### Appendix 1. Literature Review Highlights With All Studies Published After 2005 Markov Model

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect Studied</th>
<th>Cohort</th>
<th>Mortality/Morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular focus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Laughlin-Tommaso, et al. Cardiovascular and metabolic morbidity after hysterectomy with ovarian conservation: a cohort study. Menopause 2017; 25 (5): 483-492<sup>15</sup>. | CAD, CHF, & Stroke all stratified by ages less than or =35 36-50, and >50 | Olmstead County, MN women as part of Rochester Epi Project records linkage system. | Case control of HYS with ovarian conservation vs no surgery. Adjusted models:  
- CAD (coronary artery disease) HR 2.49 (1.39-4.47) p=0.002  
- Congestive Heart Failure (CHD) HR 4.59 (1.32-15.94) p=0.02  
- Stroke 1.14 (0.50-2.58) p=0.75  
Age 36-50  
- CAD HR 1.34 (1.07-1.68) p=0.01  
- CHF HR 0.63 (0.42-0.95) p=0.03  
- Stroke HR 1.22 (0.88-1.67)  
Age >50  
- CAD HR 1.15 (0.85-1.56) p=0.35  
- CHF HR 0.84 (0.60-1.17) p=0.30  
- Stroke HR 0.80 (0.56-1.14) p=0.22  
See Table 2 in the main manuscript. |
| Lai et al. The risk of stroke after bilateral salpingo-oophorectomy at hysterectomy for benign diseases: A nationwide cohort study. Maturitas 2018; 114:27-33<sup>24</sup>. | Stroke risk, all types and by subtype, by HYS vs HYS+BSO, stratified by age and post-surgery estrogen therapy | Taiwanese nationwide population-based retrospective cohort study using insurance claims data | No significant association between BSO and risk of incident stroke or subtype of stroke.  
- Women >50 years who underwent BSO and used estrogen post-operatively, risk of stroke decreased 64% compared to HYS alone |
| **Morbidity & Mortality from Multiple Causes**   |                                                   |                                             |                                                                                   |
| Rocca et al. Survival patterns after oophorectomy in premenopausal women: a population-based cohort study. Lancet oncology 2006; 7:821-828<sup>25</sup>. | Cancer incidence, vascular cause of death, neuro or mental health, respiratory, other causes | Mayo Clinic Cohort Study of Oophorectomy and Aging | Women w/ BSO <45 and no estrogen therapy had increased risk of cancers (esp estrogen related), non-cancer neuro or mental health, and total all cause. |
| Rivera et al. Increased cardiovascular mortality in early bilateral oophorectomy. Menopause 2009; 16(1):15-23<sup>3</sup>. | CVD listed anywhere on death certificate | Mayo Clinic Cohort Study on Oophorectomy and Aging | Differences related to age at surgery, use of estrogen, and difference btw CVD listed as reason for death vs CVD listed anywhere on death certificate |
| Jacoby et al. Oophorectomy vs Ovarian conservation with Hysterectomy. Archives of Internal Medicine 2011; 171(8): 760-768<sup>13</sup>. | CVD Hip fracture Cancer | Women’s Health initiative Observational Study. | No significant increased risk of CVD in women w/ BSO vs hysterectomy alone (total fatal and non-fatal CHD HR 1.00, CI 0.85-1.18).  
BSO did not confer increased fracture risk (HR 0.83, CI 0.63-1.101)  
Women <40 at time of BSO had decreased breast cancer risk (HR 0.36 CI 0.14-0.951). |

Rush SK, MA X, Newton MA, Rose SL. A revised Markov Model evaluating oophorectomy at the time of benign hysterectomy: age 65 years revisited. Obstet Gynecol 2022;139.  
The authors provided this information as a supplement to their article.  
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<table>
<thead>
<tr>
<th>Source</th>
<th>Study Title &amp; Citation</th>
<th>Primary Outcomes</th>
<th>WHI Estrogen-Alone Trial</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manson et al.</td>
<td>Menopausal Hormone Therapy and Health Outcomes During the Intervention and Extended Poststopping Phases of the Women's Health Initiative Randomized Trials. Jama 2013; 310(13): 1353-1368&lt;sup&gt;8&lt;/sup&gt;.</td>
<td>Primary: CHD &amp; breast cancer Global Index: CHD, breast cancer, stroke, pulmonary embolus, colorectal cancer, endometrial cancer, hip fracture, death</td>
<td>During Intervention: In the hysterectomy arm with estrogen alone use (and BSO was performed in about 40% of those with hysterectomy, including the arm that got estrogen and the placebo arm): Stroke: HR 1.35 (1.07-1.70), p=0.01 Hip fracture: HR 0.67 (0.46-0.96), p=0.03 DVT: 1.48 (1.06-2.07) p=0.02 All Cardiovascular events: 1.11 (1.01-1.22) P=0.03 Vertebral fracture: 0.64 (0.44-0.93) p=0.02 All fracture: HR 0.72 (0.64-0.80) p&lt;0.001 In the intervention arm when age at randomization was used to stratify, then colorectal cancer, all-cause mortality, global index and total MI were significantly different by age. In follow-up, age groups remained significant for global index and total MI, where estrogen was protective at younger ages and seemed to be associated with greater risk later in life. Global index ages 50-59 HR 0.82 (0.68-0.98) Ages 60-69 HR 1.03 (0.92-1.15) Ages 70-79 HR 1.10 (0.97-1.25) p =0.01 Total MI ages 50-59 HR 0.60 (0.39-0.91) Ages 60-69 HR 1.03 (0.82-1.31) Ages 70-79 HR 1.25 (0.95-1.65) p=0.007</td>
<td></td>
</tr>
<tr>
<td>Parker et al.</td>
<td>Long-term Mortality Associated with Oophorectomy compared with Ovarian Conservation in the Nurses' Health Study. Obstetrics &amp; Gynecology 2013; 121(4): 709-716&lt;sup&gt;10&lt;/sup&gt;.</td>
<td>Death from CHD, stroke, breast cancer, epithelial ovarian cancer, lung cancer, colorectal cancer, total cancer and all cause</td>
<td>None of the p values in the multivariate analysis were significant for risk after hysterectomy comparing +/- BSO, except for breast cancer Breast cancer &lt;50 yrs HR 0.82 (0.60-1.11) 50-59 yrs HR 1.19 (0.66-2.14) 60+ yrs HR NA All cause death HR 0.89 (0.69-1.15) p=0.05 Exposure to estrogen negated any trend toward worse outcomes after BSO for All cause Death</td>
<td></td>
</tr>
</tbody>
</table>

Rush SK, MA X, Newton MA, Rose SL. A revised Markov Model evaluating oophorectomy at the time of benign hysterectomy: age 65 years revisited. Obstet Gynecol 2022;139. The authors provided this information as a supplement to their article. ©2022 American College of Obstetricians and Gynecologists.
### Literature Review

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type</th>
<th>Participants/Study Details</th>
<th>Results/Findings</th>
</tr>
</thead>
</table>
| Rush SK, MA X, Newton MA, Rose SL          | Article                     | A revised Markov Model evaluating oophorectomy at the time of benign hysterectomy: age 65   | -no estrogen HR 1.41 (1.04-1.92)  
-estrogen 1.05 (0.94-1.17) p=0.03  
Lung Ca  
-no estrogen HR 1.44 (0.17-12.2)  
-estrogen HR 0.80 (0.58-1.12)  
CHD  
-no estrogen 2.35 (0.76-7.26)  
-estrogen 0.91 (0.63-1.31) p=0.02  
CVD  
-no estrogen HR 1.60 (0.68-3.74)  
-estrogen HR 1.00 (0.76-1.33) p=0.01 |
| Gierach et al. Long-term Overall           | Literature                  | Overall and disease specific mortality 52,846 Breast Cancer Detection and Demonstration    | Multivariate analysis adjusted for BMI, smoking, hormone therapy, alcohol use and birth cohort.  
Among all women not stratified by age, BSO did not increase all-cause mortality risk: HR 1.01 (CI 0.96-1.04)  
By age:  
BSO at 35 HR 1.20, CI 1.08-1.34  
By age 50 all-cause mortality NOT increased  
HYS w/o BSO also increased all-cause mortality at ages 35 and 40:  
-HR 35 yrs 1.10 CI 1.00-1.20  
-HR 40 yrs 1.08 CI 1.01-1.15  
BSO was associated with cancer in the following ways:  
Reduction in cancer deaths if performed by age 50: HR 0.89, CI 0.81-0.98; Age 55 HR 0.88, CI 0.80-0.97  
BSO associated with increased risk of colorectal and pancreatic cancers, but only significantly at certain ages  
BSO increased non-cancer death risk with strongest association if BSO performed by age 35  
-HR at 35 yrs 1.25 CI 1.10-1.42  
Risk remained increased at age 55, but less so  
-HR at 55 yrs 1.08 CI 1.01-1.14  
BSO associated with increased risk of death from CHD at all ages up to age 55, but attenuated as age increases at time of surgery  
HR 35 yrs 1.56 CI 1.29-1.89  
HR 40 yrs 1.37 CI 1.19-1.58  
HR 45 yrs 1.28 CI 1.14-1.43  
HR 50 yrs 1.20 CI 1.08-1.32  
HR 55 yrs 1.10 CI 1.00-1.21  
Association with stroke not very clean by age, sometimes decreased and sometimes increased depending on age evaluated |
| Mytton et al. Removal of all ovarian tissue  | Article                     | All-cause mortality and specifically by Premenopausal women undergoing Deaths by the following:  | (after cox regression, all in favor of ov conservation btw 35-45) |

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| Pre-menopausal patients with benign disease: study using routine data and data linkage. The British Medical Journal 2017; 356:j372 http://dx.doi.org/10.1136/bmj.j37228. | heart disease, cancer and suicide. | benign HYS between 35 and 45 years, with ovarian conservation vs BSO | - All cause death HR 0.64 (0.55-0.73) p<0.001  
- Heart disease death HR 0.50 (0.28-0.90) p=0.02  
- Cancer death HR 0.54 (0.45-0.65) p<0.001  
-- breast HR 0.61 (0.39-0.94) p=0.03  
-- colon cancer HR 0.47 (0.25-0.88) p=0.02  
-- lung cancer HR 0.95 (0.58-1.57) p=0.85  
-- ovarian cancer HR 0.21 (0.09-0.50) p<0.001 – considered to be spurious whereby BSO was performed for abnormal masses on ovaries |
| --- | --- | --- | --- |
| Breast Cancer Risk | Breast cancer risk after HYS+BSO vs HYS with partial ovary removal or tubal ligation vs partial ovary removal w/o HYS | Women’s CARE study, multi-site retrospective case-control study to evaluate breast cancer risk factors in white and black women ages 35-64 | BSO = OR 0.63 (0.52-0.75)  
- partial ovary removal with HYS = OR 0.75 (0.60-0.96)  
- partial ovary removal w/o HYS = OR 0.87 (0.70-1.09)  
- HYS no removal of ovary = OR 0.81 (0.69-0.95)  
- tubal sterilization = OR 0.98 (0.86-1.11) |
| Nichols et al. Postoophorectomy estrogen use and breast cancer risk. Obstetrics & Gynecology 2012; 120(1): 27-3628. | Breast cancer risk | Case control study with phone interview re HRT | HYS+BOS with HRT initiated after age 40 associated with increased breast cancer, but decreased risk if HYS+BOS and hormones before age 40 |
HYS w/ BSO OR 0.68 |
| Ovarian Cancer Risk | Ovarian Cancer Rates After Hysterectomy With and Without Salpingo-oophorectomy. Obstetrics & Gynecology 2014; 123(1):65-7214. | Ovarian Cancer Rates after HYS with and without BSO | Rate of ovarian cancer per 100,000 person years:  
- after HYS alone = 26.2 (CI 15.5-37)  
- after HYS + USO = 17.5 (CI 0.0-39.1)  
- after HYS + BSO = 1.7 (CI 0.4-3)  
Compared to HYS alone, HR of HYS+BSO was 0.12 (CI 0.05-0.28) |
| Dixon-Suen et al. The Association Between Hysterectomy and Ovarian Cancer Risk: A Population-Based Record-Linkage Study. JNCI 2019; 111(10):1097-110317. | Ovarian Cancer Risk after HYS alone | Cohort Study including data linkage for West Australian women (n=837,942) | HYS alone not associated with risk of ovarian cancer, HR –0.98 (CI 0.85-1.11). This holds true across age at procedure, time periods, and different surgical approaches. If HYS performed for endometriosis or fibroids, there seems to be ovarian cancer risk reduction:  
-HYS for endometriosis, decreased ovarian cancer risk, HR 0.17 (CI 0.12-0.24)  
-HYS for fibroids, decreased ovarian cancer risk, HR 0.27 (CI 0.20-0.36) |
<table>
<thead>
<tr>
<th>Cancer Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer incidence</td>
</tr>
<tr>
<td>Prospective observational</td>
</tr>
<tr>
<td>HYS with BSO before 45 27% risk reduction, NNT 333</td>
</tr>
<tr>
<td>HYS without BSO before 45 with 20% risk reduction, NNT 450</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reoperation Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reoperation after HYS</td>
</tr>
<tr>
<td>Rochester Epi Project data retrospective</td>
</tr>
<tr>
<td>Incidence of oophorectomy 3.5% at 10-year follow-up, 6.2% at 20-year follow up, 9.2% at 30-year follow up</td>
</tr>
</tbody>
</table>

BSO bilateral salpingo-oophorectomy, CAD coronary artery disease, CVD cardiovascular disease, CHD coronary heart disease, CHF congestive heart failure, HR hazard ratio, HRT hormone replacement therapy, HYS hysterectomy, OR odds ratio

Summary:

The present document is rendered from R markdown, which interleaves text and chunks of R code to reproduce computations reported in the main manuscript.

Our calculations model survival rates for women who have received either hysterectomy, HYS, or HYS in combination with bilateral salpingo-oophorectomy, BSO. For either surgical treatment (HYS or HYS + BSO) performed at one of various ages, we simulate a large synthetic cohort of treated women forward through annual or five-year time increments, keeping track of the proportion who die by various causes. Transition rates for finite-state, discrete time Markov chain are derived from hazard ratios obtained through literature review. Simulation under any fixed transition rates leads to various endpoints, such as the proportion of each cohort that remains alive by age 80. We assess uncertainty in the survival rates by propagating hazard-ratio uncertainty. Specifically, we use reported confidence intervals on hazard ratios to seed a literature posterior distribution for a Bayesian analysis. We repeatedly sample hazard ratios from this distribution and simulate cohort dynamics from each parameter setting in order to obtain uncertainty assessments on each survival endpoint.

The intervention HYS + BSO before age 50 will likely result early menopause and thus lack of estrogen. As an add-on calculation, we also consider the scenario when estrogen therapy is involved where we apply the same simulation semantics to cohorts with HYS + BSO + estrogen therapy and specifically receiving the surgical treatment before age 50.

Model structure:

Base matrix

Primary calculations are based upon an 8-state Markov chain whose states are: (1) dead by coronary heart disease, (2) dead by stroke, (3) dead by breast cancer, (4) dead by ovarian cancer, (5) dead by lung cancer, (6) dead by colorectal cancer, (7) dead by other natural causes or other risk factors, and (8) alive. An entire cohort starts in state 8 and evolves stochastically over time by elementary Markovian rules (note that states 1 – 7 are absorbing). Initially we consider a cohort incrementing in steps of 5-years, starting at \( t_0 = 45 \) and continuing for \( n = 7 \) steps until the cohort reaches age \( t_n = 80 \).

For \( i = 1,2,\ldots,n \), let \( M_i \) be the \( 8 \times 8 \) transition matrix giving probabilities that a healthy woman age \( t_{i-1} \) (i.e., in state 8) will be in any of the 8 states 5 years later.

\[
\begin{pmatrix}
1 & 0 & \cdots & 0 \\
0 & 1 & \cdots & 0 \\
\vdots & \ddots & \ddots & \vdots \\
0 & 0 & \cdots & 1 \end{pmatrix}
\]

\[
\begin{pmatrix}
p_{11}^i & p_{12}^i & \cdots & p_{18}^i \\
p_{21}^i & p_{22}^i & \cdots & p_{28}^i \\
\vdots & \ddots & \ddots & \vdots \\
p_{81}^i & p_{82}^i & \cdots & p_{88}^i \\
\end{pmatrix}
\]

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The first 7 entries of the last row are probabilities that a woman of age $t_{i-1}$ will die by a given cause by age $t_i$. The survival probability is the complement, $p_i^8 = 1 - \sum_{j=1}^7 p_i^j$. To set these matrices numerically, we pulled survival data from the Centers for Disease Control (CDC) https://gis.cdc.gov/Cancer/USCS/DataViz.html, which we did on 12/13/2019. In some cases, one-year rather than five-year survival rates were available. We use the method proposed in Parker et al, 2005, to convert one-year rates to five-year rates: $R_5 = 1 - \exp(-5R_1)$, where $R_1$ and $R_5$ are one-year and five-year respectively. We expect a proportion $R_1$ of the cohort to have died by that risk factor over one year; thus, over five years, we expect a proportion $(1 - R_1)^5$ proportion to not have died by that risk factor, which is approximately $1 - R_1 \approx \exp(-R_1)$ for small $R_1$, and thus the approximation: $R_5 = 1 - \exp(-5R_1)$.

# base transition matrices

# time 45-80, 5 year cycle

# convert 1-year rate to 5-year rate: 1 - exp(-5x), where x is the 1-year mortality rate
# as in Parker 2005

conv = function(x){
  return(1 - exp(-5 * x))
}

# ovarian cancer
# mortality rate of ovarian cancer for women who have not gone through HSY or BSO, 5-year cycle starting at 45, 45-49, 50-54,..., 75-79

oc = c(0.000253, 0.000455, 0.000689, 0.00102, 0.0014, 0.0018, 0.0023)

# breast cancer
# mortality rate of breast cancer for referent women

bc = c(0.001, 0.0016, 0.0022, 0.0028, 0.0034, 0.0042, 0.0052)

# lung cancer
# mortality rate of lung cancer for referent women, 1-year rate, then converting to 5-year rate

lc = c(0.85, 2.4, 5.5, 8.8, 13.2, 19.8, 26.6) / 10000
lc = conv(lc)

# colorectal cancer
# mortality rate of colorectal cancer for referent women, 1-year rate, then converting to 5-year rate

cc = c(0.87, 1.42, 2.05, 2.8, 3.9, 4.9, 7.14) / 10000
cc = conv(cc)

# Coronary heart disease (CVD)

chd = c(0.00094, 0.0017, 0.0029, 0.005, 0.0082, 0.014, 0.026)
# Stroke
\[ st = c(0.000496, 0.000732, 0.001063, 0.00168, 0.003, 0.0056, 0.011) \]

# in preliminary calculations we considered hip fracture, but not in the final calculations

# hip fracture
# using parker's data, because no where else would have hip fracture related to death
\[ hf = c(0.012, 0.019, 0.028, 0.267, 0.508, 1.224, 2.108) / 100 \]

# Other
# mortality rate of other causes
\[ ot = c(0.95, 1.34, 2.03, 2.94, 4.39, 5.98, 8.58) / 100 \]

# 7 states: ovarian cancer, coronary heart disease, stroke, breast cancer, Colorectal cancer, Lung Cancer, other, health
# from 45 - 80

# there is in total 7 5-year cycles from 45 to 80
nState = 7

# hip fracture excluded
# lists of vectors of mortality rates attributed to different factors at each cycle.
vc = list()

for(i in 1:nState){
  currentCycle = paste(45 + 5 * (i - 1), 45 + 5 * i, sep = " - ")
  vc[[currentCycle]] = c(oc[i], chd[i], st[i], bc[i], cc[i], lc[i], ot[i])
}

# we do not consider the hip fracture as a risk factor for death
# comment out those codes for records
# hip fracture included
# vc_all = list()
# for(i in 1:nState){
#   currentCycle = paste(45 + 5 * (i - 1), 45 + 5 * i, sep = " - ")
#   vc_all[[currentCycle]] = c(oc[i], chd[i], st[i], bc[i], cc[i], lc[i], hf[i], ot[i])
# }

# base transition matrices for health women, from 45 - 80. 5-year as a cycle

define function getBase(vec){
  n = length(vec)
  tmpM = diag(n + 1)
  tmp = rep(0, n + 1)
  tmp[1:n] = vec
  tmp[n + 1] = 1 - sum(tmp[1:n])
}

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The table below holds information from the base matrix for cohorts at various ages (rows). Each row holds the bottom row of the respective 8 × 8 transition matrix.

```
knitr::kable(mat, digits=3, caption="Eighth rows of base transition matrices, different ages")
```

<table>
<thead>
<tr>
<th>Ovarian cancer</th>
<th>Coronary heart disease</th>
<th>Stroke</th>
<th>Breast cancer</th>
<th>Colorectal cancer</th>
<th>Lung cancer</th>
<th>Others</th>
<th>Alive</th>
</tr>
</thead>
</table>

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We assume that interventions HSY or HSY + BSO affect the base transition matrix $M_i$ through multiplicative factors on death rates. To be more precise, let $\alpha^\tau = (\alpha_1^\tau, \alpha_2^\tau, \cdots, \alpha_7^\tau)$ be a vector of hazard ratios (HRs), where $\alpha_j^\tau$ is the HR for risk-type $j$ comparing women getting HYS alone at age $\tau$ (time of intervention) to a healthy woman. These were derived from the literature and are reported in Tables 1 and 2 (main manuscript). The transition probability matrix from age $t_{i-1}$ to $t_i$ for women who received HSY alone at intervention time $\tau$ is taken to be:

$$
\begin{pmatrix}
1 & 0 & \cdots & 0 \\
0 & 1 & \cdots & 0 \\
0 & \cdots & 1 & \cdots \\
\sum_{j=1}^{7} p_{i}^{j} \alpha_{j}^{\tau} & \sum_{j=1}^{7} p_{i}^{j} \alpha_{j}^{\tau} & 1 - \sum_{j=1}^{7} p_{i}^{j} \alpha_{j}^{\tau}
\end{pmatrix}
$$

Similarly, we introduce $\beta^\tau = (\beta_1^\tau, \cdots, \beta_7^\tau)$, where $\beta_j^\tau$ is the HR comparing women who receive intervention HYS + BSO at age $\tau$ compared to HYS alone at that time. Transition rates in that cohort are taken to be:

$$
\begin{pmatrix}
1 & 0 & \cdots & 0 \\
0 & 1 & \cdots & 0 \\
0 & \cdots & 1 & \cdots \\
\sum_{j=1}^{7} p_{i}^{j} \alpha_{j}^{\tau} \beta_{j}^{\tau} & \sum_{j=1}^{7} p_{i}^{j} \alpha_{j}^{\tau} \beta_{j}^{\tau} & 1 - \sum_{j=1}^{7} p_{i}^{j} \alpha_{j}^{\tau} \beta_{j}^{\tau}
\end{pmatrix}
$$

Hazard rate uncertainty

Literature estimates of hazard rates $\alpha_j^\tau$ and $\beta_j^\tau$, for $j = 1, 2, \cdots, 7$ are accompanied by confidence intervals, which we use to express uncertainty in parameter values for the purpose of our Bayesian analysis.
Here are the specific numerical values of estimated hazards and upper confidence limits.
knitr::kable( format(alpha_mean, digits=3, caption="Literature estimated hazards (alphas) for HYS intervention" ) )

<table>
<thead>
<tr>
<th></th>
<th>before 50 ET</th>
<th>after 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>chd</td>
<td>1.34</td>
<td>1.15</td>
</tr>
<tr>
<td>stroke</td>
<td>1.22</td>
<td>0.80</td>
</tr>
<tr>
<td>breast cancer</td>
<td>0.96</td>
<td>1.01</td>
</tr>
<tr>
<td>ovarian cancer</td>
<td>0.98</td>
<td>0.98</td>
</tr>
<tr>
<td>lung cancer</td>
<td>0.92</td>
<td>0.88</td>
</tr>
<tr>
<td>colorectal cancer</td>
<td>0.84</td>
<td>0.81</td>
</tr>
</tbody>
</table>

knitr::kable( format(alpha_97.5_quantile, digits=3, caption="Upper quantile hazards for HYS intervention" ) )

<table>
<thead>
<tr>
<th></th>
<th>before 50 ET</th>
<th>after 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>chd</td>
<td>1.68</td>
<td>1.56</td>
</tr>
<tr>
<td>stroke</td>
<td>1.67</td>
<td>1.14</td>
</tr>
<tr>
<td>breast cancer</td>
<td>1.19</td>
<td>1.25</td>
</tr>
<tr>
<td>ovarian cancer</td>
<td>1.11</td>
<td>1.11</td>
</tr>
<tr>
<td>lung cancer</td>
<td>1.11</td>
<td>1.07</td>
</tr>
<tr>
<td>colorectal cancer</td>
<td>1.13</td>
<td>1.09</td>
</tr>
</tbody>
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knitr::kable( format(beta_mean, digits=3, caption="Literature estimated hazards (betas) for HYS+BSO intervention" ) )

<table>
<thead>
<tr>
<th></th>
<th>before 50 no ET</th>
<th>before 50 ET</th>
<th>after 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>chd</td>
<td>2.35</td>
<td>0.61</td>
<td>0.78</td>
</tr>
<tr>
<td>stroke</td>
<td>1.35</td>
<td>1.20</td>
<td>1.37</td>
</tr>
<tr>
<td>breast cancer</td>
<td>0.93</td>
<td>0.95</td>
<td>0.77</td>
</tr>
<tr>
<td>ovarian cancer</td>
<td>0.12</td>
<td>0.12</td>
<td>0.12</td>
</tr>
<tr>
<td>lung cancer</td>
<td>1.40</td>
<td>1.08</td>
<td>0.98</td>
</tr>
<tr>
<td>colorectal cancer</td>
<td>0.94</td>
<td>1.08</td>
<td>1.38</td>
</tr>
</tbody>
</table>

knitr::kable( format(beta_97.5_quantile, digits=3, caption="Upper quantile hazards for HYS+BSO intervention" ) )

<table>
<thead>
<tr>
<th></th>
<th>before 50 no ET</th>
<th>before 50 ET</th>
<th>after 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>chd</td>
<td>7.26</td>
<td>1.06</td>
<td>1.46</td>
</tr>
<tr>
<td>stroke</td>
<td>2.33</td>
<td>1.88</td>
<td>3.00</td>
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<tr>
<td>breast cancer</td>
<td>1.67</td>
<td>1.21</td>
<td>1.45</td>
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<td>ovarian cancer</td>
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<td>0.28</td>
</tr>
<tr>
<td>lung cancer</td>
<td>2.92</td>
<td>1.64</td>
<td>1.93</td>
</tr>
<tr>
<td>colorectal cancer</td>
<td>1.96</td>
<td>1.67</td>
<td>2.75</td>
</tr>
</tbody>
</table>
We use these statistics to inform a literature posterior distribution of hazard rates. To so we work on the log scale and treat the estimates and confidence intervals as providing information for the mean and variance of respective normal posterior distributions.

Our approach assumes that underlying hazards for death by various causes may be related to time of surgical intervention, and that any such temporal effect in the time interval 45 - 55 years is continuous, smooth (quadratic) and monotone. The quadratic, monotone interpolation (see next section) does not rely on plugged-in point estimates, but rather uses Monte Carlo to propagate uncertainty in both the quadratic change and the endpoint HRs. We use reported point estimates and confidence intervals to guide the posterior sampling of the endpoint HR's. Because these hazards are nuisance parameters relative to the target age-80 survival probability, we prefer to not make stronger assumptions, such as they stay constant over 45-55, or are a step function with a step at age 50.

Monotone, quadratic interpolation of hazard rate

Literature-reported hazards HR were available over a range, such as before or after age 50. We sought to simulate the intervention effects for times τ over a more refined grid (one-year gaps). This requires HR for interventions at ages 45,46,⋯,55. We take a flexible (quadratic) formulation and assume hazards are monotone as we postpone interventions. For simplicity, we view the available before 50 HR as HR at age 45, and we view HR after 50 as HR at age 55. Taking these two endpoints, we interpolate HRs at other intervention ages using monotone, quadratic interpolation. Let $h_0$ be the HR at age 45 and $h_1$ be the HR at age 55. We map the ages $\tau \in \{45,46,\cdots,55\}$ to $\tau^* \in \{0,0.1,\cdots,1\}$, and consider the interpolated hazard to be $f(\tau^*) = (h_0 - h_1) + h_1$ for endpoint hazards $h_0$ and $h_1$. Quadratic $f$ entails $f(\tau^*) = a(\tau^*)^2 + b\tau^* + c$ and the endpoints constraints $f(0) = 1,f(1) = 0$, thus we have $c = 1$ and $b = -1 - a$. For monotonicity, we restrict $f(\tau^*) < 0$, and thus $2\tau^*a + b < 0$ or equivalently $2\tau^*a - a - 1 = (2\tau^* - 1)a - 1 < 0$ at the range $\tau^*$ from 0 to 1, which gives $-1 < a < 1$. We do not assume that this monotone quadratic function is known; rather we sample uniformly from coefficients $a$ in $[-1,1]$ in the Bayesian computation. The direction of monotonicity (increasing or decreasing) depends on the ranking of simulated HRs at the endpoints 45 and 55.

```r
# monotone, quadratic interpolation of hazard rate
quad = function(start,end){
  a = runif(1,-1,1)
  b = -1 - a
  c = 1

  mean_age_start = 
  mean_age_end =
  t = ((45:55) - 45) / 10

  res = (a*t^2 + b*t + c) * (start - end) + end
  return(res)
}

x = 45:55
tmp = quad(1,0)
plot(x,tmp,type = "l",col = "green",xlab = "intervention time",ylab = "interpolation for hazards")
#abline(1,-1,col = "red",lwd = 2)
for(i in 1:100){
  tmp = quad(1,0)
}
```

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Posterior computations

Above we have specified base transition matrices for a cohort of women evolving over time from age 45. We have also formulated hazards associated with interventions HYS or HYS + BSO when the intervention happens at some year \( \tau \) between 45 and 55. We have formulated log-normal posterior distributions for the hazards, and so these induce posterior distributions for the target quantities of interest, namely overall survival to age 80 or death by a specific cause by that age. Mathematically we could obtain the target quantities by careful matrix multiplications. A simpler-to-code but computationally more intensive approach is via simulation, which we report below. We also found that simulation was quite helpful in preliminary exploratory computations and also diagnostic checks. Below we create a synthetic cohort of \( N=10000 \) women that we propagate by the selected transition rates. To handle uncertainty in the hazards we sample these from literature posteriors \( n_{\text{sim}}=500 \) times.

The simulation procedure is as follows: \( n_{\text{sim}} \) times we sample hazard rates from the literature posterior (log normal, using literature-based moments). For the two interventions (HYS alone (keep ovaries) to HYS + BSO (remove ovaries)) and various intervention times \( \tau \), we construct relevant transition matrices and we simulate cohorts of size \( N \) up to age 80. We thus simulate the posterior distribution (given literature data) of target survival probabilities:

\[
P(\text{survival to age 80}|\text{HYS + BSO at age } \tau)
\]

and

\[
P(\text{survival at age 80}|\text{HYS alone at age } \tau).
\]
We also investigate specific risk factors, e.g.

\[ P(\text{death by stroke before or at age 80}|\text{HYS + BSO at age } \tau) \]

and

\[ P(\text{death by stroke before or at age 80}|\text{HYS alone at age } \tau). \]

Note that the probabilities above are population properties that depend on parameters (e.g. hazard rates) which we know only approximately. By simulating the hazard rates from log-normal, literature-derived posterior distributions, we have induced posterior distributions for the target rates above. We summarize these induced posterior samples in Figure 1 (main manuscript) and we also compare whether one intervention is better than the other at age \( \tau = 50 \).

For code, we design a function simHelper, which wraps the calculations to simulate N women for a random set of hazard rates. It yields a list containing the counts of states along the simulated path for both interventions. We then call the simHelper function nsim=500 times to collect information on the induced posterior distributions.

```r
# Prepare for survival computations:
library("survival")
library("survminer")

## Loading required package: ggplot2
## Loading required package: ggpubr
library("ggplot2")
library("patchwork")

# set the seed
set.seed(312345126)

We have function get HR to fetch the mean and 97.5% quantile of a log-normal hazard ratio posterior for a risk factor.

```r
# function map a risk factor to the row number in alpha and beta matrices
mapRisk = function(risk){
  vec = c("chd","stroke","breast cancer","ovarian cancer","lung cancer", "colorectal canc er")
  index = which(vec == risk)
  if (length(index) > 0){
    return(index)
  }else{
    return(0)
  }
}

# function to return (mean,97.5%quantile) parameters with respect to specified risk, treatment(trt) and status (before 50 / after 50, using ET or not)
# specifically status = 1 => before 50
# status = 2 => after 50

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# status = 3 => before 50 and ET

gethR = function(risk,trt,status){
  if(!(trt %in% c("HYS","BSO"))){
    message("error: unexpected treatment symbol")
    return()
  }
  if(!(status %in% c(1,2,3))){
    message("error: unexpected status symbol")
    return()
  }
  if(trt == "HYS" & status == 3){
    message("error: HYS only has 2 states")
    return()
  }
  if(trt == "HYS"){
    mat_mean = alpha_mean
    mat_upper = alpha_97.5_quantile
    iCol = status
  } else{
    mat_mean = beta_mean
    mat_upper = beta_97.5_quantile
    if(status == 3){
      iCol = 2
    } else if(status == 1){
      iCol = 1
    } else{
      iCol = 3
    }
  }

  index = mapRisk(risk)
  if(index == 0){
    message("error: unexpected risk factor")
    return()
  }

  return(c(mat_mean[index,iCol],mat_upper[index,iCol]))
}

With the parameters fetched by getHR function, we can use sampleHR to random sample hazard ratios with respect to a risk factor.

# get sampled log HR of CVD
# mn: mean of the log normal

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# up: 97.5% quantile
randomHR = function(mn,up){
    return(log(rlnorm(1, mean = log(mn), sd = (log(up) - log(mn)) / 1.96)))
}

sampleHR = function(risk){
    # risk is associated disease causing death

    # intervention time before 50, HYS alone, referent healthy women
    trt = "HYS"
    vec = getHR(risk,trt,1)
    up = vec[2]  ## 97.5% quantile
    mn = vec[1]  ## mean
    start_HYS = randomHR(mn,up)

    # intervention time after 50, HYS alone, referent healthy women
    vec = getHR(risk,trt,2)
    up = vec[2]
    mn = vec[1]
    end_HYS = randomHR(mn,up)

    # before 50, HYS + BSO, referent HYS alone
    trt = "BSO"
    vec = getHR(risk,trt,1)
    up = vec[2]
    mn = vec[1]
    start_BSO_noET = randomHR(mn,up) + start_HYS

    # after 50, HYS + BSO, referent HYS alone
    vec = getHR(risk,trt,2)
    up = vec[2]
    mn = vec[1]
    end_BSO = randomHR(mn,up) + end_HYS

    # before 50, HYS + BSO but using estrogen, referent healthy women
    vec = getHR(risk,trt,3)
    up = vec[2]
    mn = vec[1]
    BSO_ET = randomHR(mn,up)

    res = list()
    # HYS alone
    res$conerved = c(start_HYS,end_HYS)
    # HYS + BSO

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res$removed = c(start_BSO_noET,end_BSO)
# HYS + BSO + ET
res$estrogen = BSO_ET

return(res)

# we do not consider hip fracture here
# get_HR_HF = function(){
#   # HR for hip fracture
#
#   # start_HYS = 0
#   #
#   # end_HYS = 0
#
#   # up = 1.86
#   # mn = 0.91
#   #
#   # start_BSO_noET = randomHR(mn,up)
#   #
#   # up = 2.04
#   # mn = 0.84
#   # end_BSO = randomHR(mn,up)
#   #
#   # ## estrogen
#   # up = 1.43
#   # mn = 0.94
#   # BSO_ET = randomHR(mn,up)
#   #
#   # res = list()
#   #
#   # res$conserved = c(start_HYS,end_HYS)
#   #
#   # res$removed = c(start_BSO_noET,end_BSO)
#   #
#   # res$estrogen = BSO_ET
#   #
#   # return(res)
Below are functions used to run the simulation. They include functions to: (1) return desired transition matrices given the
intervention time and the treatment, (2) simulate cohort given the intervention time and treatment, from user specified
starting age (usually is the intervention time) to age 80, and (3) get proportions of people falling into each category, e.g.
survival, dead by stroke, etc, at age 80.

# simulation related functions

# no for ovariance conserved
# cycle for which cycle(age)
getTran = function( CVD_no, CVD, ST_no, ST, BC_no, BC, OV_no, OV,
                   cc_no, cc, lc_no, lc, cycle, mul = 1){

  i = cycle

  # initial base transition
  # set to ovarian conserverd(OC) or removed(OO)
  OC = base[[i]]
  OO = base[[i]]

  col = ncol(base[[i]])
  OC[col, 1] = OC[col, 1] * OV_no
  OC[col, 2] = OC[col, 2] * CVD_no
  OC[col, 3] = OC[col, 3] * ST_no
  OC[col, 5] = OC[col, 5] * cc_no
  OC[col, 6] = OC[col, 6] * lc_no
  OC[col, 7] = OC[col, 7]

  # multiplicative factor to linear interpolate the different starting time
  # for example, start at 47, then the transition from 47 to 49, mul = 3/5 since we
  # only have 3 out of 5 year cycle
  OC = OC * mul

  # probability continue to survive
  OC[col, col] = 1 - sum(OC[col, 1:(col - 1)])

  # same as above but for ovaries removed
  OO[col, 1] = OO[col, 1] * OV
  OO[col, 2] = OO[col, 2] * CVD
  OO[col, 3] = OO[col, 3] * ST

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```
OC[col, 7] = OC[col, 7]

OO = OO * mul

OC[col, col] = 1 - sum(OC[col, 1:(col - 1)])

return(list(OC, OO))
```

# hip fracture considered
# we do not consider the scenario involving hip fracture
# genTranHf = function(CVD_no,CVD,ST_no,ST,BC_no, BC, OV_no,OV, cc_no,cc,lc_no, lc,hf_no, hf,cycle, mul = 1){
#  
#     i = cycle
#     for (i in 1:5) {
#         OC = base_all[[i]]
#         OO = base_all[[i]]
#         
#         col = ncol(base_all[[i]])
#         OC[col, 1] = OC[col, 1] * OV_no * mul
#         OC[col, 2] = OC[col, 2] * CVD_no * mul
#         OC[col, 3] = OC[col, 3] * ST_no * mul
#         OC[col, 4] = OC[col, 4] * BC_no * mul
#         OC[col, 5] = OC[col, 5] * cc_no * mul
#         OC[col, 6] = OC[col, 6] * lc_no * mul
#         OC[col, 7] = OC[col, 7] * hf_no * mul
#         OC[col, 8] = OC[col, 8] * mul
#         OC[col, col] = 1 - sum(OC[col, 1:(col - 1)])
#         
#         OO[col, 1] = OO[col, 1] * OV * mul
#         OO[col, 2] = OO[col, 2] * CVD * mul
#         OO[col, 3] = OO[col, 3] * ST * mul
#         OO[col, 5] = OO[col, 5] * cc * mul
#         OO[col, 6] = OO[col, 6] * lc * mul
#         OO[col, 7] = OO[col, 7] * hf * mul
#         OO[col, 8] = OO[col, 8] * mul
#         OO[col, col] = 1 - sum(OO[col, 1:(col - 1)])
#         
#     }
#     
#     return(list(OC, OO))
# }
# get transition matrix,
# given intervention time ii and cycle index
simCyc = function(intervention,cycle,hf = F, estro = F, mul = 1){
```
# intervention: integer, 1 - 11 ==> represent intervention time from age 45 to 55
# hf: boolean, indicator for if hip fracture is considered (deprecated)
# estro: boolean, indicator for if estrogen was used
# mul: 1/5, 2/5, 3/5, 4/5, 1 ==> represent linear interpolate 5-year transition probabilities to cover 1 to 5 years range.
# cycle: integer, 1 - 7 ==> represent 45-49,...,75-79

# get hazard ratio of coronary heart disease
# conserved and removed
# before 50 and after 50
res = sampleHR("chd")

HR_CVD_no = quad(res$conserved[1], res$conserved[2])
CVD_no_use = exp(HR_CVD_no[intervention])

# state of using estrogen
# if using estrogen, we only consider comparison of one data point
# that is before 50, no need to interpolate
if (estro == F){
    HR_CVD = quad(res$removed[1], res$removed[2])
    CVD_use = exp(HR_CVD[intervention])
}else{
    CVD_use = exp(res$estrogen)
}

# HR of stroke
res = sampleHR("stroke")

HR_st_no = quad(res$conserved[1], res$conserved[2])
st_no_use = exp(HR_st_no[intervention])

if (estro == F){
    HR_st = quad(res$removed[1], res$removed[2])
    st_use = exp(HR_st[intervention])
}else{
    st_use = exp(res$estrogen)
}

# HR of breast cancer
res = sampleHR("breast cancer")

HR_BC_no = quad(res$conserved[1], res$conserved[2])
bc_no_use = \text{exp}(\text{HR\_BC\_no}[\text{intervention}])

\text{if}(\text{estro} == F)\
\quad \text{HR\_BC} = \text{quad}([\text{res}\_\text{removed}_1], [\text{res}\_\text{removed}_2])
\quad \text{bc\_use} = \text{exp}(\text{HR\_BC}[\text{intervention}])
\text{else}\
\quad \text{bc\_use} = \text{exp}(\text{res}\_\text{estrogen})
\}

\text{res} = \text{sampleHR}(\text{"ovarian cancer"})

\text{HR\_OV\_no} = \text{quad}([\text{res}\_\text{conserved}_1], [\text{res}\_\text{conserved}_2])
\text{ov\_no\_use} = \text{exp}(\text{HR\_OV\_no}[\text{intervention}])

\text{if}(\text{estro} == F)\
\quad \text{HR\_OV} = \text{quad}([\text{res}\_\text{removed}_1], [\text{res}\_\text{removed}_2])
\quad \text{ov\_use} = \text{exp}(\text{HR\_OV}[\text{intervention}])
\text{else}\
\quad \text{ov\_use} = \text{exp}(\text{res}\_\text{estrogen})
\}

\text{res} = \text{sampleHR}(\text{"colorectal cancer"})

\text{HR\_CC\_no} = \text{quad}([\text{res}\_\text{conserved}_1], [\text{res}\_\text{conserved}_2])
\text{cc\_no\_use} = \text{exp}(\text{HR\_CC\_no}[\text{intervention}])

\text{if}(\text{estro} == F)\
\quad \text{HR\_CC} = \text{quad}([\text{res}\_\text{removed}_1], [\text{res}\_\text{removed}_2])
\quad \text{cc\_use} = \text{exp}(\text{HR\_CC}[\text{intervention}])
\text{else}\
\quad \text{cc\_use} = \text{exp}(\text{res}\_\text{estrogen})
\}

\text{res} = \text{sampleHR}(\text{"lung cancer"})

\text{HR\_LC\_no} = \text{quad}([\text{res}\_\text{conserved}_1], [\text{res}\_\text{conserved}_2])
\text{lc\_no\_use} = \text{exp}(\text{HR\_LC\_no}[\text{intervention}])

\text{if}(\text{estro} == F)\
\quad \text{HR\_LC} = \text{quad}([\text{res}\_\text{removed}_1], [\text{res}\_\text{removed}_2])
\quad \text{lc\_use} = \text{exp}(\text{HR\_LC}[\text{intervention}])
\text{else}\
\quad \text{lc\_use} = \text{exp}(\text{res}\_\text{estrogen})
\}
# whether consider hip fracture or not
# deprecated
if(hf){
  #res = get_HR_HF()

  #HR_HF_no = quad(res$conserved[1],res$conserved[2])
  #hf_no_use = exp(HR_HF_no[ii])

  #HR_HF = quad(res$removed[1],res$removed[2])
  #hf_use = exp(HR_HF[ii])

  #tm = genTranHf(CVD_no_use,CVD_use,st_no_use,st_use,
  #                bc_no_use,bc_use,ov_no_use,
  #                ov_use,cc_no_use,cc_use,lc_no_use,lc_use,hf_no_use,hf_use,cycle,mul)
  tm = NULL
}
else{
  tm = getTran(CVD_no_use,CVD_use,st_no_use,st_use,
                bc_no_use,bc_use,ov_no_use,
                ov_use,cc_no_use,cc_use,lc_no_use,lc_use,cycle,mul)
}
return(tm)

# run the simulation and
# return counts of people falling into each states at each cycle
simHelper = function(N,intervention,start = 1,hf = F, estro = F){
  # N: integer, total number of people entered the simulation
  # intervention: integer, 1 - 11 ==> represent intervention time from age 45 to 55
  # start: integer == at what cycle to start

  # mul: 1/5,2/5,3/5,4/5,1 ==> represent linear interpolate 5-year transition probabilities to cover 1 to 5 years range.
  mul = (intervention - 1) %% 5 / 5

  # number of cycle, 45-49, 50 - 54,...,75-79
  Ncycle = 7

  # transition matrices for conserved (OC) and removed (OO)
  OC = list()
  OO = list()

  # end cycle will always be 75-79
  end = Ncycle

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# get transition matrices
for(cycle in 1:Ncycle){
  if(cycle == start){
    # need to consider if interpolating the current 5-year transition matrix
    tm = simCyc(intervention,cycle,hf,estro,mul)
  }else{
    tm = simCyc(intervention,cycle,hf,estro)
  }

  OC[[cycle]] = tm[[1]]
  OO[[cycle]] = tm[[2]]
}

# get probabilities of alive transferring to other states
# bottom row of the transition matrix
prb_OC = list()
prb_OO = list()
col = ncol(OC[[1]])
for (i in 1:Ncycle) {
  prb_OC[[i]] = OC[[i]][col, ]
  prb_OO[[i]] = OO[[i]][col, ]
}

# counts of people falling to different states at each cycle, from start to end
counts_OC = list()
counts_OO = list()

# total people entering the simulation
N1 = N
N2 = N

# start can be set to 1 or 2
# as we consider different starting age between 45 to 55. (overlay with the first two cycles 45-49, 50-54)
for (i in start:end) {
  counts_OC[[i - start + 1]] = rmultinom(1, size = N1, prb_OC[[i]])
  N1 = counts_OC[[i - start + 1]][col]
  counts_OO[[i - start + 1]] = rmultinom(1, size = N2, prb_OO[[i]])
  N2 = counts_OO[[i - start + 1]][col]
}
res = list()
res[[1]] = counts_OC
res[[2]] = counts_OO
return(res)

# get the survival rate at age 80 for both treatment
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simSurvival = function(N,intervention,start = 1,hf = F, estro = F){
    res = simHelper(N,intervention,start,hf,estro)
    n = length(res[[1]][[1]])
    # HYS alone
    tmp1 = res[[1]][[length(res[[1]])]][n] / N
    # HYS + BSO
    tmp2 = res[[2]][[length(res[[2]])]][n] / N
    return(c(tmp1,tmp2))
}

# convert previous counts at each cycle(simHelper)
# to cumulative proportions for a specified state(indexed by J)
sim = function(N,intervention,J,start = 1,hf = F,estro = F){
    res = simHelper(N,intervention,start = start,hf = hf,estro = estro)
    ct_OC = res[[1]]
    ct_OO = res[[2]]
    n_ = length(ct_OC)
    CVD_num = rep(0, length(n_))
    CVD_denom = rep(0, length(n_))
    CVD_num_OO = rep(0, length(n_))
    for (i in 1:n_){
        if(i == 1){
            CVD_num[i] = ct_OC[i][J]
            CVD_num_OO[i] = ct_OO[i][J]
        }else{
            CVD_num[i] = CVD_num[i-1] + ct_OC[i][J]
            CVD_num_OO[i] = CVD_num_OO[i-1] + ct_OO[i][J]
        }
    }
    CVD_denom[n_ - i + 1] = 80 - (i - 1) * 5
    res = list()
    res[[1]] = c(0, CVD_num/N)
    res[[2]] = c(0, CVD_num_OO/N)
    res[[3]] = c(CVD_denom[1] - 5 + (i - 1) %% 5, CVD_denom)
    return(res)
}

# get counts of a specified state (chd, stroke, breast cancer,...) over each cycle
getData = function(res,Name){
    HYS = res[[1]]
    BSO = res[[2]]
    I = which(rownames(HYS[[1]]) == Name)
    vec1 = c()
    vec2 = c()
    for(i in 1:length(HYS)){
        vec1 = c(vec1,HYS[[i]][I])
        vec2 = c(vec2,BSO[[i]][I])
    }
}
Specifically, below is one example of using the simHelper function, which simulate a cohort given the cohort size, intervention time starting age, and the usage of estrogen. It keeps track of how many people falling into each category along the path to age 80 under HYS and HYS + BSO separately.

```r
res = list()
res[[1]] = vec1
res[[2]] = vec2
return(res)
```

# This block of codes is just a demo of one run simulation

```r
N = 10000

# for example, one run of simulation, starting at 45, intervention time is 45, using estrogen when HYS + BSO
intervention = 1
res = simHelper(N, intervention, start = 1, estro = T)
# counts of N people falling into different category along the path
HYS = res[[1]]
BSO = res[[2]]
```

Table 3
Here we consider how to get Bayesian confidence interval for Table 3 (main manuscript). For example, the death rates by stroke by age 80, when the two treatments HYS and HYS + BSO are performed after age 50. We simulate \( n_{sim} = 500 \) paths of the cohort\( (N = 10000) \) for both treatments. Each path of a treatment will give death rate of stroke by age 80. We then pool over them to get mean and quantiles for the confidence interval.

```r
counts = function(simu_res, rf){
    tmp = getData(simu_res, rf)

    if(rf == "Alive"{
        n = length(tmp[[1]])
        trt1 = tmp[[1]][n]
        trt2 = tmp[[2]][n]
    } else{
        trt1 = sum(tmp[[1]])
        trt2 = sum(tmp[[2]])
    }
    cts = c(trt1, trt2)
    return(cts)
}
```

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getBayesianCI = function(START, intervention, hf=F, estro=F, N=10000, nsim=500)
{
  rfs = c("Ovarian cancer", "Coronary heart disease", "Stroke",
           "Breast cancer", "Colorectal cancer", "Lung cancer", "Alive")
  rates = list()
  for(i in 1:7){
    rates[[rfs[i]]] = matrix(0, nrow=nsim, ncol=2)
  }
  for(i in 1:nsim){
    res = simHelper(N, intervention, start = START, hf = hf, estro = estro)
    for(j in 1:7){
      rates[[rfs[j]]][i,] = counts(res, rfs[j]) / N * 100
    }
  }

  M = matrix(0, nrow = length(rfs), ncol = 2)
  UQ = matrix(0, nrow = length(rfs), ncol = 2)
  LQ = matrix(0, nrow = length(rfs), ncol = 2)
  for(i in 1:7){
    tmp = rates[[rfs[i]]]
    M[i,] = colMeans(tmp)
    UQ[i,] = apply(tmp, 2, function(x) quantile(x, 0.975))
    LQ[i,] = apply(tmp, 2, function(x) quantile(x, 0.025))
  }
  toBeRet = list()
  toBeRet["mean"] = M
  toBeRet["upper quantile"] = UQ
  toBeRet["lower quantile"] = LQ
  return(toBeRet)
}

## before 50, HYS + BSO + estrogen
result_estrogen = getBayesianCI(START = 1, intervention = 1, estro = T)

## before 50, treatments: HYS alone, HYS + BSO, HYS + BSO
result_before = getBayesianCI(START = 1, intervention = 1)

## after 50, treatments: HYS alone, HYS + BSO
result_after = getBayesianCI(START = 2, intervention = 11)

tb3 = data.frame("Surgery Time" = c("before 50", "before 50", "before 50", "after 50", "after 50"))
tb3$`Surgery` = c("HYS + BSO", "HYS + BSO", "HYS alone", "HYS + BSO", "HYS alone")
tb3$`Estrogen Use` = c("no", "yes", "no", "no", "no")
**Overall Survival**

<table>
<thead>
<tr>
<th>Time</th>
<th>Estrogen Use</th>
<th>Overall Survival</th>
<th>Cardiovascular Disease</th>
<th>Stroke</th>
<th>Breast Cancer</th>
<th>Ovarian Cancer</th>
<th>Colorectal Cancer</th>
<th>Lung Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>before</td>
<td>HYS + BSO</td>
<td>no</td>
<td>52.8 (40.7, 59.7)</td>
<td>3.1 (2.2, 4.4)</td>
<td>1.5 (1.1, 2)</td>
<td>0.1 (0.0, 1)</td>
<td>0.8 (0.5, 1.1)</td>
<td>4.2 (2.9, 5.9)</td>
</tr>
<tr>
<td>before</td>
<td>HYS + BSO</td>
<td>yes</td>
<td>66.3 (64.7, 67.8)</td>
<td>3.1 (2.2, 4.2)</td>
<td>1.6 (1.4, 1.9)</td>
<td>0.1 (0.0, 1)</td>
<td>1.1 (0.8, 1.4)</td>
<td>3.6 (2.9, 4.5)</td>
</tr>
<tr>
<td>before</td>
<td>HYS alone</td>
<td>no</td>
<td>63.5 (62.2, 64.9)</td>
<td>2.3 (1.9, 3)</td>
<td>1.6 (1.3, 1.9)</td>
<td>0.6 (0.5, 0.8)</td>
<td>0.8 (0.6, 1)</td>
<td>3 (2.6, 3.4)</td>
</tr>
<tr>
<td>after</td>
<td>HYS + BSO</td>
<td>no</td>
<td>66.9 (64.4, 66.9)</td>
<td>2.3 (1.4, 3.8)</td>
<td>1.3 (0.9, 1.8)</td>
<td>0.1 (0.0, 1)</td>
<td>1.1 (0.7, 1.5)</td>
<td>2.9 (2.4, 1)</td>
</tr>
<tr>
<td>after</td>
<td>HYS alone</td>
<td>no</td>
<td>66.4 (65.6, 67.6)</td>
<td>1.5 (1.2, 1.9)</td>
<td>1.6 (1.3, 1.9)</td>
<td>0.6 (0.5, 0.8)</td>
<td>0.7 (0.6, 0.9)</td>
<td>2.8 (2.5, 3.2)</td>
</tr>
</tbody>
</table>

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We also investigate how intervention time affects the outcomes at age 80. We consider the intervention time ranging from 45 to 55. Recall that our transition matrices cover 5 years. If we have a simulated cohort receiving the treatments at age 47, there are only 3 years to 50. To adjust that, we linearly interpolate the transition probabilities of alive to other states from 45 to 50 so that it covers 3 years. Details are in the `simHelper` function.

1-year

Below are the codes to get Figure 2 (main manuscript).

```r
nsim = 500

CVD1 = rep(0,nsim)
CVD2 = rep(0,nsim)
ST1 = rep(0,nsim)
ST2 = rep(0,nsim)
BC1 = rep(0,nsim)
BC2 = rep(0,nsim)
OV1 = rep(0,nsim)
OV2 = rep(0,nsim)
SUV1 = rep(0,nsim)
SUV2 = rep(0,nsim)
CC1 = CC2 = SUV1
LC1 = LC2 = SUV2
#HF1 = HF2 = SUV1

tmp = rep(0,11)
sv1 = sv2 = ch1 = ch2 = st1 = st2 = bc1 = bc2 = ov1 = ov2 = cc1 = cc2 = l1c1 = l1c2 = hf1 = hf2 = tmp

svU1 = svU2 = chU1 = chU2 = stU1 = stU2 = bcU1 = bcU2 = ovU1 = ovU2 = ccU1 = ccU2 = l1cU1 = l1cU2 = hfU1 = hfU2 = tmp

svL1 = svL2 = chL1 = chL2 = stL1 = stL2 = bcL1 = bcL2 = ovL1 = ovL2 = ccL1 = ccL2 = l1cL1 = l1cL2 = hfL1 = hfL2 = tmp

for(ii in 1:11){
    pos = ceiling(ii / 5)

    for(i in 1:nsim){
        tmp = sim(N,ii,2,start = pos)
        ll = length(tmp[[1]])
        CVD1[i] = tmp[[1]][ll]
        CVD2[i] = tmp[[2]][ll]
    }
}
```

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tmp = sim(N, ii, 3, start = pos)
ST1[i] = tmp[[1]][ll]
ST2[i] = tmp[[2]][ll]

tmp = sim(N, ii, 4, start = pos)
BC1[i] = tmp[[1]][ll]
BC2[i] = tmp[[2]][ll]

tmp = sim(N, ii, 1, start = pos)
OV1[i] = tmp[[1]][ll]
OV2[i] = tmp[[2]][ll]

tmp = sim(N, ii, 5, start = pos)
CC1[i] = tmp[[1]][ll]
CC2[i] = tmp[[2]][ll]

tmp = sim(N, ii, 6, start = pos)
LC1[i] = tmp[[1]][ll]
LC2[i] = tmp[[2]][ll]

#if(hf){
  # tmp = sim(N, ii, 7, start = pos)
  # HF1[i] = tmp[[1]][ll]
  # HF2[i] = tmp[[2]][ll]
  #}

tmp = simSurvival(N, ii, start = pos)
SUV1[i] = tmp[1]
SUV2[i] = tmp[2]

}sv1[ii] = mean(SUV1)
sv2[ii] = mean(SUV2)

svU1[ii] = quantile(SUV1, probs = 0.975)
svL1[ii] = quantile(SUV1, probs = 0.025)
svU2[ii] = quantile(SUV2, probs = 0.975)
svL2[ii] = quantile(SUV2, probs = 0.025)

ch1[ii] = mean(CVD1)
ch2[ii] = mean(CVD2)

chU1[ii] = quantile(CVD1, probs = 0.975)
chL1[ii] = quantile(CVD1, probs = 0.025)
chU2[ii] = quantile(CVD2, probs = 0.975)
chL2[ii] = quantile(CVD2, probs = 0.025)
\text{st1}[ii] = \text{mean}(ST1) \\
\text{st2}[ii] = \text{mean}(ST2) \\
\text{stU1}[ii] = \text{quantile}(ST1, \text{probs} = 0.975) \\
\text{stL1}[ii] = \text{quantile}(ST1, \text{probs} = 0.025) \\
\text{stU2}[ii] = \text{quantile}(ST2, \text{probs} = 0.975) \\
\text{stL2}[ii] = \text{quantile}(ST2, \text{probs} = 0.025) \\
\text{bc1}[ii] = \text{mean}(BC1) \\
\text{bc2}[ii] = \text{mean}(BC2) \\
\text{bcU1}[ii] = \text{quantile}(BC1, \text{probs} = 0.975) \\
\text{bcL1}[ii] = \text{quantile}(BC1, \text{probs} = 0.025) \\
\text{bcU2}[ii] = \text{quantile}(BC2, \text{probs} = 0.975) \\
\text{bcL2}[ii] = \text{quantile}(BC2, \text{probs} = 0.025) \\
\text{ov1}[ii] = \text{mean}(OV1) \\
\text{ov2}[ii] = \text{mean}(OV2) \\
\text{ovU1}[ii] = \text{quantile}(OV1, \text{probs} = 0.975) \\
\text{ovL1}[ii] = \text{quantile}(OV1, \text{probs} = 0.025) \\
\text{ovU2}[ii] = \text{quantile}(OV2, \text{probs} = 0.975) \\
\text{ovL2}[ii] = \text{quantile}(OV2, \text{probs} = 0.025) \\
\text{cc1}[ii] = \text{mean}(CC1) \\
\text{cc2}[ii] = \text{mean}(CC2) \\
\text{ccU1}[ii] = \text{quantile}(CC1, \text{probs} = 0.975) \\
\text{ccL1}[ii] = \text{quantile}(CC1, \text{probs} = 0.025) \\
\text{ccU2}[ii] = \text{quantile}(CC2, \text{probs} = 0.975) \\
\text{ccL2}[ii] = \text{quantile}(CC2, \text{probs} = 0.025) \\
\text{lc1}[ii] = \text{mean}(LC1) \\
\text{lc2}[ii] = \text{mean}(LC2) \\
\text{lcU1}[ii] = \text{quantile}(LC1, \text{probs} = 0.975) \\
\text{lcL1}[ii] = \text{quantile}(LC1, \text{probs} = 0.025) \\
\text{lcU2}[ii] = \text{quantile}(LC2, \text{probs} = 0.975) \\
\text{lcL2}[ii] = \text{quantile}(LC2, \text{probs} = 0.025) \\

\# hf1[ii] = \text{mean}(HF1) \\
\# hf2[ii] = \text{mean}(HF2) \\

\# sum(CVD2 > CVD1) / nsim 
}

\text{numc} = 6 \\
\text{L} = \text{c}(\text{svL1}, \text{chL1}, \text{stL1}, \text{bcL1}, \text{ccL1}, \text{lcL1}, \text{svL2}, \text{chL2}, \text{stL2}, \text{bcL2}, \text{ccL2}, \text{lcL2}) \\
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U = c(svU1,chU1,stU1,bcU1,ccU1,lcU1,svU2,chU2,stU2,bcU2,ccU2,lcU2)

#L1 = rep(c("HYS alone L","HYS + BSO L"),each = 11 * numc)
#U1 = rep(c("HYS alone U","HYS + BSO U"),each = 11 * numc)
df = data.frame(val = c(sv1,ch1,st1,bc1,cc1,lc1,sv2,ch2,st2,bc2,cc2,lc2), L = L, U = U ,type = rep(c("HYS alone","HYS + BSO"),each = 11 * numc))

df$typ = as.factor(c(rep(c("survival","death by CVD","death by stroke","death by BC","death by CC","death by LC"),each = 11),
                    rep(c("survival","death by CVD","death by stroke","death by BC","death by CC","death by LC"),each = 11)))

df$age = rep(45:55,2 * numc)

#head(df)
format(df, digits=3)

##         val       L       U      type             typ age
## 1   0.63506 0.62204 0.64696 HYS alone        survival  45
## 2   0.63540 0.62340 0.64726 HYS alone        survival  46
## 3   0.63560 0.62459 0.64686 HYS alone        survival  47
## 4   0.63538 0.62360 0.64625 HYS alone        survival  48
## 5   0.63559 0.62420 0.64800 HYS alone        survival  49
## 6   0.65711 0.64619 0.66850 HYS alone        survival  50
## 7   0.65609 0.64400 0.66726 HYS alone        survival  51
## 8   0.65483 0.64279 0.66761 HYS alone        survival  52
## 9   0.65354 0.64188 0.66551 HYS alone        survival  53
## 10  0.65177 0.63984 0.66485 HYS alone        survival  54
## 11  0.68517 0.67035 0.69826 HYS alone        survival  55
## 12  0.06467 0.05585 0.07461 HYS alone    death by CVD  45
## 13  0.06419 0.05594 0.07200 HYS alone    death by CVD  46
## 14  0.06317 0.05585 0.07190 HYS alone    death by CVD  47
## 15  0.06162 0.05460 0.06946 HYS alone    death by CVD  48
## 16  0.06125 0.05425 0.06865 HYS alone    death by CVD  49
## 17  0.05916 0.05160 0.06681 HYS alone    death by CVD  50
## 18  0.05856 0.05050 0.06660 HYS alone    death by CVD  51
## 19  0.05801 0.04954 0.06556 HYS alone    death by CVD  52
## 20  0.05751 0.04870 0.06785 HYS alone    death by CVD  53
## 21  0.05664 0.04785 0.06586 HYS alone    death by CVD  54
## 22  0.05338 0.04370 0.06415 HYS alone    death by CVD  55
## 23  0.02358 0.01920 0.02865 HYS alone death by stroke  45
## 24  0.02265 0.01820 0.02705 HYS alone death by stroke  46
## 25  0.02189 0.01790 0.02610 HYS alone death by stroke  47
## 26  0.02101 0.01720 0.02510 HYS alone death by stroke  48
## 27  0.02017 0.01655 0.02450 HYS alone death by stroke  49
## 28  0.01874 0.01510 0.02270 HYS alone death by stroke  50
## 29  0.01812 0.01450 0.02200 HYS alone death by stroke  51
## 30  0.01732 0.01340 0.02100 HYS alone death by stroke  52
## 31  0.01673 0.01350 0.02060 HYS alone death by stroke  53
## 32  0.01616 0.01280 0.02025 HYS alone death by stroke  54
## 33  0.01487 0.01165 0.01905 HYS alone death by stroke  55
<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>0.01643</td>
<td>0.01385</td>
<td>0.01930</td>
<td>HYS alone</td>
<td>death by BC</td>
</tr>
<tr>
<td>35</td>
<td>0.01653</td>
<td>0.01380</td>
<td>0.01930</td>
<td>HYS alone</td>
<td>death by BC</td>
</tr>
<tr>
<td>36</td>
<td>0.01677</td>
<td>0.01425</td>
<td>0.01960</td>
<td>HYS alone</td>
<td>death by BC</td>
</tr>
<tr>
<td>37</td>
<td>0.01699</td>
<td>0.01400</td>
<td>0.01990</td>
<td>HYS alone</td>
<td>death by BC</td>
</tr>
<tr>
<td>38</td>
<td>0.01738</td>
<td>0.01480</td>
<td>0.02030</td>
<td>HYS alone</td>
<td>death by BC</td>
</tr>
<tr>
<td>39</td>
<td>0.01549</td>
<td>0.01285</td>
<td>0.01815</td>
<td>HYS alone</td>
<td>death by BC</td>
</tr>
<tr>
<td>40</td>
<td>0.01580</td>
<td>0.01330</td>
<td>0.01850</td>
<td>HYS alone</td>
<td>death by BC</td>
</tr>
<tr>
<td>41</td>
<td>0.01618</td>
<td>0.01355</td>
<td>0.01885</td>
<td>HYS alone</td>
<td>death by BC</td>
</tr>
<tr>
<td>42</td>
<td>0.01656</td>
<td>0.01405</td>
<td>0.01910</td>
<td>HYS alone</td>
<td>death by BC</td>
</tr>
<tr>
<td>43</td>
<td>0.01687</td>
<td>0.01400</td>
<td>0.01980</td>
<td>HYS alone</td>
<td>death by BC</td>
</tr>
<tr>
<td>44</td>
<td>0.01411</td>
<td>0.01160</td>
<td>0.01710</td>
<td>HYS alone</td>
<td>death by BC</td>
</tr>
<tr>
<td>45</td>
<td>0.00815</td>
<td>0.00620</td>
<td>0.00940</td>
<td>HYS alone</td>
<td>death by CC</td>
</tr>
<tr>
<td>46</td>
<td>0.00808</td>
<td>0.00625</td>
<td>0.00950</td>
<td>HYS alone</td>
<td>death by CC</td>
</tr>
<tr>
<td>47</td>
<td>0.00813</td>
<td>0.00620</td>
<td>0.00980</td>
<td>HYS alone</td>
<td>death by CC</td>
</tr>
<tr>
<td>48</td>
<td>0.00812</td>
<td>0.00630</td>
<td>0.01000</td>
<td>HYS alone</td>
<td>death by CC</td>
</tr>
<tr>
<td>49</td>
<td>0.00820</td>
<td>0.00635</td>
<td>0.01000</td>
<td>HYS alone</td>
<td>death by CC</td>
</tr>
<tr>
<td>50</td>
<td>0.00751</td>
<td>0.00580</td>
<td>0.00940</td>
<td>HYS alone</td>
<td>death by CC</td>
</tr>
<tr>
<td>51</td>
<td>0.00759</td>
<td>0.00555</td>
<td>0.00955</td>
<td>HYS alone</td>
<td>death by CC</td>
</tr>
<tr>
<td>52</td>
<td>0.00758</td>
<td>0.00590</td>
<td>0.00950</td>
<td>HYS alone</td>
<td>death by CC</td>
</tr>
<tr>
<td>53</td>
<td>0.00773</td>
<td>0.00600</td>
<td>0.00965</td>
<td>HYS alone</td>
<td>death by CC</td>
</tr>
<tr>
<td>54</td>
<td>0.00782</td>
<td>0.00600</td>
<td>0.00980</td>
<td>HYS alone</td>
<td>death by CC</td>
</tr>
<tr>
<td>55</td>
<td>0.00676</td>
<td>0.00480</td>
<td>0.00880</td>
<td>HYS alone</td>
<td>death by CC</td>
</tr>
<tr>
<td>56</td>
<td>0.02979</td>
<td>0.02550</td>
<td>0.03445</td>
<td>HYS alone</td>
<td>death by LC</td>
</tr>
<tr>
<td>57</td>
<td>0.02973</td>
<td>0.02564</td>
<td>0.03365</td>
<td>HYS alone</td>
<td>death by LC</td>
</tr>
<tr>
<td>58</td>
<td>0.02944</td>
<td>0.02535</td>
<td>0.03325</td>
<td>HYS alone</td>
<td>death by LC</td>
</tr>
<tr>
<td>59</td>
<td>0.02935</td>
<td>0.02550</td>
<td>0.03330</td>
<td>HYS alone</td>
<td>death by LC</td>
</tr>
<tr>
<td>60</td>
<td>0.02916</td>
<td>0.02585</td>
<td>0.03275</td>
<td>HYS alone</td>
<td>death by LC</td>
</tr>
<tr>
<td>61</td>
<td>0.02863</td>
<td>0.02479</td>
<td>0.03260</td>
<td>HYS alone</td>
<td>death by LC</td>
</tr>
<tr>
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<td>survival</td>
</tr>
<tr>
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<tr>
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<td>0.51479</td>
<td>0.62228</td>
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<tr>
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</tr>
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</tr>
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<td>t1</td>
<td>t2</td>
<td>Event</td>
<td>Age</td>
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<td>------</td>
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</tr>
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<td>death by CVD</td>
</tr>
<tr>
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</tr>
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<tr>
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</tr>
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<td>death by stroke</td>
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<tr>
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<td>death by stroke</td>
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<tr>
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<td>death by stroke</td>
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<tr>
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</tr>
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<tr>
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<tr>
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<td>death by BC</td>
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<td>death by BC</td>
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<td>death by CC</td>
</tr>
<tr>
<td>112</td>
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<td>115</td>
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<td>death by LC</td>
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<td>HYS + BSO</td>
<td>death by LC</td>
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<tr>
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<td>0.04341</td>
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</tr>
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</table>
Rush SK, MA X, Newton MA, Rose SL. A revised Markov Model evaluating oophorectomy at the time of benign hysterectomy: age 65 years revisited. Obstet Gynecol 2022;139.

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Figure 2 (main manuscript) describes those mortality rates and survival proportions comparison for the two treatments with intervention time at age 45 to 55.

```r
## reorder levels
foo <- df$typ
typ <- levels(foo)
v <- c(1,2,5,4,3,6)
V <- v[foo]
bar <- reorder(foo, V)
df$typ <- bar

# plot

p = ggplot(data = df, aes(x = age,y=val)) + geom_line(aes(y = val,color = type))+ geom_line(aes(y = U,color = type)) +
geom_line(aes(y = L,color = type)) + geom_point() +
geom_ribbon(data = subset(df,type == "HYS alone"), aes(ymin = L, ymax = U, fill = type), alpha = 0.5) +
geom_ribbon(data = subset(df,type == "HYS + BSO"), aes(ymin = L, ymax = U, fill = type), alpha = 0.5) +
facet_wrap(.~typ,nrow = 4 )
#facet_wrap(.~typ,nrow = 4,scales = "free")

p = p + theme_classic() + labs(x="age at surgery", y = "") + scale_x_continuous(breaks = c(45,50,55))

#p

## to do , use separate y axis scales; 1 for first 4 and another for next 2

part2 <- c( 1:22, 67:88 )
part1 <- setdiff( 1:132, part2)

ptop = ggplot(data = df[part1,], aes(x = age,y=val)) + geom_line(aes(y = val,color = type ))+
geom_line(aes(y = U,color = type)) +
geom_line(aes(y = L,color = type)) + geom_point() +
geom_ribbon(data = subset(df[part1,],type == "HYS alone"), aes(ymin = L, ymax = U, fill = type), alpha = 0.5) +
geom_ribbon(data = subset(df[part1,],type == "HYS + BSO"), aes(ymin = L, ymax = U, fill = type), alpha = 0.5) +
facet_wrap(.~typ,nrow = 2) + ylim(0,.1)
```

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Additional Control Calculations

To assess the effect of using non-significant hazard ratios, we repeated the calculations above but forced hazard ratios to unity if their reported confidence intervals contain unity. (see Control Figure 1)
Control Figure 1: Results of a supporting control computation for comparison analogous to Fig 2 (main), but in which we have removed any factors for which prior work does not establish a nonsignificant hazard ratio.

To assess the effect of using a flexible model of hazard ratio change for interventions between age 45 and 55, we repeated the calculations using a step-function change in hazard ratios, with a step at age 50. (See Figure 3 in main manuscript)