Aspirin as an adjunct to screening for prevention of sporadic colorectal cancer: a cost-effectiveness analysis
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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Aspirin (a non-steroidal anti-inflammatory drug) used as prevention therapy (chemoprevention) for sporadic colorectal cancer, as an adjunct to widely used screening strategies. The screening strategies included flexible sigmoidoscopy every 5 years and yearly faecal occult blood testing (FS-FOBT), and colonoscopy every 10 years (COLO). The dose of aspirin was 325 mg/day.

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised the general US population.

Setting
The setting was primary care. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness evidence and resource use data were gathered from studies published between 1982 and 1998. The price year was 1998.

Source of effectiveness data
The effectiveness evidence was derived from a review of published studies.

Modelling
A Markov model was used to estimate the clinical and economic consequences of six strategies in the general US population. The strategies were natural history (no screening and no aspirin), FS-FOBT, COLO, aspirin alone (ASA), FS-FOBT with aspirin (FS-FOBT-ASA), and COLO with aspirin (COLO-ASA). Patients aged 50 years progressed through the model for 30 cycles of one year. The principal states of the model were normal, polyp, cancer (localised, regional or distant) and dead. Male and female populations were analysed separately. A screening adherence rate of 25% was used. The probabilities of existing in the principal Markov states at baseline and the transition probabilities for the natural history model were not varied.

Outcomes assessed in the review
The outcomes assessed in the review and used as model parameters were:

- the incidence of colorectal cancer with and without adenoma;
- symptomatic presentation of localised or regional cancer;
- the mortality rates from treated localised or regional cancer;
- the mean survival with distant cancer, and the mortality rate from cancer treatment;
- the sensitivity and specificity of FOBT, FS and COLO for cancer and polyp with FOBT;
- the rate of polyp and cancer within reach of FS;
- the major complication and mortality rates associated with COLO and FS;
- the reduction in colorectal cancer incidence with aspirin; and
- the rate of major aspirin-related complications, and the subsequent mortality rate.

**Study designs and other criteria for inclusion in the review**
Not reported.

**Sources searched to identify primary studies**
MEDLINE was searched from 1980 to 1999 for publications in the English language on colorectal cancer, screening, aspirin chemoprevention and aspirin-related complications.

**Criteria used to ensure the validity of primary studies**
Not stated, although the Agency for Health Care Policy and Research and the Office of Technology Assessment provided primary studies for the literature review.

**Methods used to judge relevance and validity, and for extracting data**
Not reported.

**Number of primary studies included**
Twenty-eight primary studies were included in the review.

**Methods of combining primary studies**
Not reported. However, several studies were not combined because each of them provided a single effectiveness estimate.

**Investigation of differences between primary studies**
Not reported.

**Results of the review**
The colorectal cancer incidence was age and gender specific. The range was 6 to 86 patients per 100,000 person-years with adenoma and 299 to 876 without.
Over 2 years, the symptomatic presentation of localised cancer was 22% per year, while the symptomatic presentation of regional cancer was 40% per year.

In the first 5 years, the mortality rate was 1.74% per year from treated localised cancer and 8.6% per year from treated regional cancer.

The mean survival with distant cancer was 1.9, and the mortality rate from cancer treatment was 2%.

The sensitivity of FOBT was 40% (range: 30 - 60) for cancer and 10% (range: 5 - 15) for polyp.

The sensitivity of FS for polyp or cancer within reach of sigmoidoscope was 90% (range: 80 - 95).

The sensitivity of COLO was 95% (range: 90 - 97) for cancer and 90% (range: 85 - 95) for polyp.

The specificity of FOBT was 92% (range: 87 - 97) and the specificity of FS was 95% (range: 90 - 99).

The rate of polyp or cancer within the reach of sigmoidoscope was 50%.

The major complication rate was 0.1% (range: 0.05 - 0.5) with COLO and 0.01% (range: 0.005 - 0.02) with FS. The mortality rate was 0.01% (range: 0.005 - 0.03) with COLO and 0.001% (range: 0.0005 - 0.002) with FS.

The reduction of colorectal cancer incidence with aspirin was 30% (range: 5 - 55).

The rate of major aspirin-related complications per 10,000 person-years was 2 (range: 0.5 - 5) for persons aged less than 65 years and 16 (range: 4 - 40) for those aged at least 65 years.

The mortality rate given major aspirin-related complication was 5% (range: 2 - 8).

**Measure of benefits used in the economic analysis**

Several outcome measures, such as colorectal cancer incidence, total cases of colorectal cancer, deaths and mean survival, were obtained through the Markov model. However, only the average number of life-years per person was used in the economic analysis.

**Direct costs**

A 3% discount rate was used in the analysis due to the long time horizon of the study. The resources quantities and the unit costs were not reported separately, but the unit costs per procedure were. The resource/boundary adopted was that of the third-party payer (Medicare). The costs included professional fees, median procedure expenditures and aspirin. The resource use was estimated through modelling based on the 1982 to 1998 sources. The source of the costs was the Medicare reimbursement system. The cost of aspirin was obtained from wholesale prices. The price year was 1998.

**Statistical analysis of costs**

No statistical analysis was reported, although the costs were treated stochastically in the Monte Carlo simulation.

**Indirect Costs**

No indirect costs were included.

**Currency**

US dollars ($).

**Sensitivity analysis**
Sensitivity analyses were conducted on the model inputs to assess the robustness of the results. Monte Carlo simulations were used to perform a probabilistic analysis. Each of the 3,500 iterations produced an estimate of the costs and effectiveness for each strategy. Incremental cost-effectiveness ratios (ICERs) were calculated for those strategies that were not dominated. These ICERs were then used to summarise the cost-effectiveness distribution in terms of the median and inter-quartile range. The proportion of iterations for which a strategy was dominated was also calculated.

Estimated benefits used in the economic analysis
Compared with no screening, the incidence of colorectal cancer decreased by 65% with FS-FOBT or COLO, and by 75% with FS-FOBT-ASA or COLO-ASA.

There were 4,361 cases of colorectal cancer per 100,000 persons with no intervention, 1,895 per 100,000 persons with FS-FOBT, and 1,693 per 100,000 persons with COLO.

The addition of aspirin further reduced cancer incidence. There were 1,258 cases per 100,000 persons with FS-FOBT-ASA, and 1,109 cases per 100,000 persons with COLO-ASA.

When 25% of the population was screened, the total number of deaths was 48,064 with FS-FOBT, 48,080 with COLO, 47,994 with FS-FOBT-ASA, and 47,951 with COLO-ASA.

There were 129 aspirin-related deaths. The mean (3%) discounted life-year per person was 18.721 with FS-FOBT, 18.719 with COLO, 18.734 with FS-FOBT-ASA, and 18.734 with COLO-ASA.

Cost results
The cost of natural history (no screening, no aspirin) was $830 per person.

The costs were increased to $2,005 per person with FS-FOBT and to $2,125 per person with COLO.

When aspirin was added, FS-FOBT-ASA cost $2,105 per person and COLO-ASA cost $2,237 per person.

The results were similar for both men and women.

Synthesis of costs and benefits
An incremental cost-effectiveness analysis was performed to combine the costs and benefits.

The FS-FOBT strategy cost $15,451 per life-year in men and $18,639 in women.

COLO cost $18,6256 per life-year in men and $22,329 in women.

The introduction of aspirin was not cost-effective as an adjunct to FS-FOBT, because FS-FOBT-ASA was dominated by FS-FOBT alone (less costly and more effective). It was, however, cost-effective as an adjunct to COLO, but at a high incremental cost of $149,161 per life-year gained of COLO-ASA over COLO.

The sensitivity analyses indicated that the results were highly dependent on the magnitude of aspirin's chemopreventive effect, the rate of screening adherence in the population, and the aspirin-related complication rates.

In Monte Carlo simulations, compared with no intervention, the median ICER was $17,668 per life-year gained for FS-FOBT (inter-quartile range: 14,497 - 21,143; 98% of the values within 7,506 - 28,500 per life-year), and $22,649 per life-year gained for COLO (inter-quartile range: 16,525 - 28,861; 98% of the values within 8,466 - 37,436 per life-year).

The addition of aspirin generally increased the costs and reduced the life-years gained. FS-FOBT dominated FS-FOBT-ASA in 68% of the iterations, while COLO dominated COLO-ASA in 55% of the iterations.
Authors' conclusions
Aspirin as an adjunct to screening was not cost-effective in many cases. When aspirin was used in persons adhering to both forms of screening (flexible sigmoidoscopy and faecal occult blood testing, or colonoscopy), the additional decrease in cancer deaths was generally offset by aspirin-related deaths. Aspirin used for chemoprevention was, therefore, unlikely to be cost-effective. Aspirin appears to have been cost-effective in non-screened populations, but it was much less effective than screening. Thus, aspirin cannot be considered a substitute for screening. The effect of screening in populations already using aspirin was also investigated. The results showed screening to be cost-effective in patients already taking aspirin. The conclusions applied to both men and women.

CRD COMMENTARY - Selection of comparators
The reason for the selection of the comparators was clear. The use of aspirin as an adjunct to screening strategies was compared with the current practice of no aspirin in the general population. FS-FOBT and COLO were selected because they represented accepted screening strategies in the USA. You should consider whether they are commonly used in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness estimates were obtained from a review of the literature. The search methods were reported whereas the study designs and the criteria to ensure the validity of the primary studies were not. Further, while some estimates were obtained from the synthesis of several studies, the authors did not consider the impact of differences between the primary studies when estimating the effectiveness measures.

Validity of estimate of measure of benefit
The benefits were estimated through modelling. The instrument used to derive a measure of health benefit was the Markov model. This appears to have been appropriate for simulating the natural history of the disease.

Validity of estimate of costs
The cost estimates used in the study were specific to the Medicare setting. All the categories of costs relevant to the perspective of the study were included in the analysis. The analysis did not include cardiovascular disease expenditures, and their impact on the analysis was difficult to evaluate. The unit costs were only reported for the procedures. Details of the resource use were not provided. The source of the cost data was reported. Appropriate discounting was performed.

Other issues
The authors made several comparisons of their results with those from other studies, and their conclusions were confirmed in recent trials. The issue of the generalisability of the study results to other settings was addressed by performing extensive sensitivity analyses on the model, which appeared robust to variations in the basic inputs. The study referred to the general population and this was reflected in the conclusions of the analysis. The authors noted some limitations of their analysis, which had been reported earlier. Finally, the ranking of the possible alternatives (thus, the incremental cost-effectiveness analysis) was calculated in three different scenarios (all persons screened, no persons screened, and 25% of persons screened), as these represented three possible situations in the real world.

Implications of the study
The main implication of the study in terms of public policy is that aspirin cannot be considered a substitute for screening. Screening alone was not only cost-effective, but also aspirin as an adjunct to screening was unlikely to be beneficial for the prevention of colorectal cancer. The authors strongly believe that "public policy efforts must focus on improving screening adherence".

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**Other publications of related interest**


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