APPENDIX I

Estimation of Age-Specific Breast Cancer Incidence among BRCA1/2 Mutation Carriers in the Absence of Risk-Reducing Interventions

To simulate clinical outcomes for BRCA1/2 mutation under different risk-reducing interventions, we need estimates of the incidence of breast cancer for BRCA1 and BRCA2 mutation carriers who did not undergo any risk-reducing interventions, including PO. We rely on the meta-analysis on BRCA1/2 mutation penetrance in Reference (1) to derive breast cancer incidence in the absence of PO and PM. However, this meta-analysis does not report the prevalence of PO. To calculate breast cancer incidence in the absence of PO for this meta-analysis cohort, we required an estimate of the prevalence of PO and the ages at which patients underwent PO in this cohort. We obtained such estimates in Reference (12) because it incorporated a large number of the participants who were included in the meta-analysis cohort of Reference (1). Reference (12) reported that 30% of women had undergone PO by age 45. Hence, we performed a back-calculation (presented below) to remove the effect of PO, assuming that the breast cancer incidence reported by the meta-analysis in Reference (1) were affected by an unreported PO prevalence of approximately 30% by age 45 as reported in Reference (12). We derived estimates separately for BRCA1 and BRCA2 mutation carriers. Following we present our algorithm to backcalculate age-specific breast cancer incidence among BRCA1/2 mutation carriers in the absence of PO.

To estimate breast cancer incidence in the absence of any risk-reducing intervention, we considered a single birth cohort, women born in 1980, who have not been diagnosed with breast or ovarian cancer by age 25. Single-year age-specific breast and ovarian cancer incidence rates were determined from Reference (1), which reported 5-year age group rates; we assumed that these rates corresponded to the mid-age of the 5-year interval (i.e. ages 27, 32, 37… 62, 67 years), and determine incidence for other ages by linear interpolation. Cancer rates were converted into annual probabilities assuming exponential distribution with a constant hazard within each one-year age interval. Our base case incidence inputs included these annual probabilities derived from (1) for ages 25-69,

adjusted for PO utilization effect on BC incidence from ages 45-69 using the algorithm presented below. Breast and ovarian cancer incidence for ages 70-84 were also obtained by linear interpolation between the incidence calculated for age 69 and the incidence reported in the Surveillance, Epidemiology and End Results (SEER) registry for age 85+, in the era before mammographic screening (1975-1981) (25). Breast cancer incidence for women of age 85+ was kept constant, corresponding to that of SEER for ages 85+.

To derive breast cancer incidence in the absence of PO we assumed that 30% of BRCA1/2 mutation carriers undergo PO at an average age of 45 years, based on Reference (12). We expressed the risk reduction due to PO for breast cancer in terms of a hazard ratio (HR), denoted by α, equal to 0.5 based on Reference (15). For ovarian cancer, proportional reduction in probability of ovarian cancer diagnosis, denoted by β, was assumed to be equal to 0.2 based on Reference (12).

In the meta-analysis of Reference (1), subjects were "censored at the age at first cancer diagnosis, at the age at death, at the age at last follow-up, or at age 70, whichever came first". We assumed that censoring due to age at last follow-up and death were equivalent for women who did and did not undergo PO. However, we did take into account a difference in censoring due to ovarian cancer diagnosis between these groups. In effect, ovarian cancer diagnosis was the only censoring event considered for the purpose of computations.

For women at age *i,* let:

$p_{0,i}$ represent the probability of being diagnosed with breast cancer during the $[i,i+1)$ age interval among women who did not undergo PO, in the absence of competing events;

$p_{A,i}$ represent the probability of breast cancer diagnosis in the $[i,i+1)$ age interval, taken from the meta-analysis of BRCA1/2 mutation carriers (1), assuming 30% of women have PO at 45 years old;

$g_{0,i}$ represent the probability of being diagnosed with ovarian cancer during the $[i,i+1)$ age interval among women who did not undergo PO, in the absence of competing events (derived from the meta-analysis of BRCA1/2 mutation carriers (1));

$g_{1,i}$ represent the probability of being diagnosed with ovarian cancer during the $[i,i+1)$ age interval among women who undergo PO, in the absence of competing events.

To apply the protective effect of PO for ovarian cancer as a proportional probability reduction, we solve for $g_{1,i}$ using the following equation:

$$g_{1,i} = \beta g_{0,i} \cdot \frac{1-\prod_{k=1}^{i-1}(1-g_{0,k})}{1-\beta\prod_{k=1}^{i-1}(1-g_{0,k})}.$$

Let

$Q_{0,i}$ represent the number of women at the beginning of the age interval $[i,i+1)$ who are at risk of developing breast cancer and who do not undergo PO;

$Q_{1,i}$ represent the number of women at the beginning of the age interval $[i,i+1)$ who are at risk of developing breast cancer and who undergo PO at age 45;

The expected populations at risk at the beginning of the age interval $[i,i+1)$ are equal to:
$Q_{0,i} = Q_{0,i-1}(1-p_{0,i-1})(1-g_{0,i-1})$ and

$Q_{1,i} = Q_{1,i-1}(1-p_{0,i-1})^{\alpha}(1-g_{1,i-1}).$

For a hypothetical cohort of N 45 year-old women with BRCA1 or BRCA2 mutations, we assumed that PO is performed at the beginning of the [45, 46) age interval among 30% of the women; thus, $Q_{0,45} = 0.7N$ and $Q_{1,45} = 0.3N$.

Let

$B_{0,i}$ represent the expected number of non-censored breast cancer patients who were diagnosed in the age interval $[i,i+1)$ and do not undergo PO at age 45;

$B_{1,i}$ represent the expected number of non-censored breast cancer patients who were diagnosed in the age interval $[i,i+1)$ and undergo PO at age 45;

Further, we assume that cancer risk-reduction due to PO at age 45 persists indefinitely. Here we also assume that breast and ovarian cancers occur uniformly and independently within one-year age intervals.

For age $i = 45, 46, \ldots, 69$, $B_{0,i}$ and $B_{1,i}$ are computed as:

$B_{0,i} = Q_{0,i}(p_{0,i} - 0.5p_{0,i}g_{0,i})$ and

$$B_{1,i} = Q_{1,i}\left[\left(1-(1-p_{0,i})^{\alpha}\right) - 0.5\left(1-(1-p_{0,i})^{\alpha}\right)g_{1,i}\right].$$

Let:

$O_{0,i}$ represent the expected number of breast cancer patients who were censored due to an ovarian cancer diagnosis, in the age interval $[i,i+1)$, and who do not undergo PO at age 45;

$O_{1,i}$ represent the expected number of breast cancer patients who were censored due to an ovarian cancer diagnosis, in the age interval $[i,i+1)$, and who undergo PO at age 45;

The expected number of censoring events (an ovarian cancer diagnosis before a breast cancer diagnosis) is:

$O_{0,i} = Q_{0,i}(g_{0,i} - 0.5p_{0,i}g_{0,i})$ and

$O_{1,i} = Q_{1,i}\left[g_{i,i} - 0.5\left(1-(1-p_{0.i})^{\alpha}\right)g_{1,i}\right]$.

Lastly, we build the set of equations for $p_{A,i}$ given by:

$$p_{A,i} = \frac{B_{0,i} + B_{1,i}}{Q_{0,i} + Q_{1,i} - 0.5(O_{0,i} + O_{1,i})},$$

where $i = 45, 46, \ldots, 69$ and we sequentially solve for $p_{0,i}$.

Our resulting estimates for breast cancer incidence in the absence of any risk-reducing interventions are presented in Figure 1. In Table 2, we presented a sensitivity analysis that demonstrates the how our assumptions on the prevalence of PO and the age of PO effect our estimates of breast cancer incidence in the absence of PO.