

Supplementary Table1. High Risk Criteria

AJ High Risk Criteria for FH positive group (used in clinical genetics units)	
Volunteer should fulfil any one of the following criteria. (Volunteer / proband should either have been affected by cancer or be a first degree relative (FDR) of an affected family member).	
1)	FDR with breast cancer (<50 years)
2)	FDR with ovarian cancer* (any age)
3)	Personal history of breast cancer (<50 years)
4)	Personal history of ovarian cancer* (any age)
5)	FDR with Male Breast Cancer (MBC) (any age)
6)	Personal history (men) of MBC (any age)
*Equivalence of history of ovarian/ primary peritoneal cancer (PPC)/ fallopian tube cancer (FTC) for HR criteria	
Extended High-risk criteria for referral of FM negative volunteers to the regional genetic units	
Volunteer should fulfil any one of the following criteria. (Volunteer /proband should either have been affected by cancer or be a FDR of an affected family member. Criteria should be fulfilled on the same side of the family)	
Families with ovarian* cancer (HOC) or breast and ovarian*cancer (HBOC)	
1)	≥2 individuals with ovarian cancer* who are FDR
2)	One ovarian cancer* and 1 breast cancer <50 years who are FDR
3)	One ovarian cancer* and 2 breast cancers <60 years who are FDR
4)	Criteria 1, 2, and 3 can be modified where paternal transmission is occurring i.e. families where affected relatives are related by second degree through an unaffected intervening male relative and there is an affected sister are eligible.
5)	Breast cancer in volunteer/ proband (≤50 years) and mother (or sister) with both breast and primary ovarian cancer* (in the same person)
Families with Breast cancer only (HBC)	
6)	Breast cancer in volunteer/ proband (≤50 years) and any one of the following- a) breast cancer in mother (age of onset being ≤30 years in one and ≤50 years in the other) or b) b/l breast cancer in mother or sister (≤50 years onset of first)
7)	≥4 breast cancers
8)	3 breast cancers related by FDR and a) one ≤30 years or b) two ≤40 years (and all ≤60 years) or c) one MBC (≤60 years) and other two ≤50years
Male Breast Cancer (MBC)	
9)	Two MBC (≤60 years) in the family and proband is a FDR of one of them
Mutation Positive families	
10)	Known non-FM in the family
11)	Known h/o mutation in the family, though unable to trace/ identify exact pathogenic mutation and testing negative for 3 FM.
*Equivalence of history of ovarian/ PPC/ FTC for HR criteria	
**Cases of b/l breast cancer- each breast cancer may have same count as one relative	

AJ- Ashkenazi Jewish; b/l – bilateral; FH- family history; FM- founder mutation; FTC- fallopian tube cancer; HR- high risk; MBC- male breast cancer; PPC- primary peritoneal cancer

Supplementary Table 2. Detailed Explanation of Costs

Explanation

Genetic Counselling and Testing

The cost of genetic testing and counselling was based on the median pre-test counselling time (45 minutes, IQR=5) in the GCaPPS study and the national the unit cost assumed for genetic-counselling=£44/hour of client contact from PSSRU Unit costs of Health and Social Care 2010.[1, 2] The cost takes into account a 71% uptake rate of testing from found in the GCaPPS study. 1034 (71%) of 1450 people who expressed an interest in testing by making a genetic counselling appointment and 89% of 1168 who attended counselling underwent BRCA testing. As there was no difference in uptake rates between people with and without strong FH of cancer, a similar uptake rate has been assumed for costing both FH and population screening arms.

Risk reducing salpingo-oophorectomy (RRSO)

The cost of RRSO was based on national reference costs for an upper genital tract laparoscopic/endoscopic intermediate procedure.[3] Costs of HRT[4] assumes HRT is given from average age of RRSO to the average age of menopause (51 years).

Ovarian Cancer Costs:

Costs for ovarian cancer diagnosis and treatment were derived from national reference costs and a recent ovarian cancer guideline developed by NICE.[3, 5] We assumed that the cost of diagnosis to include a pelvic examination, ultrasound scan, CA125 test, CT scan, percutaneous biopsy and peritoneal cytology.

The cost of treatment included the reference cost for a lower and upper genital tract very complex major procedure and administration of chemotherapy based on 6 cycles of carboplatin and paclitaxel treatment. It was assumed that in years -1 and -2 treated survivors would have a further three consultant visits, a CT scan and 4 CA125 tests each year. In years 3 to 5 post-surgery it was assumed that survivors would have 2 consultant visits and 2 CA125 tests. We were conservative in our cost-estimates and did not include costs for additional investigations, treatment of recurrence or management of complications in the analysis.

Costs for terminal care for ovarian cancer were derived from end-of-life costs for cancer patients based on a report from the National Audit Office, UK.[6]

In line with NICE recommendations future healthcare costs not associated with ovarian cancer were not considered.[7]

Breast Screening

Cost of breast cancer screening assumes for the non-carriers (or untested population) routine mammography of 8 mammograms between 50 to 70 years in line with the UK NHS breast cancer screening programme.[8] Cost of breast screening for BRCA carriers is based on annual mammogram from 40-69 years and annual MRI breast from 30-49 years in line with NICE guidelines for familial breast cancer.[9]

Risk reducing mastectomy (RRM)

Cost of RRM is obtained from NHS reference costs[3] and is weighted for a 21% complication rate.[10, 11].

Chemoprevention (as part of sensitivity analysis)

Prophylaxis (5 years) with Tamoxifen (premenopausal) or Raloxifene (post menopausal) for BRCA carriers who have not had breast cancer, as per NICE guidelines.[9] A meta-analysis has shown a breast cancer risk reduction by 38%.[12] Costs taken from the BNF.[4]

Breast Cancer Costs

Assumptions and costs for Breast Cancer diagnosis and treatment are derived predominantly from UK based data including the 'National costing report: Implementing NICE guidance (Feb 2009)' from NICE, which provides estimates of the national cost impact arising from implementation of NICE guidelines for diagnosis and treatment of early

and locally advanced breast cancer and advanced breast cancer in England, UK[13]; from UK Department of Health NHS reference costs 2010-2011[3]; and from other relevant NICE guidelines on breast cancer care in general and high risk populations[9, 14, 15].

It is assumed that in the general population: 10% breast cancer is non-invasive Ductal Carcinoma In situ (DCIS); 90% breast cancer is invasive; 95% of invasive breast cancer is early and locally advanced (stages 1, 2 and 3: 41% Stage-1, 45% stage-2, 9% stage-3[13, 16-18]); 5% of invasive breast cancer is advanced breast cancer (stage 4)[13, 16, 17]; 35% of early & locally advanced breast cancer will progress to advanced breast cancer (NICE costing report, 2009).[13] In BRCA carriers, 20% of cancers are DCIS and 80% invasive (61% stage1).[11, 19]

The cost of diagnosis includes the triple test of clinical examination, mammogram, ultrasound (US) & biopsy.

Mean prevalence of Axillary lymph node metastasis in early invasive breast cancer is 31.4% (obtained from systematic reviews conducted within the NICE breast cancer guideline[15] and breast cancer clinical outcome measures (BCCOM) project[20]). A 30% node positive rate is assumed for BRCA breast cancer (based on screening studies in familial breast cancer, breast cancer case series and Early Breast Cancer Trialists' Collaborative Group data).[19, 21-24]

Cost of Sentinel lymph node biopsy (SLNB): SLNB is used to stage the axilla for early invasive breast cancer and no evidence of lymph node (LN) involvement on Ultrasound (US)/ negative US-guided biopsy (73% invasive cancers) is obtained from NICE national costing report.[13]

Cost of axillary lymph node dissection (ALND) for lymph node positive cancers (31% early and locally advanced invasive cancers).[13, 15] Cost of ALND is assumed to be 25% of cost of breast surgery in line with the NICE guideline development group recommendation.[13]

Breast Surgery Costs: This includes, costs of breast conserving surgery (assumed for all non-invasive cancers, and 75% of early/locally advanced (stage 1-3) invasive cancers); and costs of mastectomy with reconstruction (for 25% early/locally advanced cancers). Costs are obtained from the national NHS reference costs.[3]

Radiotherapy and Chemotherapy: Invasive breast cancers who are not low risk[20, 25, 26] receive adjuvant treatment in line with NICE guidelines. Costs include, radiotherapy costs for 60% of early invasive/locally advanced, radiotherapy and chemotherapy costs for 40% early invasive/locally advanced and chemotherapy costs for all advanced cancers.

Radiotherapy costs include planning and 40Gy in 15 fractions over 3 weeks (NICE guidelines[15]) or palliative treatment, taken from national NHS reference costs.[3]

Chemotherapy costs based on polychemotherapy,[21] include cost of administration, costs of 1st and 2nd line therapy and toxicity from NICE guidelines.[13, 14]

All costs are adjusted for BRCA breast cancers for difference in stage at presentation and 20% being non-invasive.

70% of general population invasive breast cancers are ER positive; 15% of early invasive breast cancers are HER2 positive and 25% of patients with advanced breast cancer are HER2 positive[14, 15]. 27% of BRCA1 and 67% of BRCA2 breast cancers are ER positive, while 5% of BRCA1 and 14% of BRCA2 breast cancers are HER2 positive.[22-24, 27-29]

Cost of ER and HER2 testing is included for all breast cancers and obtained from a local NHS trust.

Endocrine therapy costs: In line with NICE guidelines[13, 15], ER positive invasive breast cancers receive Tamoxifen 20mg/day (premenopausal)/ Anastrozole 1mg/day (postmenopausal) for 5 years: costed from the BNF.[4] Rates are adjusted for BRCA carriers, ER positivity and menopause status.

Biphosphonate costs: 74% of patients with advanced breast cancer will develop bone metastases and 65% of patients with bone metastases (48% advanced breast cancers) would be offered bisphosphonates.[13, 30, 31] In line with NICE guidelines, costs (from BNF[4]) are based on the assumption that 50% of these patients receive oral clodronate and oral ibandronic acid, and 50% receive intravenous zoledronic acid or pamidronate.[13]

Cost of Trastuzumab: For HER2 positive patients, given at 3-week intervals for 1 year or

until disease recurrence (whichever is the shorter period) in line with NICE guidelines and costs obtained from NICE costing report for early and locally advanced/ advanced breast cancer.[13]

Of note 35% of early/locally advanced breast cancer progress to advanced breast cancer (NICE guidelines).[13] Recurrence rates for early/locally advanced breast cancer (from the USA National Surgical Adjuvant Breast and Bowel Project (NSABP)): 15.9% for node positive[32] and 11% for node negative[33] breast cancer giving a composite recurrence rate of 12.6% weighted for 31% node positive and 69% node negative disease. Recurrence rate for advanced or metastatic breast cancer is 66%, based on a reported 34% relapse free survival at 5yrs.[34]

Follow up Costs: All were followed up with annual mammograms and six monthly consultations. All stage 4 cancers get a MRI scan. These costs also included a progression rate of 35% from early and locally advanced to advanced disease,[13] and 66% relapse rate for advanced disease.[34]

Costs for terminal care for breast cancer were derived from end-of-life costs for cancer patients based on a report from the National Audit Office, UK.[6] In line with NICE recommendations future healthcare costs not associated with breast cancer were not considered.[7]

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