Supplementary Table 1: 10-year risk of EOC without surgery

|  |  |  |
| --- | --- | --- |
| **Current age (years)** | **BRCA1 (%)** | **BRCA2 (%)** |
| 30–39 | 5 | 5 |
| 40–44 | 10 | 5 |
| 45–49 | 10 | 10 |
| 50–54 | 15 | 10 |
| 55–59 | 10 | 10 |
| 60–64 | 10 | 5 |
| 65–69 | 10 | 5 |
| 70–79 | 10 | 5 |

Abbreviations: EOC, epithelial ovarian cancer.
Source: [1]

Supplementary Table 2: 10-year risk of BC without surgery

|  |  |  |
| --- | --- | --- |
| **Current age (years)** | **BRCA1 (%)** | **BRCA2 (%)** |
| 20–25 | 5 | 1 |
| 26–30 | 5 | 2 |
| 31–35 | 5 | 5 |
| 36–40 | 10 | 2 |
| 41–45 | 10 | 10 |
| 46–50 | 15 | 10 |
| 51–55 | 15 | 10 |
| 56–60 | 10 | 10 |
| 61–65 | 10 | 15 |
| 66–70 | 10 | 15 |

Abbreviations: BC, breast cancer.
Source: [1]

Supplementary Table 3: Risk reductions following RRS

|  |  |  |
| --- | --- | --- |
| **EOC** | **BRCA1 HR** | **BRCA2 HR** |
| RRBSO | 0.16 | 0.12 |
| RRM | 1.00 | 1.00 |
| RRM+RRBSO | 0.16 | 0.12 |
| **BC** | **BRCA1 HR** | **BRCA2 HR** |
| RRBSO | 0.51 | 0.39 |
| RRM | 0.10 | 0.09 |
| RRM+RRBSO | 0.05 | 0.05 |

Abbreviations: BC, breast cancer; EOC, epithelial ovarian cancer; HR, hazard ratio; RRBSO, risk-reducing bilateral salpingo-oophorectomy; RRM, risk-reducing mastectomy; RRS, risk-reducing surgery.
Sources: [2-9]

Supplementary Table 4: 5-year net survival with EOC and BC

|  |  |  |
| --- | --- | --- |
| **Age range (years)** | **EOC (%)** | **BC (%)** |
| <45 | 76.5 | 88.1 |
| 45–54 | 59.1 | 90.6 |
| 55–64 | 49.5 | 90.1 |
| 65–74 | 38.7 | 91.4 |
| 75+ | 20.9 | 87.1 |

Abbreviations: BC, breast cancer; EOC, epithelial ovarian cancer.
Source: [10]

Supplementary Table 5: Summary of costs in the model

| **Component** | **Cost**  | **Source** |
| --- | --- | --- |
| **Testing and counselling** |  |  |
| BRCA test | CAD 675(USD478) | Estimate |
| Genetic counselling | CAD 306(USD287) | Estimate |
| **RRS** |  |  |
| RRBSO | CAD4,835(USD3,421) | Kwon J et al.[11] Inflated to 2016. |
| RRM | CAD6,711(USD4,749) | Pataky R et al.[13] |
| **Cancer treatment**  |  |  |
| EOC, with surgery (first year cost) | CAD40,420(USD28,603) | Estimate for ovarian cancer. Cost of surgery from Ontario Case Costing Initiative [14] |
| EOC, without surgery (cost in subsequent years until death) | CAD34,412(USD24,352) | Estimate [15] |
| BC, with surgery (one-off cost) | CAD29,629(USD20,967) | Pataky et al [16], inflated to 2016 costs [17] |
| BC, without surgery (one-off cost if prior RRM had been performed) | CAD23,796(USD16,840) | Assumed to be cost of BC minus RRM [16, 17] |
| **Palliative care** |  |  |
| EOC | CAD14,687(USD11K) | Hollander et al [18], inflated to 2016 costs [17] |
| BC | CAD29,993(USD22K) | Pataky et al [16], inflated to 2016 costs [17] |
| All-cause mortality | CAD14,687(USD11K) | Hollander et al [18], inflated to 2016 costs [17] |

Abbreviations: BC, breast cancer; EOC, epithelial ovarian cancer; RRBSO, risk-reducing bilateral salpingo-oophorectomy; RRM, risk-reducing mastectomy, RRS, risk-reducing surgery.

Supplementary Table 6: Summary of utility values in the model

|  |  |  |
| --- | --- | --- |
| **Utility by age for females** |  |  |
| **Age (years)** | **Utility for females, mean (95% CI)** |
| <30 | 0.87 (0.86, 0.89) |
| 30–39 | 0.87 (0.87, 0.88) |
| 40–49 | 0.84 (0.83, 0.86) |
| 50–59 | 0.83 (0.81, 0.84) |
| 60–69 | 0.82 (0.81, 0.84) |
| 70–79 | 0.81 (0.80, 0.83) |
| >79 | 0.81 (0.78, 0.84) |
| **Cancer-related utilities** |  |  |
| **Time from diagnosis** | **EOC** | **BC** |
| Year 1 | 0.50 | 0.71 |
| Year 2 | 0.65 | 0.72 |
| Year 3 | 0.67 | 0.73 |
| Year 4 | 0.69 | 0.74 |
| Year 5 | 0.70 | 0.76 |
| Year 6+ | 0.72 | 0.77 |
| **Health state utilities**  |  |  |
| **Health state** | **Utility in controls, mean (SD)** |
| Perfect health | 1.00 |
| RRBSO | 0.90 (0.14) |
| RRM | 0.88 (0.17) |
| RRBSO and RRM | 0.79 (0.21) |

Abbreviations: BC, breast cancer; CI, confidence interval; EOC, epithelial ovarian cancer; RRBSO, risk-reducing bilateral salpingo-oophorectomy; RRM, risk-reducing mastectomy; SD, standard deviation.
Sources: [19-21]

Supplementary Table 7: Inputs for probabilistic sensitivity analysis

| **Parameter** | **Base** | **SE** | **Distribution** |
| --- | --- | --- | --- |
| **Model setup** |
| Discount rate (costs) | 1.5% | 0.004 | Beta |
| Discount rate (utilities) | 1.5% | 0.004 | Beta |
| Time horizon (years) | 50 | – | None |
| **EOC risk** |
| 10-year risk BRCA1: Age 30–39 | 5% | 0.01 | Beta |
| 10-year risk BRCA1: Age 40–44 | 10% | 0.01 | Beta |
| 10-year risk BRCA1: Age 45–49 | 10% | 0.01 | Beta |
| 10-year risk BRCA1: Age 50–54 | 15% | 0.02 | Beta |
| 10-year risk BRCA1: Age 55–59 | 10% | 0.01 | Beta |
| 10-year risk BRCA1: Age 60–64 | 10% | 0.01 | Beta |
| 10-year risk BRCA1: Age 65–69 | 10% | 0.01 | Beta |
| 10-year risk BRCA1: Age 70–79 | 10% | 0.01 | Beta |
| 10-year risk BRCA2: Age 30–39 | 5% | 0.01 | Beta |
| 10-year risk BRCA2: Age 40–44 | 5% | 0.01 | Beta |
| 10-year risk BRCA2: Age 45–49 | 10% | 0.01 | Beta |
| 10-year risk BRCA2: Age 50–54 | 10% | 0.01 | Beta |
| 10-year risk BRCA2: Age 55–59 | 10% | 0.01 | Beta |
| 10-year risk BRCA2: Age 60–64 | 5% | 0.01 | Beta |
| 10-year risk BRCA2: Age 65–69 | 5% | 0.01 | Beta |
| 10-year risk BRCA2: Age 70–79 | 5% | 0.01 | Beta |
| **BC risk** |
| 5-year risk BRCA1: Age 20–25 | 5% | 0.01 | Beta |
| 5-year risk BRCA1: Age 26–30 | 5% | 0.01 | Beta |
| 5-year risk BRCA1: Age 31–35 | 5% | 0.01 | Beta |
| 5-year risk BRCA1: Age 36–40 | 10% | 0.01 | Beta |
| 5-year risk BRCA1: Age 41–45 | 10% | 0.01 | Beta |
| 5-year risk BRCA1: Age 46–50 | 15% | 0.02 | Beta |
| 5-year risk BRCA1: Age 51–55 | 15% | 0.02 | Beta |
| 5-year risk BRCA1: Age 56–60 | 10% | 0.01 | Beta |
| 5-year risk BRCA1: Age 61–65 | 10% | 0.01 | Beta |
| 5-year risk BRCA1: Age 66–70 | 10% | 0.01 | Beta |
| 5-year risk BRCA2: Age 20–25 | 1% | 0.00 | Beta |
| 5-year risk BRCA2: Age 26–30 | 2% | 0.00 | Beta |
| 5-year risk BRCA2: Age 31–35 | 5% | 0.01 | Beta |
| 5-year risk BRCA2: Age 36–40 | 2% | 0.00 | Beta |
| 5-year risk BRCA2: Age 41–45 | 10% | 0.01 | Beta |
| 5-year risk BRCA2: Age 46–50 | 10% | 0.01 | Beta |
| 5-year risk BRCA2: Age 51–55 | 10% | 0.01 | Beta |
| 5-year risk BRCA2: Age 56–60 | 10% | 0.01 | Beta |
| 5-year risk BRCA2: Age 61–65 | 15% | 0.02 | Beta |
| 5-year risk BRCA2: Age 66–70 | 15% | 0.02 | Beta |
| **RRBSO** |
| BRCA1: Estimated age of surgery | 54 | 5.74 | Normal |
| BRCA1: Uptake rate ≥ estimated age | 44% | 0.06 | Beta |
| BRCA2: Estimated age of surgery | 54 | 5.74 | Normal |
| BRCA2: Uptake rate ≥ estimated age | 44% | 0.06 | Beta |
| BRCA1: EOC HR | 0.16 | 0.27 | Log-normal |
| BRCA1: BC HR | 0.51 | 0.13 | Log-normal |
| BRCA2: EOC HR | 0.12 | 0.34 | Log-normal |
| BRCA2: BC HR | 0.39 | 0.16 | Log-normal |
| **RRM** |
| BRCA1: Estimated age of surgery | 44 | 5.61 | Normal |
| BRCA1: Uptake rate ≥ estimated age | 21.1% | 0.06 | Beta |
| BRCA2: Estimated age of surgery | 44 | 5.61 | Normal |
| BRCA2: Uptake rate ≥ estimated age | 21.1% | 0.06 | Beta |
| BRCA1: BC HR | 0.10 | 0.60 | Log-normal |
| BRCA2: BC HR | 0.09 | 0.60 | Log-normal |
| **RRBSO + RRM** |
| EOC HR: BRCA1 | 0.16 | 0.27 | Log-normal |
| BC HR: BRCA1 | 0.05 | 0.79 | Log-normal |
| EOC HR: BRCA2 | 0.12 | 0.34 | Log-normal |
| BC HR: BRCA2 | 0.05 | 0.79 | Log-normal |
| **Cumulative survival probability** |
| Males: Age 0–101 | – | – | Beta |
| Females: Age 0–101 | – | – | Beta |
| **Ovarian cancer: 5-year survival rate** |
| Age range <45 | 76.5% | 0.10 | Beta |
| Age range 45–54 | 59.1% | 0.08 | Beta |
| Age range 55–64 | 49.5% | 0.06 | Beta |
| Age range 65–74 | 38.7% | 0.05 | Beta |
| Age range 75+ | 20.9% | 0.03 | Beta |
| **Breast cancer: 5-year survival rate** |
| Age range <45 | 88.1% | 0.09 | Beta |
| Age range 45–54 | 90.6% | 0.08 | Beta |
| Age range 55–64 | 90.1% | 0.08 | Beta |
| Age range 65-74 | 91.4% | 0.08 | Beta |
| Age range 75+ | 87.1% | 0.09 | Beta |
| **Costs** |
| BRCA test – index case | CAD 675(USD478) | CAD 86.10(USD60.93) | Gamma |
| Tumour testing – index case | CAD 306(USD287) | CAD 39.03(USD36.59) | Gamma |
| Genetic counselling – index case | CAD 300(USD212) | CAD 38.27(USD27.08) | Gamma |
| BRCA test – family members | CAD 675(USD478) | CAD 86.10(USD60.93) | Gamma |
| Tumour testing – family members | CAD 108(USD101) | CAD 13.78(USD12.91) | Gamma |
| Genetic counselling – family members | CAD 300(USD212) | CAD 38.27(USD27.08) | Gamma |
| RRBSO total cost | CAD4,835(USD3,421) | CAD616.68(USD436.40) | Gamma |
| RRM total cost | CAD6,711(USD4,749) | CAD 855.95(USD605.71) | Gamma |
| EOC – cost with surgery | CAD40,420(USD28,603) | CAD5,155.69(USD3648) | Gamma |
| BC – cost with surgery | CAD29,629(USD20,967) | CAD3,779.32(USD2674) | Gamma |
| EOC – cost without surgery | CAD34,412(USD24,352) | CAD4,389.35(USD3106) | Gamma |
| BC – cost without surgery | CAD23,796(USD16,840) | CAD3,035.31(USD2147) | Gamma |
| Palliative care – EOC | CAD14,687(USD11K) | CAD1,873.38(USD1414) | Gamma |
| Palliative care – BC | CAD29,993(USD22K) | CAD3,825.70(USD2887) | Gamma |
| Palliative care – all-cause | CAD14,687(USD11K) | CAD1,873.38(USD1414) | Gamma |
| **Utilities** |
| Perfect health – controls | 1.00 |   | None |
| RRBSO – controls | 0.90 | 0.08 | Beta |
| RRM – controls | 0.88 | 0.09 | Beta |
| RRM & RRBSO – controls | 0.79 | 0.10 | Beta |
| BRCA mut positive test result – controls | 1.00 | 0.06 | Beta |
| RRBSO – BRCA mut positive | 0.95 | 0.07 | Beta |
| RRM – BRCA mut positive | 0.88 | 0.09 | Beta |
| RRM & RRBSO – BRCA mut positive | 0.84 | 0.09 | Beta |
| BRCA mut positive test result – BRCA mut positive | 1.00 | 0.06 | Beta |
| Age-related utilities: Males age 1–101 | – | – | Beta |
| Age-related utilities: Females age 1–101 | – | – | Beta |
| EOC: Year 1 | 0.50 | 0.06 | Beta |
| EOC: Year 2 | 0.65 | 0.08 | Beta |
| EOC: Year 3 | 0.67 | 0.09 | Beta |
| EOC: Year 4 | 0.69 | 0.09 | Beta |
| EOC: Year 5 | 0.70 | 0.09 | Beta |
| EOC: Year 5+ | 0.72 | 0.09 | Beta |
| BC: Year 1 | 0.71 | 0.09 | Beta |
| BC: Year 2 | 0.72 | 0.09 | Beta |
| BC: Year 3 | 0.73 | 0.09 | Beta |
| BC: Year 4 | 0.74 | 0.09 | Beta |
| BC: Year 5 | 0.76 | 0.10 | Beta |
| BC: Year 5+ | 0.77 | 0.10 | Beta |
| **Duration of disutility** |
| Duration of effect (yrs): Perfect health | – | – | None |
| Duration of effect (yrs): RRBSO | 1.00 | 0.06 | Log-normal |
| Duration of effect (yrs): RRM | 1.00 | 0.06 | Log-normal |
| Duration of effect (yrs): RRM & RRBSO | 1.00 | 0.06 | Log-normal |
| Duration of effect (yrs): BRCA mut positive test result | 1.00 | 0.06 | Log-normal |
| Duration of effect (yrs): Death | – | – | None |
| **Population generation** |
| Number of index cases | 2,786 | – | None |
| Index population: Mean age | 50 | 6.38 | Normal |
| Index population: Age SD | 5.00 | – | None |
| Index population: Probability germline BRCA mut positive | 12% | 0.02 | Beta |
| Index population: % BRCA1 | 62% | 0.08 | Beta |
| First-degree: Probability of BRCA mutation if index case is BRCA mutation positive | 50% | 0.06 | Beta |
| Mother: Mean age (relative to index) | 30 | 3.83 | Normal |
| Mother: Age SD | 5 |   | None |
| Father: Mean age (relative to index) | 32 | 4.12 | Normal |
| Father: Age SD | 5 |   | None |
| Siblings: Mean number | 0.61 | 0.13 | Log |
| Siblings: Number SD | 0.5 |   | None |
| Siblings: Mean age (relative to index) | 0 |   | None |
| Siblings: Age SD | 5 |   | None |
| Siblings: Gender (probability female) | 50.41% | 0.06 | Beta |
| Children: Mean number | 1.91 |   | None |
| Children: Number SD | 1 |   | None |
| Children: Mean age (relative to index) | –30 | 3.83 | Normal |
| Children: Age SD | 5 |   | None |
| Children: Gender (probability female) | 50.41% | 0.06 | Beta |
| Second-degree: Probability of BRCA mutation if index case is BRCA mutation positive | 25% | 0.03 | Beta |

Abbreviations: BC, breast cancer; EOC, epithelial ovarian cancer; HR, hazard ratio; mut, mutation; RRBSO, risk-reducing bilateral salpingo-oophorectomy; RRM, risk-reducing mastectomy; SD, standard deviation; SE, standard error; yrs, years.

Supplementary Table 8: Budget impact for testing vs no testing over 5 years

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Year 1** | **Year 2** | **Year 3** | **Year 4** | **Year 5** |
| Testing costs | CAD24,495K | CAD 0 | CAD 0 | CAD 0 | CAD 0 |
| USD17,334K | USD 0 | USD 0 | USD 0 | USD 0 |
| Counselling costs | CAD3,662K | CAD 0 | CAD 0 | CAD 0 | CAD 0 |
| USD2,591K | USD 0 | USD 0 | USD 0 | USD 0 |
| RRS costs | CAD3,553K | CAD 241,445 | CAD 192,305 | CAD 179,677 | CAD 232,066 |
| USD2,514K | USD170,859 | USD136,085 | USD127,148 | USD164,221 |
| OC costs | -CAD 80,840 | -CAD230,503 | -CAD287,311 | -CAD327,731 | -CAD321,723 |
| -USD57,206 | -USD163,116 | -USD203,316 | -USD231,919 | -USD227,667 |
| BC costs | -CAD 59,259 | -CAD118,517 | -CAD48,147 | -CAD118,517 | -CAD177,776 |
| -USD41,934 | -USD83,869 | -USD104,836 | -USD83,869 | -USD125,803 |
| Palliative costs | CAD0 | -CAD29,993 | CAD45,299 | -CAD29,374 | -CAD44,680 |
| USD0 | -USD22,640 | USD34,193 | -USD22,172 | -USD33,726 |
| **Total costs** | **CAD31,571K** | **-CAD137,569** | **-CAD197,854** | **-CAD295,945** | **-CAD312,113** |
| **USD22,341K** | **-USD98,766** | **-USD137,874** | **-USD210,812** | **-USD222,975** |

Supplementary Figure 1: Cost-effectiveness plane for the base-case analysis

Abbreviations: QALYs, quality adjusted life years.

Supplementary Figure 2: Cost-effectiveness acceptability curve for the base-case analysis



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