Table 1-S: Health states in the Markov model, subsequent states and resource use (Supplement)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Nr | Abbreviation | Health state | Description | Subsequent states | Resource use |
| *1**2**3**4* | Healthy | Healthy\_BRCA1Healthy\_BRCA2Healthy\_ other mutationHealthy\_no mutation | Alive and free of disease (BC/OC). Subsequent states prophylactic surgery only possible for women tested positive for BRCA1/2 | HealthyBCOCDeath*State of post prophylactic surgery (BRCA1/2)a* | Genetic testing Screening (usual care)Intensified screeningProphylactic surgery |
| *5**6* | pProphMTXb  | ProphMTX\_BRCA1 (2 substates)ProphMTX\_BRCA2 (2 substates) | State after prophylactic mastectomy (bilateral).*(tested BRCA1/2 only)*Substates: A testing and MTX in last cycle; B testing and MTX more than one cycles ago) | pProphMTXOCDeathPost prophylactic OMTX*c* | Prophylactic surgery (OVX) |
| *7**8* | pProphOTXd | ProphOTX\_BRCA1 (2 substates)ProphOTX \_BRCA2 (2 substates) | State after prophylactic ovarectomy *(tested BRCA1/2 positive only)*Substates: A testing and MTX in last cycle; B testing and MTX more than one cycles ago) | pProphOTXBCDeathPost prophylactic OMTX*c*  | Prophylactic surgery (MTX)Intensified screening  |
| *9**10* | pProphOMTXe | ProphOMTX\_BRCA1ProphOMTX\_BRCA2 | State after prophylactic ovarectomy and mastectomy (bilateral) *(tested BRCA1/2 only)* | pProphOMTXDeath |  |
| *11**12**13**14* | BCf  | BC\_BRCA1 (5 substates)*g*BC\_BRCA2 (5 substates)*g*BC\_other mutation (5 substates)*g*BC\_no mutation (5 substates)*g* | State with diagnosed breast cancer, transition probabilities due to tumor stage (in situ, T1, T2, T3, T4) | pBC no MTX pBC\_si\_MTX DeathpBC \_bi\_MTX*h* | Treatment costs (depending on severity of disease according to tumor state)End-of-life care |
| *15**16* | *BC\_OVX* | BC\_OVX\_BRCA1 (5 substates)gBC\_OVX\_BRCA2 (5 substates)g | State with diagnosed breast cancer after OVX (tested BRCA1/2 only), transition probabilities due to tumor stage (in situ, T1, T2, T3, T4) | pBC no MTX\_OVX pBC bilateral MTX\_OVXpBC single MTX\_OVXDeath | Treatment costs (depending on severity of disease according to tumor state)End-of-life care  |
| *17**18**19**20* | OCi | OC\_BRCA1 (4 substates)*g*OC\_BRCA2 (4 substates)*g*OC\_other mutation (4 substates)*g*OC\_no mutation (4 substates)*g* | State with diagnosed ovarian cancer, transition probabilities due to FIGO stage (1, 2, 3, 4)  | pOCDeath | Treatment costs (depending on severity of disease according to FIGO stage)End-of-life care  |
| *21**22**23**24* | pBC no MTX | pBC no MTX\_BRCA1 (5 substates)*g*pBC no MTX\_BRCA2 (5 substates)*g*pBC no MTX\_other mutations (5 substates)*g*pBC no MTX\_no mutations (5 substates)*g* | State after breast cancer (no MTX) Indication specific mortality due to tumor stage | pBC no MTXContralateralRecurrencepOCADeath | Hormone therapy Tumor after-careTreatment of distant metastasesEnd-of-life care |
| *25**26* | pBC\_no MTX\_OVX  | pBC no MTX\_BRCA1 (5 substates)*g*pBC no MTX\_BRCA2 (5 substates)*g* | State post OVX after breast cancer (tested BRCA1/2 positive only)Indication specific mortality due to tumor stage | pBC no MTXContralateralRecurrenceDeath | Hormone therapy Tumor after-careTreatment of distant metastasesEnd-of-life care |
| *27**28* | pBC\_bl\_MTXj | pBC\_bl\_MTX\_BRCA1 (5 substates)*g*pBC\_bl\_MTX\_BRCA2 (5 substates)*g* | State after breast cancer and bilateral MTX (tested BRCA1/2 only); Indication specific mortality due to tumor stage | DeathOC | Hormone therapy Tumor after-careTreatment of distant metastasesEnd-of-life care |
| *29**30* | pBC\_bl\_MTX\_OVX j | pBC\_bl\_MTX\_OVX\_BRCA1 (5 substates) *g*pBC\_bl\_MTX\_OVX\_BRCA2 (5 substates)*g* | State after breast cancer and bilateral MTX in patients with prophylactic OVX; indication specific mortality due to tumor stage | Death | Hormone therapy Tumor after-careTreatment of distant metastasesEnd-of-life care |
| *31**32**33**34* | pBC\_si\_MTX | pBC\_si\_MTX\_BRCA1 (5 substates)*g*pBC\_si\_MTX\_BRCA2 (5 substates)*g*pBC\_si\_MTX\_ other mutations (5 substates)*g*pBC\_si\_MTX\_ no mutations (5 substates)*g* | State after breast cancer and therapeutic (single) MTX**;** indication specific mortality due to tumor stage  | pBC\_si\_MTX ContralateralpOCDeath | Hormone therapy Tumor after-careTreatment of distant metastasesEnd-of-life care  |
| *35**36* | pBC\_si\_MTX\_OVX | pBC\_si\_MTX\_OVX\_BRCA1 (5 substates)*g*pBC\_si\_MTX\_OVX\_BRCA2 (5 substates)*g* | State after breast cancer and therapeutic (single) MTX in patients with prophylactic OVX tested BRCA1/2 only | pBC\_si\_MTX\_OVX ContralateralDeath | Hormone therapy Tumor after-careTreatment of distant metastasesEnd-of-life care  |
| *37**38**39**40* | pOC | pOC\_BRCA1pOC\_BRCA2pOC\_ other mutationspOC\_ no mutations  | State after ovarian cancer. Indication specific mortality due to tumor stage | pOC Death | Tumor after-careEnd-of-life care  |
| *41**42**43**44* | Rec\_BC | Rec\_BC\_BCRA1Rec\_BC\_BRCA2Rec\_BC\_other mutationsRec\_BC\_no\_mutations | State with recurrence of breast cancer  | Rec\_BCDeath | BC treatmentTreatment of distant metastasesEnd-of-life care |
| *45**46**47**48* | Contra\_BC | Contra\_BC\_BRCA1Contra\_BC\_BRCA2Contra\_BC\_other mutationsContra\_BC\_ no mutations | State with contralateral breast cancer  | Contra\_BCDeath | BC Treatment Treatment of distant metastasesEnd-of-life care |
| *49* | Death | Death  | General and indication specific mortality  | Absorbing state |  |

a: Post prophylactic surgery (MTX; OVX; OVX/MTX) in healthy women with BRCA1/2 mutation only in the year of access to the model and the first year after entry.

b: Assumption: after MTX breast cancer not possible.

c: Only possible for women who were tested and received prophylactic MTX or OVXin the cycle before.

d: Assumption: after prophylactic OTX ovarian cancer not possible.

e: Assumption: after OMTX breast/ovarian cancer not possible.

f: Assumption: Ovarian cancer at the same time not possible.

g: Substates are defined according to the stage of the tumor at diagnosis.

h: Subsequent states bilateral MTX only possible for women for BRCA1/2. Assumption: Therapeutic and prophylactic surgery within the same cycle.

i: Assumption: Breast cancer at the same time not possible.

j: Therapeutic and prophylactic surgery within the same cycle. Assumption: No recurrence and no contralateral BC.

Table 2-S: Epidemiological and clinical input parameter (Supplement)

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameter**  | **Description** | **Distribution** | **Reference** |
| **Age**  | **Mutations** | **Tumor stage** | **Years** |
| **Distribution**  |
| Genetic testing (model) | Percentage of women undergoing genetic testing after genetic counselling | Age-specific | --  | -- | Year of entry/ first subsequent year | GC-HBOC |
| Potential Index patients BRCA1/2 (Calculation of cohort) | Women with breast cancer and confirmed mutations (all) | Age-specific | Mutation/No Mutation | -- | Per year | ([1](#_ENREF_1)) ([2](#_ENREF_2)),Own calculation |
| Potential Index patients BRCA1/2 Index patients (Calculation of cohort) | Women with breast cancer and confirmed mutations  | Age-specific | BRCA1/BRCA2/Other | -- | Per year | ([1](#_ENREF_1)) GC-HBOC,Own calculation |
| Healthy women (25-69) with index patient | Women without breast cancer and confirmed mutations  | Age-specific | BRCA1/BRCA2/Other | -- | Per year | GC-HBOC,Own calculation |
| **Participation rate** |
| **Intensified screening program**  | All identified mutation carriers (predictive genetic testing, women with mutations)  | Age-specific | BRCA1/BRCA2/Other | -- | Year of entry and Subsequent years | GC-HBOC  |
| **Genetic testing** (calculation of cohort) | Per index patient;by the mutation of the index patient | Age-specific | -- | -- | Year of entry | GC-HBOC |
| **Prophylactic surgery** | Mastectomy | Age-specific | BRCA1/ BRCA2 | -- | Year of entry and Subsequent year  | GC-HBOC |
|  | Ovariectomy | Age-specific | BRCA1/ BRCA2 | -- | Year of entry Subsequent year | GC-HBOC |
|  | Mastectomy and ovariectomy | Age-specific | BRCA1/ BRCA2 | -- | Year of entry and Subsequent year | GC-HBOC |
|  | No surgery | Age-specific | BRCA1/ BRCA2 | -- | Year of entry | GC-HBOC |
| **Screening (usual care)** |  |  |  |  |  |  |
| Usual care BE | All Women  |  |  |  | Per year | ([3](#_ENREF_3)) |
| Usual care MX | All Women |  |  |  | Per year | ([4](#_ENREF_4)) |
| **Treatment breast cancer** | Mastectomy, single and/ or bilateral+/- other treatment | -- | BRCA1/BRCA2/Othernone | In situ, T1, T2  | Per year | GC-HBOC  |
|  | Therapeutic MTX single | --  |  | In situ, T1, T2 | Per year | GC-HBOC |
|  | Prophylactic MTX of the other side  | --  | BRCA1/BRCA2/Othernone | In situ, T1, T2, T3, T4 | Per year | GC-HBOC |
|  | Breast-saving procedures | --  | BRCA1/BRCA2/Othernone | In situ, T1, T2, T3, T4 | Per year | ([5](#_ENREF_5)) |
|  | Treatment  |  | --  | In situ, T1, T2, T3, T4 | Per year | ([5](#_ENREF_5)) |
| **Treatment ovarian cancer** | Ovariectomy + chemo | --  | --  | FIGO I, II, III, IV | Per year | ([6](#_ENREF_6)) |
| **Screening Sensitivity** |
| **Breast examination** | Sensitivity for diagnosing breast cancer | --  | --  | -- |  | ([7](#_ENREF_7)) |
| **Mammography screening** | Sensitivity for diagnosing breast cancer | Age-specific a | --  |  |  | ([8](#_ENREF_8)) |
| **Multimodal screening**  | Sensitivity for diagnosing breast cancer for women with BRCA1/2 mutations | -- | BRCA1/ BRCA2 |  |  | GC-HBOCExpert opinion |
|  | Sensitivity for diagnosing breast cancer for women with other mutations | -- | other |  |  | ([9](#_ENREF_9)) |
| **Incidence** |
| **Risk group specific incidences** | Breast cancer | Age-specific | BRCA1/ BRCA2 | -- | Per year | ([10](#_ENREF_10)) |
|  |  | Age-specific | Other | -- | Per year | Own calculations, ([11](#_ENREF_11)) |
|  |  | Age-specific | None | -- | Per year | ([12](#_ENREF_12)) |
|  | Ovarian cancer | Age-specific | BRCA1/BRCA2 | -- | Per year | ([10](#_ENREF_10)) |
|  |  | Age-specific | Other | -- | Per year | Own calculations, ([11](#_ENREF_11)) |
|  |  | Age-specific | None | -- | Per year | ([12](#_ENREF_12)) |
| **Tumor stage of ovarian cancer** |  | -- | -- | FIGO I, II, III, IV |  | ([13](#_ENREF_13)) |
| **Tumor stage of breast cancer** | Self-examination | -- |  | In situT1T2T3T4 | Per year | ([14](#_ENREF_14)) |
|  | Clinical breast cancer examination | -- |  | Per year | ([14](#_ENREF_14)) |
|  | MX Screening | -- |  | Per year | ([15](#_ENREF_15)) |
|  | Intensified screening program prevalence screening | -- | BRCA1 | Per year | GC-HBOC |
|  |  |  | BRCA2 |  | GC-HBOC |
|  |  |  | Other |  | GC-HBOC |
|  | Intensified screening program incidence screening | -- | BRCA1 | Per year | GC-HBOC |
|  |  |  | BRCA2 | Per year | GC-HBOC |
|  |  |  | other |  | Per year | GC-HBOC |
| **Probabilities** |
| **Mortality** | Background mortality |  |  | -- |  | ([16](#_ENREF_16)), own calculation  |
|  | Indication specific for breast cancer, according to tumor size |  |  | In situ, T1, T2, T3, T4? | Per year | ([17](#_ENREF_17)) |
|  | Indication specific for ovarian cancer |  |  | FIGO I+II, III, IV | Per year | ([18](#_ENREF_18)) |

a: from 50 years to 69 years: 50-54 years: 72.9%; 55-59 years: 73.8%; 60-69 years: 73.3%.

Categorized with a period over 5 years for the age ≥25 and ≤64 and an averaged for the age ≥65.

BE: breast examination; GC-HBOC: German Consortium for Hereditary Breast and Ovarian Cancer; MX: X-ray mammography.

Table 3-S: Costs for screening and testing (Supplement)

|  |  |  |  |
| --- | --- | --- | --- |
| **Item** | **Unit costs [€]** | **Number of units** | **Resources** |
| **Genetic Testing base case** |
| V1 gene analysis (index patient) a | 2,615.63 | One-time per entry | GC-HBOC, own calculations c  |
| V2 gene analysis (index patient) b | 8,444.74 | One-time per entry | GC-HBOC, own calculations c |
| Predictive gene testing | 170.00 | One-time | GC-HBOC |
| **Genetic Testing sensitivity analysis: hypothetical development of costs for testing (reduced to one tenth)** |
| V1 gene analysis (index patient) a | 866.89  | One-time per entry | -- |
| V2 gene analysis (index patient) b | 1,449.80 | One-time per entry | -- |
| Predictive gene testing | 17.00 | One-time | -- |
| **Genetic Testing sensitivity analysis: perspective development of costs for testing (according to current price development)** |
| V1 gene analysis (index patient) a | 1,419.91 | One-time per entry | -- |
| V2 gene analysis (index patient) b | 3,661.88 | One-time per entry | -- |
| Predictive gene testing | 50.00 | One-time | -- |
| **Genetic testing sensitivity analysis: doubling of the rate of use of predictive gene testing per index patient** |
| V1 gene analysis (index patient) a | 1,307.81 | One-time per entry | -- |
| V2 gene analysis (index patient) b | 4,222.37 | One-time per entry | -- |
| **Genetic testing sensitivity analysis: tripling of the rate of use of predictive gene testing per index patient** |
| V1 gene analysis (index patient) a | 871.88 | One-time per entry | -- |
| V2 gene analysis (index patient) b | 2,814.91 | One-time per entry | -- |
| **Screening program - intensified screening programs** |
| Intensified screening program 1 | 560.00 | One-time per year | GC-HBOC |
| Intensified screening program 2 d  | 560.00 | One-time per year | GC-HBOC |
| Prophylactic mastectomy 1 | 8,620.84 | One-time | Own calculations according to information of GC-HBOC |
| Prophylactic ovariectomy 2 | 4,990.59 | One-time | Own calculations according to information of GC-HBOC |
| **Screening program – usual care** |
| Clinical breast examination  | 18.49 | Once a year | ([19](#_ENREF_19)) / ([20](#_ENREF_20)) e |
| [Mammography screening](http://www.linguee.de/englisch-deutsch/uebersetzung/mammography%2Bscreening.html) | 62.65 | Every two years f  | ([19](#_ENREF_19)) / ([20](#_ENREF_20)) g |
| Clinical breast examination - diagnostic | 2.72 | Additional charge for all participants | Own calculations; assumption: false positive rate of 3%; analogous to mammography screening |
| [Mammography screening](http://www.linguee.de/englisch-deutsch/uebersetzung/mammography%2Bscreening.html) - diagnostic | 4.59 | Additional charge for all participants | Own calculations; information on invasive and not invasive diagnostics: cooperative association for MX screening |

a: including costs for gene analysis for the index patient and genetic counselling for relatives

b: including costs for gene analysis for 4 women, to identify the index patient and genetic counseling for relatives of the identified index patient

c: gene analysis for the index patient (complete genetic analysis): 2,600€; counselling of relatives: 900€; predictive gene testing of healthy relatives: 170€. The costs are first calculated for each mutation BRCA1 (1.38), BRCA2 (1.37) and other mutations (1.27) with the proportion of participants per index patient and for further cost calculations the mean of these 3 costs per mutation is used.

d: for patients ≤30 and ≥50 years: breast ultrasound, clinical breast examination and MRT, for patients ≤40 and ≥50 years additionally X-ray mammography, clinical breast examination

e: EBM01730: Cancer screening for women

f: participation rate according to cooperative association for MX screening

g: EBM 01750: X-ray examination

1: Renewed operation within the first 5 years after mastectomy, further physician visits connected to possible complications and side effects of the prophylactic operation are not included.

2: Hormone replacement therapy after ovariectomy, further physician visits connected to possible complications and side effects of the prophylactic operation are not included.

3: Further physician visits for healthy mutation carriers connected to their genetic risks not taken into account.

4: Limited to initial procedures.

Table 4-S: Costs for treatment of breast cancer (Supplement)

|  |  |  |  |
| --- | --- | --- | --- |
| **Item** | **Unit costs [€]** | **Number of units** | **Resources** |
| **Primary therapy – surgery** |
| Breast conserving surgery | 3,721.92 | Once in the year of treatment | ([21](#_ENREF_21)) |
| Mastectomy | 4,193.77 | Once in the year of treatment | DRG fee-per-case catalogue (frequencies according to InEK) |
| **Possible interventions connected to primary therapy after surgery** |
| Radiation therapy | 2,226.61 | Once in the year of treatment | Own calculations according to information of KBV; recommendations of S3 guideline (30 sessions in 6 weeks); EBM Uniform Value Scale catalogue |
| Chemotherapy | 15,532.43 | Once in the year of treatment | Own calculations: ([22](#_ENREF_22)); mean costs for patients with average risk |
| Hormone therapy | 173.56 | Once in the year of treatment | ([23](#_ENREF_23)) |
| Chemotherapy with subsequent hormone therapy | 15,619.21 | Once in the year of treatment | Own calculations (chemotherapy ([22](#_ENREF_22)) plus costs for 6-month hormone therapy) |
| Advanced breast cancer | 19,631.97 | Lump sum for palliative treatment for not operated patients | Own calculation based on expert knowledge (Schmutzler) for costs for primary therapy and assumptions for use of resources |
| End of life care/ palliative treatment end of life: 4 weeks: 50% at home/ 50% at hospice) | 8,689.15 | Per indication-specific mortality | ([24](#_ENREF_24)) |
| Distant metastases | 7,214.15 | Annually  | ([24](#_ENREF_24)) |
| **After care** |
| Assumption: lump-sum for after care | 243.09 | Annually | ([24](#_ENREF_24)) |
| After care after bilateral mastectomy | 103.54 | Annually | Own calculation based on assumption of gynecological examination 2x per year within the additional lump-sum for after care plus rectoscopy/ proctoscopy and ultrasound examination of genital organs once per year |
| Hormone therapy during after care | 173.56 | Annually  | ([23](#_ENREF_23)) |
| Distant metastases | 7,214.15 | Annually  | ([24](#_ENREF_24)) |
| End of life care/ palliative treatment end of life: 4 weeks: 50% at home/ 50% at hospice) | 8,689.15 | Per indication-specific mortality | ([24](#_ENREF_24)) |
| **Recurrence of breast cancer** |
| Locoregional recurrence in the year of occurrence | 18,473.27 | First year  | ([25](#_ENREF_25)) |
| Locoregional recurrence in the years after the year of entry | 2,718.06 | Annually in the years after the year of entry | ([25](#_ENREF_25)) |
| Contralateral; costs for the year when it occurred  | 22,059.24 | First year  | ([25](#_ENREF_25)) |
| Contralateral  | 2,718.06 | Annually in the years after the year of entry | ([25](#_ENREF_25)) |
| Distant metastases | 7,214.15 | Annually  | ([24](#_ENREF_24)) |
| End of life care/ palliative treatment end of life:4 weeks: 50% at home/ 50% at hospice) | 8,689.15 | Per indication-specific mortality | ([24](#_ENREF_24)) |

Costs are not taken into account for

* Complications and side effects of the breast cancer treatment, e.g. hospitalizations associated with chemotherapy (SIVIDON)
* Remedies and adjuvants within treatment and after care
* End-of-life costs not within the per indication-specific mortality
* Rehabilitation measures

Table 5-S: Costs for treatment of ovarian cancer (Supplement)

|  |  |  |  |
| --- | --- | --- | --- |
| **Item** | **Unit costs [€]** | **Number of units** | **Resources** |
| **Primary therapy – surgery** |
| Ovariectomy  | 3,225.66 | Once in the year of treatment | ([21](#_ENREF_21)) |
| **Chemotherapy**  |
| Chemotherapy FIGO I and II (early stage) | 3,386.64 | Once in the year of treatment | Costs for therapy with carboplatin (6 cycle of monotherapy) ([26](#_ENREF_26)) |
| Chemotherapy FIGO III and IV (advanced stage) | 8,047.25 | Once in the year of treatment | Costs for therapy with carboplatin AUC 5 and paclitaxel 175mg/m2 for 3 hours i.v. (6 cycle every 3 weeks) ([26](#_ENREF_26)) |
| End of life care/ palliative treatment end of life:4 weeks: 50% at home/ 50% at hospice) | 8,689.15 | Per indication-specific mortality | ([24](#_ENREF_24)) |
| **After care** |
| After care | 126.75 | Annually | Own calculation based on assumption of gynecological examination 2x per year within the additional lump-sum for after care plus rectoscopy/ proctoscopy and ultrasound examination of genital organs once per year |

Costs are not taken into account for:

* Complications and side effects of the breast cancer treatment, e.g. hospitalizations associated with chemotherapy (SIVIDON)
* Remedies and adjuvants within treatment and after care
* End-of-life costs not within the per indication-specific mortality
* Rehabilitation measures

Table 6-S: Costs after 10 years for the options “steady demand” and “increased demand” differentiated according to used parameters

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Steady demand [€]** | **Increased demand [€]** | **Incremental costs [€]** |
| Genetic testing (one index patient) |  10,448,673 €  |  99,795,968 €  | +89,347,296 €  |
| Intervention |  6,135,318 €  |  46,116,076 €  | +39,980,758 €  |
| Usual care |  3,432,881 €  |  2,913,243 €  |  -519,638 €  |
| Primary therapy for breast cancer |  20,263,628 €  |  18,086,057 €  |  -2,177,571 €  |
| Recurrence /contralateral |  1,440,065 €  |  1,497,115 €  | +57,050 €  |
| After care for breast cancer |  2,876,294 €  |  2,429,921 €  |  -446,373 €  |
| Treatment and after care (OCa) |  5,179,911 €  |  4,406,138 €  |  -773,773 €  |
| **Total**  |  **49,776,770 €**  |  **175,244,518 €**  | +125,467,748 €  |
| Abb.: OCa: Ovarian cancer. |  |  |

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