier to faecal DNA analysis. Third, small samples of stool, rather than whole stools, could be analysed effectively, facilitating collection and storage of specimens for analysis. Finally, the proportion of mutant DNA molecules in faecal DNA ranged from 1·1% to 10·6%. Thus, techniques to assess faecal DNA mutations in patients with colorectal tumors. 17 were found to have BAT26 alterations. Examples of the results from this assay are shown in the figure. All 17 faecal DNA samples yielding a positive BAT26 test were subsequently found to have been derived from patients with colorectal cancer (table).
Cancer is malignant in the sense that its natural course is fatal, meaning that its case–fatality rate in the absence of curative treatment would be 100% if there were no role for other causes of death. Given the opportunity, it would kill every person with the disease. With screening, the idea is to achieve early diagnosis and, thereby, early treatment, which is presumed to be curative in more cases than later treatment. The idea, therefore, is to reduce the case–fatality rate. The authors of the Malmö study—once one of two accepted treatment. The idea, therefore, is to reduce the case–fatality rate—refer only to the overall result (63 vs 66) and its associated "relative risk" and 95% CI (0·96 [0·68–1·35]), supplementing this information with the corresponding even more inclusive all-cause mortality ratio (0·98 [0·93–1·04]). Moreover, since they did not examine the studies for characteristics other than "methodological quality", they pooled the overall result from Malmö with that of a Canadian study, despite very different regimens and durations of screening and follow-up.

Screening in the Canadian study continued for only 3–4 years after study entry, and follow-up stopped at the point at which follow-up in the Malmö study started to show fewer breast-cancer deaths among those screened. In Malmö, the screening continued throughout the 10–11 years of follow-up. When the duration of screening in a trial that compares screening with no screening (rather than early intervention with late intervention) is too short, nowhere during follow-up does the mortality ratio decline all the way to the case–fatality ratio (which characterises early intervention relative to late intervention). For the fatality ratio to become fully apparent, in the appropriate interval of follow-up, the duration of screening must exceed the difference between the maximum and the minimum of the time lag from screening-associated early diagnosis to the death in the prevention of which early intervention is essential.

The delay principle addressed above is not in dispute. In its spirit, then, and also accepting Olsen and Gotzsche’s conclusion that valid evidence derives mainly from the Malmö trial, we call attention to our figure. Screening in older women seems to have provided for a 100%–45%–55% reduction in case–fatality rate and thereby, after the requisite delay, in cause-specific mortality.

**Conflict of interest statement**

None declared.


The complete version of this paper can be found at http://image.thelancet.com/extras/1093web.pdf

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