Appendix 1

Modelling design and estimated effects of breast cancer interventions

Modelling health effects of breast cancer control

We used a simplified breast cancer model to simulate the impact of six interventions on the course of breast cancer in Afr-E and Sear-D. Each intervention was compared with no intervention (i.e., no breast cancer treatment or active case finding). All interventions were introduced starting in the year 2005 for a period of 10 years, after which no breast cancer interventions were available, and the maximum follow-up was 100 years, which is in line with the WHO-CHOICE guidelines on CEA (see General Appendix A) Following this standardized approach, we assumed that interventions were performed optimally. The outcomes of our analysis were life years adjusted for disability (DALYs) and the total costs of breast cancer treatment and follow-up for each of the six interventions.

Model assumptions

Interventions

In recent years, many developments in diagnosing and treating breast cancer have taken place, and we could analyze a large number of interventions in our model. However, we confined the model to a small set of basic interventions to allow comparability among the sub-regions. The six interventions we included are described in Table 3 in the main text

Model structure

Six mutually exclusive health states were included: healthy (no breast cancer); American Joint Committee on Cancer (1) stages I, II, III, and IV breast cancer; and death from breast cancer. Regional age-adjusted population estimates of breast cancer incidence, breast cancer prevalence, percentage of prevalent cases treated, and background mortality rates were based on WHO Burden of Disease study estimates for 2000 (2). The key elements of the model were the stage distribution of both prevalent and incident cases and the case fatality rate for untreated and treated patients (Appendix Table A1.2). Following WHO-CHOICE guidelines the interventions were aimed at initial disease treatment only, but patients could relapse or progress after initial diagnosis; therefore, we filtered out the effect of treating patients whose disease progressed. It was assumed that patients could progress only to stage IV breast cancer and that progression followed a constant rate (3). Stage distributions for prevalent cases were derived from registry data (Appendix Table A1.1). The stage distribution of prevalent cases in North America was based on the U.S. National Cancer Data Base (NCDB) (4). The stage distribution of prevalent cases in Africa and Asia was based on registry data from Southeast Asia (5). In the no-intervention scenario, the stage distribution of incident cases and stage-specific case fatality rates were based on registry data from Southeast Asia (5) and applied to both world sub-regions. The case fatality rates for treated patients were derived from the U.S. National Cancer Data Base (NCDB) (4). In the optimal breast cancer program scenario, the stage distribution of incident cases and stage-specific case fatality rates were based on data from the NCDB (4) for both world sub-regions.

Health state valuation

The disability weight (DW) of breast cancer patients (Table 3 in the main text) was based on the WHO Global Burden of Disease study (6). Using NCDB data on stage distribution (4) and DW data from several sources (7-9) we arrived at stage specific DW estimates. The DW of the susceptible population was derived from this value and took into account all disease in a population except breast cancer.

Costs

All costs were calculated and are presented in this report in 2005 international dollars. Two types of costs for health services were distinguished: patient-level costs, which were incurred for individual patients, and program-level costs, which were incurred at a level above that of the patient.

Patient-level costs

Patient-level patterns of resource use (i.e., initial evaluation, local treatment, and follow-up were based on clinical practice guidelines (10-11) (Appendix Table A3.1). These costs included evaluation of women without breast cancer; it was assumed that only 6% of all presenting women were diagnosed with breast cancer (12). Screening in the optimal cancer program included costs of mammography screening in women aged 50-70 years and further diagnostics tests on referral (Table 1). Detailed lists of all tests and procedures were retrieved from a South-African database (13) and validated for western countries by a team of oncologists. Unit costs were retrieved from the WHO-CHOICE database on prices of traded and non-traded goods (www.who.int/evidence/cea). Unit costs of health center visits and hospital inpatient days were based on a report by Adam et al. (14). We combined unit costs with resource use patterns to estimate the total costs per patient treated.

Program-level costs

We based estimated quantities of resources required to start up and maintain each intervention for 10 years (e.g., personnel, materials and supplies, media, transport, maintenance, utilities, and capital) at national, provincial, and district levels on a series of evaluations made by regional costing teams in both WHO world sub-regions and validated against the literature (15) We obtained unit cost estimates of program-level resources (e.g., the salaries of central administrators, capital costs of vehicles, storage, offices, and furniture) from a review of the literature, which was supplemented by primary data from several countries (the full list of unit cost estimates is available at www.who.int/evidence/cea). The process and methodology for estimating program costs have been described in detail elsewhere (15-16).

References

1. AJCC. AJCC cancer staging manual. New York: Springer-Verlag, 2002.
2. Shibuya K, Mathers CD, Boschi-Pinto C, Lopez AD, Murray CJ. Global and regional estimates of cancer mortality and incidence by site: II. Results for the global burden of disease 2000. BMC Cancer 2002;2:37.
3. Engel J, Eckel R, Kerr J, et al. The process of metastasisation for breast cancer. Eur J Cancer 2003;39:1794-806
4. Bland KI, Menck HR, Scott-Conner CE, Morrow M, Winchester DJ, Winchester DP. The National Cancer Data Base 10-year survey of breast carcinoma treatment at hospitals in the United States. Cancer 1998;83:1262-73..
5. Sankaranarayanan R, Black RJ, Parkin DM. Cancer survival in developing countries. Lyon: International Agency for Research on Cancer, 1998:173.
6. Murray CJL, Lopez AD. The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. Global burden of disease and injury series: Volume 1. Cambridge, MA: Harvard School of Public Health, 1996.
7. Norum J, Olsen JA, Wist EA. Lumpectomy or mastectomy? Is breast conserving surgery too expensive? Breast Cancer Research and Treatment 45: 7–14, 1997.

8. Launois R, Reboul-Marty J, Henry B, Bonneterre J. A cost-utility analysis of second-line chemotherapy in metastatic breast cancer. Docetaxel versus paclitaxel versus vinorelbine. Pharmacoeconomics 1996;10:504-21.
9. de Koning HJ, van Ineveld BM, van Oortmarssen GJ, et al. Breast cancer screening and cost-effectiveness; policy alternatives, quality of life considerations and the possible impact of uncertain factors. Int J Cancer 1991;49:531-7.
10. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology – version 1.2004. Breast cancer [guideline on the internet]: NCCN; c-2004 [updated 2004 March 19; cited 2005 Jan 20] Available from: http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf., 2004.
11. M.D. Anderson Cancer Center. Clinical Practice guideline of the M.D. Anderson Cancer Center, Breast cancer [guideline on the internet]: MDACC; c-2004 [updated 2003 September 2; cited 2005 Jan 20] Available from: http://utm-ext01a.mdacc.tmc.edu/mda/cm/CWTGuide.nsf/0/e0377163611243e3862563c3007c3703/$FILE/Br%20Noninvasive%20Group%20V5.pdf
12. Flobbe K, van der Linden ES, Kessels AG, van Engelshoven JM. Diagnostic value of radiological breast imaging in a non-screening population. Int J Cancer 2001;92:616-8.
13. World Health Organization Department of Essential Health Technologies. Essential Health Care Technology Planning package [homepage on the internet]. Geneva: WHO; c-2005 [cited Jan 20 2005] Available from: http://www.who.int/medical_devices/appropriate_use/en/.
14. Adam T, Evans DB, Murray CJ. Econometric estimation of country-specific hospital costs. Cost Eff Resour Alloc 2003;1:3.
15. Johns B, Baltussen R, Hutubessy R. Programme costs in the economic evaluation of health interventions. Cost Eff Resour Alloc 2003;1:1.
16. Johns B, Baltussen R. Accounting for the cost of scaling-up health interventions. Health Econ 2004;13:1117-24.
17. World Health Organization, Department of Essential Health Technologies. Essential Health Care Technology Package (EHTP) [Web page]. Geneva, Switzerland: World Health Organization, 2005. Available at http://www.who.int/medical_devices/appropriate_use/en accessed January 20, 2010.

Table A1.1. Patient-level resource use patterns for breast cancer interventions

Procedure	Resource	Resource use per patient per year [a]	Unit cost (I$) AFR-E[b]	Unit cost (I$ SEAR-D[b]
Diagnosis				
	Bilateral mammography	1	36.05	36.08
	Complete blood count	1	13.09	13.16
	Liver function tests	1	10.62	10.53
	Alkaline phosphatase assay	1	22.48	22.43
	Fine needle aspiration or core needle biopsy	1	41.86	41.17
	Chest X-ray	1	22.86	22.40
	ECG	0.5	20.99	20.39
	Bone scan	0.25	160.23	159.70
	Ultrasonography of the liver	0.25	18.60	17.41
	Outpatient visit (health centre)	1	5.21	4.95
	Outpatient visit (hospital)	1	11.99	11.15
Non-breast cancer examination[c]				
	Bilateral mammography	1	36.05	36.08
	Ultrasonography of the liver	0.28	18.60	17.41
	Fine needle aspiration or core needle biopsy	0.27	41.86	41.17
	Outpatient visit (hospital)	1	11.99	11.15
Treatment of breast cancer detected at Stage I	Lumpectomy with axillary dissection	1	164.87	158.74
	Radiotherapy course[d]	1	1652.74	1504.61
	Endocrine therapy[e]	0.5	0.10/dose	0.10/dose
	Hospital bed days	2	25.80	24.24
	Outpatient visit (hospital)	1	11.99	11.15
Treatment of breast cancer detected at Stage II	Lumpectomy with axillary dissection	1	164.87	158.74
	Radiotherapy course[d]	1	1652.74	1504.61
	Endocrine therapy[e]	0.5	0.10/dose	0.10/dose
	Hospital bed days	2	25.80	24.24
	Outpatient visit (hospital)	1	11.99	11.15
Treatment of breast cancer detected at Stage III	Mastectomy with axillary dissection	1	169.87	163.41
	(Neo)adjuvant chemotherapy course[f]	1	380.89	372.44
	Radiotherapy course[d]	1	1652.74	1504.61
	Endocrine therapy[e]	0.5	0.10/dose	0.10/dose
	Hospital bed days	6	25.80	24.24
	Outpatient visit (hospital)	1	11.99	11.15
Treatment of breast cancer detected at Stage IV	(Neo)adjuvant chemotherapy[f]	1	380.86	372.44
	Endocrine therapy[e]	0.5	0.10/dose	0.10/dose
	Bisphosphonate therapy		44.09	44.09
	Hospital bed days	2	25.80	24.24
	Outpatient visit (hospital)	1	11.99	11.15
Follow-up 1-5 (per year)				
	Bilateral mammography	2	36.05	36.08

	Pelvic examination	0.5	5.66	5.13
	Endocrine therapy	0.5	0.10/dose	0.10/dose
	Outpatient visit (health centre)	2	5.21	4.95
Follow-up 6-10 (per year				
	Bilateral mammography	1	36.05	36.08
	Pelvic examination	0.5	5.66	5.13
	Endocrine therapy	0.5	0.10/dose	0.10/dose
	Outpatient visit (health centre)	2	5.21	4.95
Screening for breast cancer				
	Bilateral mammography	1	36.05	36.08
	Ultrasonography of the liver	0.28	18.60	17.41
	Fine needle aspiration or core needle biopsy	0.27	41.86	41.17

[a] Based on clinical practice guidelines (10-11) (USA, 2003, 2004). NCCN and MD Anderson guidelines in particular are useful for indicating treatment steps, as they can be detailed to a certain level. Therefore these guideline were selected for identifying generic treatment steps, relevant for this analysis.

[b] Based on WHO-CHOICE unit cost database (www.who.int/cea) and WHO database on medical devices (17). (2005)

[c] Includes resource use of initial evaluation of women without breast cancer who were initially suspected of having breast cancer (12). (Flobbe et al.2001, identify a single prevalence for the number of women presenting without breast cancer in a non-screening population)

[d] Includes a standard dose of 50 Gy on an outpatient basis .

[e] Consists of 20 mg tamoxifen per day for 5 years.

[f] Consists of four, 21-day cycles of doxorubicin (60 mg/m^2) and cyclophosphamide (830 mg/m^2) supplemented with 4 mg dexamethasone, given on an outpatient basis.

Appendix 2
Modelling design and costs of cervical cancer interventions

Modelling heath effects

Most important aspect of the modelling design and intervention effects on cervical cancer are presented in the main text. Table A2.1 provides an overview of the treatment procedure costs.

Costs

Screening & Prevention
The screening interventions that were modelled were Pap smear, HPV-DNA testing, Visual Inspection with acid (VIA) at some or all of the following frequencies (annually, tri-annually and penta-annually between the ages of 20-65 or 30-65, thrice-a-lifetime at ages 35, 40, 45, or once-a-lifetime at age 40).

These interventions include screening and lesion removal in scenarios where no treatment (radiotherapy, surgery or chemotherapy) for cancers is available. In scenarios where programmes screen every 1, 3 or 5 years, no intervention is offered for low grade lesions since their growth or disappearance will be regularly monitored.

In scenarios with less frequent screening schedules (once or thrice-a-lifetime) involving Pap or HPV, screening will result in around 72.25% of women with low grade lesions receiving cryotherapy (based on 85% being targeted for cryotherapy adjusted by a 15% loss to follow-up). Around 12.75% of women with low grade lesions will receive a colposcopy examination (based on 15% being targeted adjusted for loss to follow-up), with 11.8% (after a further 15% follow-up loss) eventually receiving eitherLEEP (loop electrosurgical excision procedure), conanization or a simple hysterectomy. In total 83.1% of women with low grade lesions have their lesions removed. Using VIA techniques, the initial loss to follow-up is avoided in what is in fact a “see and treat” scenario. Therefore 85% of women with low grade lesions receive cryotherapy, resulting in a removal of 95.4% of all low grade lesions.

For high grade lesions, the more frequent screening schedules (every 1, 3 or 5 years) involving Pap or HPV, will result in around 56.7% of women with high grade lesions receiving a colposcopy (including biopsy) examination (based on 66.7% being targeted for colposcopy adjusted by a 15% loss to follow-up). 56.7% will receive cryotherapy during the same visit. Around 28.3% (i.e. one third adjusted for a 15% loss) will receive either LEEP, conanization or a simple hysterectomy. In total, 85.0% of high grade lesions will be removed.

The less frequent screening schedules (once or thrice a lifetime) involving Pap or HPV, will result in around 63.7% of women with high grade lesions receiving cryotherapy (based on 75% being targeted for cryotherapy directly, without a colposcopy, adjusted by a 15% loss to follow-up). Around 21.2% will receive a colposcopy examination (based on 25% being targeted adjusted for 15% loss to follow-up), with 18.1% (after a further 15% follow-up loss) eventually receiving either conanization or a simple hysterectomy. In total, 81.8% of high grade lesions are removed. Using VIA techniques, the initial loss to follow-up is averted. Therefore 75% of women with high grade lesions receive cryotherapy, resulting in a removal of 93.1% of all high grade lesions.

Provision was made for repeat Pap and HPV smears in 7% of screenings, based on UK targets (2). For a tri-annual Pap screening, programme costs (i.e. any costs not incurred at point of contact), were based on an estimate of around four administrative posts (for notification, coordination, follow-up and monitoring) per million inhabitants of each region, in addition to an estimate of costs for media, office space and other items. Programme costs for other screening interventions were proportionally adjusted to reflect the type of activities required (e.g. less frequent interventions require fewer overhead staff). Programme costs for other regions were adjusted to reflect differences in the population size and density.

In addition, the costs for each hypothetical programme included a provision for national-level posts for management, monitoring and evaluation (*personal communication*, Julietta Patnick, NHS Cancer Screening Programmes) and provision for training of staff (e.g. for smear-taking, smear-reading and vaccination).

Quantities (labour, rooms, drugs, disposable and reusable equipment) for the delivery of screening tests and treatment procedures were based mainly on data from the WHO Collaborating Centre for Essential Health Technologies (EHTP) data base (*personal communication*, Peter Heinman).

Prevention
Our model was based on delivering three doses of the vaccination to all females aged 12 in their school setting. All females who do not attend schools were assumed to be vaccinated in health centres.

Treatmen**t**
Stage-specific treatment protocols were based on current standard practice in developed nations (3, 4). Based on the distribution of cancer cases between stages (5) and the probability of receiving a procedure, it was estimated that for local cancers (Stages 1a1 to 2a), 3% receive a conanization (all at stage 1a1), 10% a simple hysterectomy (all at stage 1a1), 78% a radical hysterectomy, 45% radiotherapy and 45% chemotherapy, 15% intercavity radiation brachytherapy. For regional cancers (Stages 2b to 3b), everyone receives radiotherapy, chemotherapy and intercavity brachytherapy. For distant cancers, all persons at stage 4a receive radiotherapy and chemotherapy, while all persons at stage 4b receive palliative chemotherapy based on cisplatin with gemcitabine or plaxitaxel (6,7) and 50% receive palliative radiotherapy.

We took into account the approximately 11.6%, 30% and 13.0% of local, regional and distant cases that were estimated to suffer a relapse (8,9) approximately one year after their initial therapy (10). Most relapsing persons would have additional radiotherapy and chemotherapy, while around 7.5% would have extensive extenuration surgery.

Health state valuation

An average disability weight (DW) of 0.075 based on the WHO Global Burden of Disease study (11) was applied to the time spent across all the stages of cervical cancer, yielding an average health state valuation (HSV) for cervical cancer of 0.925. The DW of the susceptible population was derived from this value and took into account all disease in a population except cervical cancer.

References

1. Ginsberg; GM; Lauer JA. Johns BP, Sepulveda CR. Screening, Prevention and Treatment of Cervical Cancer - A Global and Regional Generalized Cost Effectiveness Analysis. ***Vaccine.*** 2009;27;43; 6060-79. Epub 2009 July 31.
2. Eddy DM. Screening for Colorectal cancer. Annals of Internal Medicine 1990;113:373-84.

3. Waggoner SE. Cervical Cancer. Lancet 2003;361;2217-25.
4. National Cancer Institute Recommendations: US National Institute of Health http://cancer.gov/cancertopics/pdq/treatment/cervical/healthprofessional. Accessed Jan 3rd 2006.
5. Benedet JL, Odicino F, Maisonneuve P et al. Carcinoma of the cervix uteri. Jnl Epidemiology and Biostatistics 2001;6;1;5-44. European data from 1993-1995
6. Rose PG, Blessing JA, Gershenson DM, et al.: Paclitaxel and cisplatin as first-line therapy in recurrent or advanced squamous cell carcinoma of the cervix: a gynecologic oncology group study. J Clin Oncol 17 (9): 2676-80, 1999.
7. Burnett AF, Roman LD, Garcia AA, et al.: A phase II study of gemcitabine and cisplatin in patients with advanced, persistent, or recurrent squamous cell carcinoma of the cervix. Gynecol Oncol 76 (1): 63-6, 2000.
8. Cancer Care Center. Cancer Overviews. Http//www.cancercarecenter.org. Accessed 25/05/05
9. Benedet JL, Odicino F, Maisonneuve P et al. Carcinoma of the cervix uteri. Jnl Epidemiology and Biostatistics 2001;6;1;5-44.
10. van Nagell Jr JR, Rayburn W, Donaldson ES et al. Therapeutic implications of patterns of recurrence in cancer of the uterine cervix. Cancer 1979;44;2354-2361.
11. Murray CJL, Lopez AD. The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. Global burden of disease and injury series: Volume 1. Cambridge, MA: Harvard School of Public Health, 1996.

Table A2.1 Cervical cancer: unit costs ($I at 2005 price levels) of treatment procedures

	Afr-E	**Sear-D**
Brachytherapy	320	305
Post-Hysterectomy Brachytherapy	225	214
Chemotherapy (a)	85	85
Colposcopy	9.54	7.87
Cold-Knife Conanization	36	30
Cryotherapy	14	12
Externuration Surgery (b)	1177	1077
Palliative Chemotherapy(c)	203	202
Radiotherapy	50	45
Radical Hysterectomy (d)	460	428
Simple Hysterectomy (e)	372	358

(a) 4000mg Flouracil, 80mg Cisplatin and 0.22mg Metoclopromide.
(b) includes 12 days of hospitalization
(c) 244mg Plaxitaxel, 120mg Cisplatin and 0.22mg Metoclopromide.
(d) includes 5 days hospitalization
(e) includes 4 days hospitalization

Sources: refs (5, 16) in main article

Appendix 3

Modelling design, costs and estimated effects of colorectal cancer interventions

Modelling heath effects

To date, there have only been four randomized trials on Fecal Occult Blood Tests (FOBT) (1), the longest trial based on 18 years of follow up (2) reported decreases in incidence of colorectal cancer of 20% and 17% for annual and biennial screening respectively. Since these randomized trials reported results of guaiac FOBT as opposed to immunological tests, all the results in this paper relate to guaiac FOBT testing. Results from current randomized sigmoidoscopy trials (a once-per-lifetime study performed in the UK and a penta-annual USA study that included additional annual FOBT testing), are not yet published. To date, there have been no randomized trials of colonoscopy.

Evidence is not available from randomized trials of the efficacy of various screening interventions (except for FOBT). Therefore researchers often rely on modelling techniques in order to estimate the effects of screening for colorectal cancer. As a result of variations in quality, specification and parameter values, model results vary considerably.

Since no single model can be regarded as a "gold-standard", we constructed our own model using a spreadsheet to estimate the effects of various screening interventions aimed at the general population aged 50 to 80 years old. The model allowed for examining the effects of varying the frequency of screening and age at time of screening. This model was based on demographic data from the WHO AmrA region (i.e. Canada, Cuba and the USA) and colorectal cancer incidence rates from the SEER registry in the USA for the period 1995-2000 (3). Age-specific polyp incidence was estimated from prevalence data based on the weighted average polyp prevalence from studies on populations in the USA
(4-12).

Age-specific rates of cancers originating in adenomateous polyps were calculated under the consensus-based assumption that 70% of cancers originated in adenomateous polyps (13,14) and that the average waiting time for development of cancer was ten years (15, 13,14,16,17) (assumed normally distributed with a standard deviation of four years). The incidence of polyps was matched with future incidence of cancers originating from polyps in order to calculate the conversion rates from polyps to cancers, taking into account intervening mortality. Thus a proportion of polyps at each stage were assumed to be potentially carcinogenic and placed in a waiting state from which they were allowed to become malignant at a constant rate. Cancers were assumed to wait for two years in stage A and for one year in each of the three subsequent stages, if left untreated (13,18-19).

Using stage-specific fatality rates, the expected number of cancer cases and cancer fatality were estimated under a baseline scenario of no screening. Data on sensitivity and specificity of screening for each intervention in turn (14) was used to estimate the number of persons undergoing follow-up colonoscopy (assuming 100% compliance after a positive test) and the number undergoing polypectomy during the colonoscopy. For each intervention, based on the sensitivity, specificity and frequency of screening, the model estimated the number of polyps that would progress to cancers.

Despite their being some misgivings (20), our model was based on the mainstream accepted wisdom (21) that screening enables detection and removal of potentially cancerous polyps, thereby reducing the incidence of colorectal cancer even when cancer treatment was not available.

When medical treatment is available, screening enables detection of cancers at an earlier less-severe stage, thus reducing case-fatality rates (CFR). It was assumed that persons screened positive in areas which lack availability of treatment will only benefit via reduction in incidence (via polyp removal) and not via decreases in case-fatality rate due to the lack of treatment. We assumed that there would not be a change to more frequent protocols in persons who had a polyp removed.

These modelled intervention-specific estimates of CFR reductions, together with estimates of incidence reductions (see Appendix 1) form the main inputs into the population based model described in the main text.

The effectiveness of the fruit and vegetable campaign was calculated from the results of the campaign in Victoria, Australia (22), which achieved an increased intake of around 12.4% by weight in fruit and vegetable consumption. Regional specific risk reductions were based on regional consumption patterns (23) the assumption that each 80 mg increase in average regional daily consumption results in a 1% decrease [95%CI, -3%,+2%) in colorectal cancer risk (24).

Validation of model

For a specific validation of the model, the estimated decrease in incidence due to annual FOBT screening was found to be almost equal to benchmark data from 18-year follow up of the randomized controlled trial after adjustment for the period during the trial when screening was temporarily halted, as well as adjustment for compliance (2)

For general validity, across the various interventions, the estimated decreases in incidence and fatality over and above that due to treatment all fell within the 25th and 75th percentile range of the many modelled studies (13,25-42).

Compliancy

The effects of each intervention were modified by their specific adherence or compliancy. The estimated magnitude of compliancy that was calibrated into the model was based on reported compliancy and assumptions as follows:-

Information on compliance with FOBT screening protocols were obtained from a demonstration project for annual screening (43) (i.e. 56.8%); biannual screening was assumed to result in 5% higher compliance. Compliance with screening by colonoscopy every 10 years, as well as annual FOTB combined with sigmoidoscopy every 5 years, was assumed to be the same as that found for a pre-intervention pilot study for sigmoidoscopy (44) (i.e. 45%), the greater invasiveness and more intensive preparations required for colonoscopy were assumed to be balanced by the longer interval required between screenings. Estimates of compliance for one-off screening at age 50 years was assumed to be 10% higher than that for repeated screening starting at age 50 and finishing at age 80. Due to the difficulties of estimating compliancy over a 30 year period, involving between 4 and 30 screening visits, all estimates of compliancy used in the model should be viewed as rough approximations. Intervention effectiveness was adjusted for the compliance assuming a target coverage rate of 100% for all regions.

The above is summarized in Appendix Table A3.1.

Costs

For the annual FOBT, program costs (excluding the actual costs of the FOBT), were based on an estimate of around 27 administrative posts (for notification, sending out test kits, results etc.) per 5 million population in each region in addition to a budget for media, office space and other items. Program costs for the other screening interventions and regions were adjusted to reflect the type of intervention (eg: no test kits need to be sent for sigmoidoscopy or colonoscopy), the intervention's relative frequency and the size of the target population. We assumed that in the absence of a postal system, health workers would deliver the FOBT kits by hand and the kits would be returned to laboratories en bloc from the district health centres. In addition, each program had a provision for staff training and national posts for management, monitoring and evaluation based on the British NHS Cancer Screening Programs.

Quantities (manpower time, rooms, drugs, disposable and reusable equipment) for screening tests and treatment procedures were based on the WHO Collaborating Centre for Essential Health Technologies data base. Provision was made for pre-operative work-up tests such as CT scan and Chest X-rays (45). If further data was available from published literature we adjusted the manpower time to be in accord with the published literature. For example, recent literature estimated 145.5 and 165.5 minutes average time for a colectomy [46] with and without colostomy respectively, including a provision for an assumed 10% of procedures to be carried out under combined spinal-epidural anaesthesia [47]. Proctectomies were assumed to take 60 minutes longer than colectomies.

Colonoscopy costs included not only preparation, obtaining consent, procedure and recovery time but also one full hour for pre-screening counselling. Discounted costs of lifetime care for perforated colons included hospitalization, anaesthesia, colon suture, electrocardiography, X-ray and initial care costs (48).

Unit costs of secondary and tertiary hospital in-patient days and out-patient visits http://www.who.int/evidence/ceawere based on an econometric analysis of a multinational dataset of hospital costs (49). Prices of pharmaceuticals were obtained from international (50) or from British National Health Service prices (51) adjusted to year 2005 price levels. Annual resource use per case on a stage-specific basis (i.e. initial, watchful waiting and terminal) was based on Medicare data from the USA (personal communication, Martin L. Brown, Health Services and Economic Branch, National Cancer Institute, Bethesda MD.). Liver function tests were assumed to be given monthly for one year, CT scans annually for three years, carcino-embrionic antigen tests every 6 months for three years, chest X-rays annually for 3 years and follow-up colonoscopies biannually (52). Unit costs are summarized in Appendix Table A3.2.

Health state valuation

Health state valuations (HSV), were based on the WHO Global burden of Disease study (53) BD data. These were 0.8 for time spent in the diagnosis and treatment stage, 0.8 for watchful waiting whether in a treated or not treated person, 0.25 for metastasis stage and 0.19 for terminal stage). In keeping with the GBD methodology, no additional disability weight was ascribed to a case after a person had survived five years unless they possessed a Permanent colostomy, was ascribed a HSV of 0.79 as a result of perforation of the colon occurring in 0.13% of colonoscopies and an assumed 9% of all colorectal cancer related surgical procedures (54). The DW of the susceptible population was derived from this value and took into account all disease in a population except colorectal cancer.

References

1. Towler BP, Irwig L, Glasziou P, Weller D, Kewenter J. Screening for Colorectal Cancer Using the Faecal Occult Blood Test, Hamoccult (Cochrane Review). In: The Cochrane Library, Issue 4, 2003. Chichester, UK: John Wiley & Sons, Ltd.

2. Mandel JS, Church TR, Bond JH, Ederer F. Geisser MS, Mongin SJ, Snover DC, Schuman LM. The effect of fecal occult-blood screening on the incidence of colorectal cancer. N Engl J Med 2000;343:1603-7.

3. SEER cancer registry data. http://seer.cancer.gov/faststats/html/inc_colorect.html Accessed 4th March 2004.

4. Rex DK, Smith JJ, Ulbright TM, Lehman GA. Screening colonoscopy in asymptomatic average-risk persons with negative fecal occult blood tests. Gastroenterology 1991;100:64-7.

5. Disario JA, Foutch PG, Mai HD, Pardy K, Manne RK. Prevalence and Malignant Potential of Colorectal Polyps in Asymptomatic, Average-Risk Men. American Journal of Gastroenterology 1991;86:941-5.

6. Johnson DA, Gurney MS, Volpe RJ, Jones DM, VanNess MM, Chobanian SJ, Avalos JC, Buck JL, Kooyman G, Cattau EL Jr.A prospective study of the prevalence of colonic neoplasms in asymptomatic patients with an age-related risk. Am J Gastroenterol. 1990; 85:969-74.

7. Arminski TC, McClean DW. Incidence and Distribution of Adenomateous Polyps of the Colon and Rectum based on 1,000 Autopsy Examinations. Dis Colon Rectum 1964; 19:249-61.

8. Blatt LJ. Polyps of the colon and rectum. Dis Colon Rectum. 1961;4:277-82.

9. Rickert RR, Auerbach O, Garfinkle L, Hammond EC, Frasca JM. Adenomatous lesions of the large bowel. An Autopsy Survey. Cancer 1979;43:1847-57.

10. Correa P, Strong JP, Reif A, Johnston WD. The Epidemiology of Colorectal Polyps. Cancer 1977;39:2258-64.

11. Stemmerman GN, Yatani R. Diverticulosis and polyps of the large intestine. Cancer. 1973;31:1260-70.

12. Chapman I. adamateous polypi of large intestine: incidence and distribution. Ann Surg 1963;157;223-6.

13. Wagner J, Tunis S, Brown M, Ching A, Almeida R. Cost-effectiveness of colorectal cancer screening in average risk adults. In Young G, Rozen P, Levin B eds. Prevention and early detection of colorectal cancer. London. Saunders;1996. p 321-56.

14. Wagner JL, Beheny CJ, Tunis SR, Ching A. US Congress, Office of Technology Assessment, Cost-effectiveness of Colorectal Cancer Screening in Average-Risk Adults, OTA-BP-H-146 (Washington, DC: U.S. Government Printing Office, April 1995].

15. Fletcher RH. The end of barium enemas? N Engl J Med 2000;342:1823-4.

16. Bolin TD, Korman MG, Stanton R, Talley N, Newstead GL, Donnelly N et al. Positive cost effectiveness of early diagnosis of colorectal cancer. Colorectal disease 1999;1:113-22.

17. Selby JV, Friedman GD, Queensberry CP, Weiss NS. A case-control study of screening sigmoidoscopy and mortality from colorectal cancer. N Engl J Med 1992;326:653-7.

18. Eddy DM, Nugent FW, Eddy JF, Coller J, Gilbertsen V, Gottlieb LS, Rice R, Sherlock P, Winawer S. Screening for colorectal cancer in a high-risk population. Results of a mathematical model. Gastroenterology 1987;92;682-92.

19. Ladabaum U, Chopra CL, Huang G, Scheiman JM, Chernew ME, Fendrick AM. Aspirin as an adjunct to screening for prevention of sporadic colorectal cancer. A cost-effectiveness analysis. Ann Intern Med. 2001;135:769-81.

20. Rubin PH, Waye JD, Colonoscopic Polypectomy: A critical review of the literature. Current Gastroenterology Reports 2006;8;5;430-433.

21. Winawer SJ, Zauber AG, Ho MN, O'Brien MJ, Gottleib LS, Sternberg SS, Waye JD,Schapiro M, Bond JH, Panish JF, Ackroyd F, Shike M, Kurtz RC, Hornsby-Lewis L, Gerdes H, Stewart ET and the National Polyp Study Workgroup. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl JMed 1993; 329;27;1977–1981.

22. Dixon H, Borland R, Segan C, Stafford H, Sindall C. Public Reaction to Victoria's 2 Fruit 'n' 5 Veg Every Day" Campaign and Reported consumption of Fruit and Vegetables. Preventive medicine 1998; 27:572-82.
23. Economics Research Service: United Nations Department of Agriculture. International Food Consumption Patterns. http://www.ers.usda.gov/Data/InternationalFoodDemand/Index.asp?view=PEF#IFD Accessed November 9th 2009.
24. Lock K, Pomerleau J, Causer L, Altmann DR, McKee M. The global burden of disease attributable to low consumption of fruit and vegetables: implications for the global starategy on diet. Bulletin of the World Health Organization 2005;83;100-108.
25. Vijan S, Hwang EW, Hofer TP. Which Colon Cancer Screening test? A comparison of Costs, Effectiveness, and Compliance. The American Journal of Medicine 2001;111:593-601.
26. Eddy DM. Screening for Colorectal cancer. Annals of Internal Medicine 1990;113:373-84.
27. Sonnenberg A, Delco F, Inadomi JM. Cost-effectiveness of colonoscopy in screening for colorectal cancer. Ann Intern Med 2000; 133: 573-84.
28. O'Leary BA, Olynyk JK, Neville AM, Platell CF. Cost-effectiveness of colorectal cancer screening: Comparison of community-based flexible sigmoidoscopy with fecal occult blood testing and colonoscopy. Journal of Gastroenterology and Hepatology 2004;19: 36-47.
29. Frazier AL, Colditz GA, Fuchs CS, Kuntz KM. Cost-effectiveness of screening for colorectal cancer in the general population. JAMA;2000 284:1954-61.
30. Berchi C, Bouvier V, Réaud J-M, Launoy G. Cost-effectiveness analysis of two strategies for mass screening of colorectal cancer in France. Health Economics 2004; 13;227-38.
31. Khandker RZ, Dulski JD, Kilpatrick JB, Ellis RP, Mitchell JB, Baine WB. A decision model and cost-effectiveness analysis of colorectal cancer screening and surveillance guildelines for average-risk adults. Int J Tech Assess in Health Care 2000;16;3;799-810.
32. Loeve F, Brown ML, Boer R, van Ballegooijen M, van Oortmarssen GJ, Habbema JFD. Endoscopic colorectal-cancer screening, a cost-saving analysis. Journal of the National Cancer Institute 2000;92:557-63.
33. Loeve F, Boer R, van Oortmarssen GJ, van Ballegooijen M, Habbema JDF. The MISCAN-COLON Simulation Model for the Evaluation of Colorectal CancerScreening. Computers and Biomedical Research 1999;32;13-33.
34. Geul KW, Bosman FT, van Blankenstein M, Grobbee DE, Wilson JHP. Prevention of Colorectal Cancer. Costs and Effectiveness of Sigmoidoscopy. Scand J Gastroenterol 1997;32 Suppl 223;79-87.
35. Lieberman DA, Cost-effectiveness model for colon cancer screening. Gastroenterology 1995;109;1781-90.
36. Lejeune C, Arveux P, Dancourt V, Fagnani F, Bonithon-Kopp C, Faivre J. A simulation model for evaluating the medical and economic outcomes of screening strategies for colorectal cancer. European Journal of Cancer Prevention 2003:12;77-84.
37. Ness RM, Holmes AM, Klein R, Dittus R. Cost-Utility of One-Time Colonoscopic Screening for Colorectal Cancer at Various Ages. American Journal of Gastroenterology 2000,95:1800-11.
38. Salkeld G, Young G, Irwig L, Haas M, Glasziou P. Cost-effectiveness analysis of screening by faecal occult blood testing for colorectal cancer in Australia. Aust N Z J Public Health. 1996;20:138-43.
39. Wagner J, Herdman RC, Wadhwa S. Cost effectiveness of Colorectal Cancer Screening in the Elderly. Annals of Internal Medicine 1991;115:807-17.
40. Tsuji I, Fukao A, Shoji T, Kuwajima I, Sugawara N, Hisamichi S. Cost-effectiveness Analysis of Screening for Colorectal Cancer in Japan. Tohoku J. Exp Med 1991;164;269-78.
41. Leshno M. Halperin Z, Arber N. Cost-effectiveness of Colorectal cancer Screening in the Average Risk Population. Health Care Management Science 2003,6:165-74.
42. Neilsen AR, Whynes D. Cost-effectiveness of screening for colorectal cancer: A simulation model. IMA Journal of Mathematics Applied in Medicine & Biology 1995;12:355-67.

43. Results of the first round of a demonstration pilot of screening for colorectal cancer in the United Kingdom. UK Colorectal Cancer Screening Pilot Group. BMJ. 2004 Jul 17;329[7458]:133. Epub 2004 Jul 5.
44. Atkin WS, Hart A, Edwards R, McIntyre P, Aubrey R, Wardle J, Sutton S, Cuzick J, Northover JM. Yield of neoplasia, and adverse effects of flexible sigmoidoscopy screening. Gut 1998; 42: 560-5.
45. Memorial Sloan-Kettering Camcer Center. Surgery. Common Preoperative work-up.
http://www.mskcc.org(patient_education/html/41507.cfm Accessed 15th July 2004.
46. Laparoscopic Resection of Colonic Carcinoma. EAES consensus conference
Lisbon, June 2, 2002 Consensus Proceedings.
47. Morton G, Bowler I. Combined spinal-epidural as an alternative method of anaesthesia for a sigmoid-colectomy. Anaesthesia 2001; 56: 799-820.
48. Sonnenberg A, Delco F, Inadomi JM. Cost-effectiveness of colonoscopy in screening for colorectal cancer. Ann Intern Med 2000; 133: 573-84.
49. Adam T, Evans DB, Murray CJ. Econometric estimation of country-specific hospital costs. Cost Eff Resour Alloc. 2003; Feb 26;1(1):3.
50. International Drug Price Indicator Guide. MSH, Arlington Virginia 2006.
51. British National Formulary No 47, March 2004. Published by the British Medical Association, London and the Royal Pharmaceutical Society of Great Britain, London.
52. Bolin TD, Korman MG, Stanton R, Talley N, Newstead GL, Donnelly N et al. Positive cost effectiveness of early diagnosis of colorectal cancer. Colorectal disease 1999;1:113-22.
53. Murray CJL, Lopez AD. The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. Global burden of disease and injury series: Volume 1. Cambridge, MA: Harvard School of Public Health, 1996.
54. Ginsberg GM, Lim S, Lauer JA, Johns B, Sepulveda C. Prevention, screening and treatment of colorectal cancer: a global and regional generalized cost-effectiveness analysis. Cost Effectiveness and Resource Allocation, 2010; 8: 2.

Table A3.1 Colorectal cancer: estimating intervention effectiveness

Intervention	Description	Decrease in Incidence	Decrease in Case-Fatality Rate	Compliance
FOB1	Annual Fecal Occult Blood Tests [a]	35.0%	0%	56.8%
FOB2	Biannual Fecal Occult Blood Tests [a]	21.9%	0%	61.8%
SIG5	Sigmoidoscopy every 5 years(1) [a]	38.9%	0%	45.0%
COL10	Colonoscopy every 10 years [a]	52.6%	0%	45.0%
FOB1SIG5	Annual FOBT, SIG every 5 years [a]	51.5%	0%	45.0%
FOB50	FOBT at age 50 [a]	2.6%	0%	71.8%
SIG50	Sigmoidoscopy at age 50 [a]	11.8%	0%	55.0%
COL50	Colonoscopy at age 50 [a]	25.9%	0%	55.0%
FOBSIG50	FOBT & SIG at age 50 [a]	13.2%	0%	55.0%
RX	Medical Treatment of cancers [b]	0%	91.9%	100%
FOB1RX	Combination of FOB1 & RX	35.0%	17.9%[c]	56.8%
FOB2RX	Combination of FOB2 & RX	21.9%	12.9% [c]	61.8%
SIG5RX	Combination of SIG5 & RX	38.9%	3.4% [c]	45.0%
COL10RX	Combination of COL10 & RX	52.6%	3.9% [c]	45.0%
FOB1SIG5RX	Combination of FOB1SIG5 & RX	51.5%	18.3% [c]	45.0%
FOB50RX	Combination of FOB50 & RX	2.6%	0.5% [c]	71.8%
SIG50RX	Combination of SIG50& RX	11.8%	0.3% [c]	55.0%
COL50RX	Combination of COL50& RX	25.9%	0.4% [c]	55.0%
FOBSIG50RX	Combination of FOBSIG50 & RX	13.2%	0.5% [c]	55.0%
FVCAMP	Fruit & Vegetables campaign	d)	0%	---
FVCAMPRX	Combination of FVCAMP & RX	d)	0% [c]	¨---
DRE1	Digital Rectal Exam annually [a]	17.6%	0%	50%
DRE1RX	Combination of DRE1 & RX	17.6%	1.8% [c]	50%

Notes:

Efficacy varied slightly between regions due to demographic differences.

Efficacy considered on an age-sex specific basis.

a) Denotes colonoscopy performed on all positive tests, with subsequent removal of lesions or polyps if discovered.

b) Including surgical, radiotherapy and chemotherapy.

c) In excess of decrease in CFR caused by treatment.

d) 0.49% in Afr-E and 0.40 % in Sear-D

Source: ref (6)in main article

Table A3.2 Colorectal cancer: unit costs ($I at 2005 price levels) of treatment procedures

Treatment procedure	**Afr-E**	**Sear-D**
Digital Rectal Examination	1.47	1.08
FOBT	1.97	1.80
Sigmoidoscopy, flexible diagnostic	33	28
Colonoscopy, flexible diagnostic	96	85
Colonoscopy with lesion removal	103	93
Radiotherapy session	50	41
Chemotherapy, session	124	115
Partial colectomy with anastomosis	137	93
Partial colectomy with colostomy	155	104
Total colectomy with ileostomy	153	103
Partial protectomy with reservoir	206	138
Partial protectomy with anastomosis	189	127
Complete protectomy with colostomy	205	137

Sources: ref (6) in main article