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

Study	Effect Studied	Cohort	Mortality/Morbidity
Cardiovascular focus			
Laughlin-Tommaso, et al. Cardiovascular and metabolic morbidity after hysterectomy with ovarian conservation: a cohort study. Menopause 2017; 25 (5): 483-492[15].	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: Age </=35 -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[24].	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[25].	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[3].	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[13].	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).

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LaCroix, et al. Health Outcomes after Stopping Conjugated Equine Estrogens Among Postmenopausal Women with Prior Hysterectomy: A Randomized control trial. JAMA 2011; 305(13):1305-1314[5].	Primary: CHD and invasive breast cancer Global index of risks incl CHD, invasive breast cancer, stroke, pulmonary embolus, colorectal cancer, hip fracture, death	WHI Estrogen-Alone Trial	Age differences seen in total MI by age group, with those using estrogen having lower risk. Age differences in colorectal cancer incidence by age and due to estrogen use (lower with estrogen use). Global index of risk was lower for younger women using estrogen.
Manson et al. 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[6].	Primary: CHD & breast cancer Global Index: CHD, breast cancer, stroke, pulmonary embolus, colorectal cancer, endometrial cancer, hip fracture, death	Women's Health Initiative	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<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
Parker et al. Long-term Mortality Associated with Oophorectomy compared with Ovarian Conservation in the Nurses' Health Study. Obstetrics & Gynecology 2013; 121(4): 709-716[10].	Death from CHD, stroke, breast cancer, epithelial ovarian cancer, lung cancer, colorectal cancer, total cancer and all cause	Nurses' Health Study participants with prior hysterectomy	None of the p values in the multivariate analysis were significant for risk after hysterectomy comparing +/- BSO, except for breast cancer Breast cancer <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

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			-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 and Disease –specific Mortality Associated with Benign Gynecologic Surgery Performed at Different Ages. Menopause 2014; 21(6): 592-601[16].	Overall and disease specific mortality	52,846 Breast Cancer Detection and Demonstration Project Follow-Up study participants	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 versus conserving ovarian tissue at time of hysterectomy in	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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premenopausal patients with benign disease: study using routine data and data linkage. The British Medical Journal 2017; 356:j372 http://dx.doi.org/10.1136/bng,j372[26].	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			
Press, et al. Breast Cancer Risk and Ovariectomy, Hysterectomy, and Tubal Sterilization in the Women's Contraceptive and Reproductive Experiences Study. American Journal of Epidemiology 2010; 173(1): 38-47[27].	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 eval 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): 27-36[28].	Breast cancer risk	Case control study with phone interview re HRT	HYS+BSO with HRT initiated after age 40 associated with increased breast cancer, but decreased risk if HYS+BSO and hormones before age 40
Robinson et al. Associations of Premenopausal Hysterectomy and Oophorectomy with Breast Cancer Among Black and White Women: The Carolina Breast Cancer Study, 1993-2001. American Journal of Epi 2016; 184(5): 388-399[29].	Breast cancer risk after premenopausal HYS w/ or w/o BSO	Case control study	BSO OR 0.60 HYS w/ BSO OR 0.68
Ovarian Cancer Risk			
Chan et al. Ovarian Cancer Rates After Hysterectomy With and Without Salpingo-oophorectomy. Obstetrics & Gynecology 2014; 123(1):65-72[14].	Ovarian Cancer Rates after HYS with and without BSO	Retrospective Cohort Study of women receiving care in a Kaiser system	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):1097-1103[17].	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)

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Cancer Incidence			
Gaudet et al. Oophorectomy and Hysterectomy and Cancer Incidence in the Cancer Prevention Study-II Nutrition Cohort. Obstetrics & Gynecology 2014: 123(6): 1247-1255[23].	Cancer incidence	Prospective observational	HYS with BSO before 45 27% risk reduction, NNT 333 HYS without BSO before 45 with 20% risk reduction, NNT 450
Reoperation Risk			
Casiano et al. Risk of Oophorectomy after Hysterectomy. Obstetrics & Gynecology 2013; 121(5): 1069-1074[7].	Reoperation after HYS	Rochester Epi Project data retrospective	Incidence of oophorectomy 3.5% at 10-year follow-up, 6.2% at 20-year follow up, 9.2% at 30-year follow up

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 propogating 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 sematics 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 $i = 1,2,\cdots,n$, let M_i be the 8×8 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.

$$\begin{pmatrix} 1 & 0 & \ldots & & 0 \\ 0 & 1 & \ldots & & 0 \\ & & & & \ldots \\ 0 & 0 & \ldots & 1 & 0 \\ p_i^1 & p_i^2 & \ldots & p_i^7 & p_i^8 \end{pmatrix}$$

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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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 $1 - R_1 \approx \exp(-R1)$ 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 breat 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-yea
r rate
lc = c(0.85,2.4,5.5,8.8,13.2,19.8,26.6) / 10000
lc = conv(lc)

# colo 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)
```


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```
# 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 calculatio
ns

# 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 can
cer, 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
# commment 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

getBase = function(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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```
    tmpM[n + 1,] = tmp
    return(tmpM)
}

base = list()
for(i in 1:nState){
    base[[names(vc)[i]]] = getBase(vc[[i]])
    colnames(base[[i]]) = c("Ovarian cancer","Coronary heart disease",
                            "Stroke","Breast cancer","Colorectal cancer","Lung cancer","Ot
hers","Alive")
    rownames(base[[i]]) = colnames(base[[i]])
}

# hip fracture included
# base_all = list()


# for(i in 1:nState){
#     base_all[[names(vc_all)[i]]] = getBase(vc_all[[i]])
#     colnames(base_all[[i]]) = c("Ovarian cancer","Coronary heart disease",
#                             "Stroke","Breast cancer","Colorectal cancer","Lung cancer","
hip fracture","Others","Alive")
#     rownames(base_all[[i]]) = colnames(base_all[[i]])
# }


# a matrix combine the bottom row of the transition matrix over each cycle
# each row represents the probabilities of health women converting to different states.
mat = c()

for(i in 1:nState){
  mat = rbind(mat,base[[i]][8,])
}
rownames(mat) = names(vc)
```

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 a
ges" )
```

Eighth rows of base transition matrices, different ages

	Ovarian cancer	Coronary heart disease	Stroke	Breast cancer	Colorectal cancer	Lung cancer	Others	Alive

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45-50	0.000	0.001	0.000	0.001	0.000	0.000	0.010	0.987
50-55	0.000	0.002	0.001	0.002	0.001	0.001	0.013	0.980
55-60	0.001	0.003	0.001	0.002	0.001	0.003	0.020	0.969
60-65	0.001	0.005	0.002	0.003	0.001	0.004	0.029	0.954
65-70	0.001	0.008	0.003	0.003	0.002	0.007	0.044	0.932
70-75	0.002	0.014	0.006	0.004	0.002	0.010	0.060	0.902
75-80	0.002	0.026	0.011	0.005	0.004	0.013	0.086	0.853

Surgery effects

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 α_j^τ is the HR for risk-type j comparing women getting HYS alone at age τ (time of intervention) to a healthy women. 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 τ is taken to be:

$$\begin{pmatrix} 1 & 0 & \ldots & 0 \\ 0 & 1 & \ldots & 0 \\ & & & \ldots \\ 0 & \ldots & 1 & 0 \\ p_i^1 \alpha_1^\tau & \ldots & p_i^7 \alpha_7^\tau & 1 - \sum_j p_i^j \alpha_j^\tau \end{pmatrix}$$

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

$$\begin{pmatrix} 1 & 0 & \ldots & 0 \\ 0 & 1 & \ldots & 0 \\ & & & \ldots \\ 0 & \ldots & 1 & 0 \\ p_i^1 \alpha_1^\tau \beta_1^\tau & \ldots & p_i^7 \alpha_7^\tau \beta_7^\tau & 1 - \sum_j p_i^j \alpha_j^\tau \beta_j^\tau \\ & & & . \end{pmatrix}$$

Hazard rate uncertainty

Literature estimates of hazard rates α_j^τ and β_j^τ, 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.

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```
# Store values(mean and upper quantile of hazard ratios) from Table 2 in the main manuscr
ipt
# HYS + BSO vs HYS alone

nRiskFactors = 6 # CVD, Stroke, Breast cancer, ovarian cancer, lung cancer, colorectal ca
ncer
nCategory = 3 # before 50 no ET, before 50 ET, after 50

beta_mean = matrix(0,nrow = nRiskFactors,ncol = nCategory)
beta_97.5_quantile = matrix(0,nrow = nRiskFactors,ncol = nCategory)
row_names = c("chd","stroke","breast cancer","ovarian cancer","lung cancer", "colorectal
cancer")
col_names = c("before 50 no ET","before 50 ET","after 50")
rownames(beta_mean) = row_names
colnames(beta_mean) = col_names
rownames(beta_97.5_quantile) = row_names
colnames(beta_97.5_quantile) = col_names
beta_mean[,1] = c(2.35,1.35,.93,.12,1.4,.94)
beta_mean[,2] = c(.61,1.2,.95,.12,1.08,1.08)
beta_mean[,3] = c(0.78,1.37,.77,.12,.98,1.38)

beta_97.5_quantile[,1] = c(7.26,2.33,1.67,.28,2.92,1.96)
beta_97.5_quantile[,2] = c(1.06,1.88,1.21,.28,1.64,1.67)
beta_97.5_quantile[,3] = c(1.46,3,1.45,.28,1.93,2.75)

# matrix (table 3)
nCategory = 2 # before 50, after 50
alpha_mean = matrix(0,nrow = nRiskFactors, ncol = nCategory)
alpha_97.5_quantile = matrix(0,nrow = nRiskFactors, ncol = nCategory)
col_names = c("before 50 ET","after 50")
rownames(alpha_mean) = row_names
rownames(alpha_97.5_quantile) = row_names
colnames(alpha_mean) = col_names
colnames(alpha_97.5_quantile) = col_names

alpha_mean[,1] = c(1.34,1.22,.96,.98,.92,.84)
alpha_mean[,2] = c(1.15,.8,1.01,.98,.88,.81)

alpha_97.5_quantile[,1] = c(1.68,1.67,1.19,1.11,1.11,1.13)
alpha_97.5_quantile[,2] = c(1.56,1.14,1.25,1.11,1.07,1.09)
```

Here are the specific numerical values of estimated hazards and upper confidence limits.

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```
knitr::kable( format(alpha_mean, digits=3, caption="Literature estimated hazards (alphas)
for HYS intervention" ) )
```

	before 50 ET	after 50
chd	1.34	1.15
stroke	1.22	0.80
breast cancer	0.96	1.01
ovarian cancer	0.98	0.98
lung cancer	0.92	0.88
colorectal cancer	0.84	0.81

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

	before 50 ET	after 50
chd	1.68	1.56
stroke	1.67	1.14
breast cancer	1.19	1.25
ovarian cancer	1.11	1.11
lung cancer	1.11	1.07
colorectal cancer	1.13	1.09

```
knitr::kable( format(beta_mean, digits=3, caption="Literature estimated hazards (betas) f
or HYS+BSO intervention" ) )
```

	before 50 no ET	before 50 ET	after 50
chd	2.35	0.61	0.78
stroke	1.35	1.20	1.37
breast cancer	0.93	0.95	0.77
ovarian cancer	0.12	0.12	0.12
lung cancer	1.40	1.08	0.98
colorectal cancer	0.94	1.08	1.38

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

	before 50 no ET	before 50 ET	after 50
chd	7.26	1.06	1.46
stroke	2.33	1.88	3.00
breast cancer	1.67	1.21	1.45
ovarian cancer	0.28	0.28	0.28
lung cancer	2.92	1.64	1.93
colorectal cancer	1.96	1.67	2.75

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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 approximation to interpolate to a 1-year hazards

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 $45,46,\cdots,55$. 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 $f(\tau^*) \times (h_0 - h_1) + h_1$ 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 τ^* 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 descreasing) 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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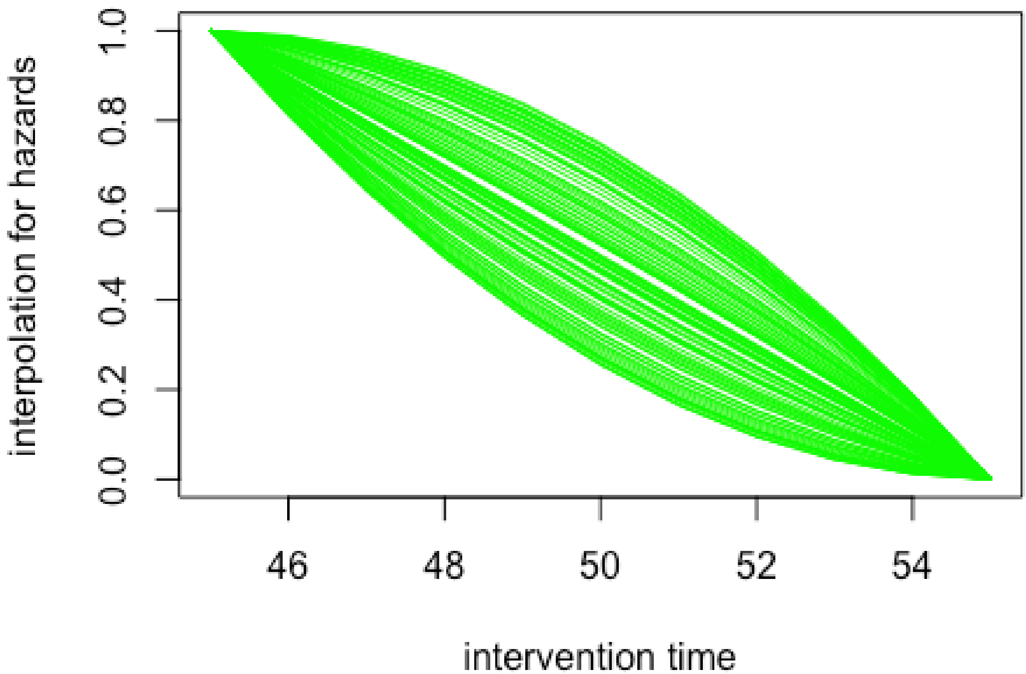
```
    lines(x,tmp,col = "green")
}
```



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 τ 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 propogate by the selected transition rates. To handle uncertainty in the hazards we sample these from literature posteriors nsim=500 times.

The simulation procedure is as follows: nsim 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 τ, 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 probabalities:

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

and

$$P(\text{survival at age 80}|\text{HYS alone at age } \tau).$$

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We also investigate specific risk factors, e.g.

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

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.

```
#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.

```
# 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, trea
tment(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$conserved = 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)
```


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```
#}
```

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, 4] = OC[col, 4] * BC_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
        OO[col, 4] = OO[col, 4] * BC
```


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```
        OO[col, 5] = OO[col, 5] * cc
        OO[col, 6] = OO[col, 6] * lc
        OO[col, 7] = OO[col, 7]

        OO = OO * mul

        OO[col, col] = 1 - sum(OO[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, 4] = OO[col, 4] * BC * 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){
```


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```
    # 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 probabili
ties 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])
```


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```
    bc_no_use = exp(HR_BC_no[intervention])

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



    res= sampleHR("ovarian cancer")

    HR_OV_no = quad(res$conserved[1],res$conserved[2])
    ov_no_use = exp(HR_OV_no[intervention])

    if(estro == F){
        HR_OV = quad(res$removed[1],res$removed[2])
        ov_use = exp(HR_OV[intervention])

    }else{
        ov_use = exp(res$estrogen)
    }

    res= sampleHR("colorectal cancer")

    HR_CC_no = quad(res$conserved[1],res$conserved[2])
    cc_no_use = exp(HR_CC_no[intervention])

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


    res= sampleHR("lung cancer")

    HR_LC_no = quad(res$conserved[1],res$conserved[2])
    lc_no_use = exp(HR_LC_no[intervention])

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


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```
    # 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,m
ul)
        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 probabili
ties 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 tranferring 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 + (ii - 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])
    }
```


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

Specifically, below is one example of using the simHelper funtion, 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.

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

N = 10000

# for example, one run of simulation, starting at 45, intervention time is 45, using estr
ogen 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 $nsim = 500$ 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.

```
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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```r
}
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
    }
  }
  ## mean
  M = matrix(0,nrow = length(rfs),ncol = 2)
  ## 97.5% quantile
  UQ = matrix(0,nrow = length(rfs),ncol = 2)
  ## 2.5% quantile
  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", "a
fter 50"))
tb3$`Surgery` = c("HYS + BSO","HYS + BSO","HYS alone","HYS + BSO","HYS alone")
tb3$`Estrogen Use` = c("no","yes","no","no","no")
```


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```r
buildstring = function(x,i,j,digits=1){
  res = paste0(round(x[['mean']][i,j],digits)," (",round(x[['lower quantile']][i,j],digit
s),",",round(x[['upper quantile']][i,j],digits),")")
  return(res)
}

getBCIforKable = function(i,result_estrogen,result_before,result_after){
  ## use of estrogen
  et = buildstring(result_estrogen,i,2)
  hys_alone_before = buildstring(result_before,i,1)
  hys_bso_before = buildstring(result_before,i,2)
  hys_alone_after = buildstring(result_after,i,1)
  hys_bso_after = buildstring(result_after,i,2)
  res = c(hys_bso_before,et,hys_alone_before,hys_bso_after,hys_alone_after)
  return(res)
}

i = 7
tb3$`Overall Survival` = getBCIforKable(i,result_estrogen,result_before,result_after)
i = 2
tb3$`Cardiovascular Disease` = getBCIforKable(i,result_estrogen,result_before,result_afte
r)
i = 3
tb3$`Stroke` = getBCIforKable(i,result_estrogen,result_before,result_after)
i = 4
tb3$`Breast Cancer` = getBCIforKable(i,result_estrogen,result_before,result_after)
i = 1
tb3$`Ovarian Cancer` = getBCIforKable(i,result_estrogen,result_before,result_after)
i = 5
tb3$`Colorectal Cancer` = getBCIforKable(i,result_estrogen,result_before,result_after)
i = 6
tb3$`Lung Cancer` = getBCIforKable(i,result_estrogen,result_before,result_after)


knitr::kable( format(tb3,caption="Baysian confidence interval, table 3 in the main" ) )
```

Surgery Time	Surgery	Estrogen Use	Overall Survival	Cardiovascular Disease	Stroke	Breast Cancer	Ovarian Cancer	Colorectal Cancer	Lung Cancer
before 50	HYS + BSO	no	52.8 (40.7,59.7)	16.8 (9.4,29.8)	3.1 (2.2,4.4)	1.5 (1.1,2)	0.1 (0,0.1)	0.8 (0.5,1.1)	4.2 (2.9,5.9)
before 50	HYS + BSO	yes	66.3 (64.7,67.8)	3.1 (2.2,4.2)	2.4 (1.8,3)	1.6 (1.4,1.9)	0.1 (0,0.2)	1.1 (0.8,1.4)	3.6 (2.9,4.5)
before 50	HYS alone	no	63.5 (62.2,64.9)	6.5 (5.6,7.4)	2.3 (1.9,3)	1.6 (1.3,1.9)	0.6 (0.5,0.8)	0.8 (0.6,1)	3 (2.6,3.4)
after 50	HYS + BSO	no	66.9 (64.4,69)	4.5 (3,6.5)	2.3 (1.4,3.8)	1.3 (0.9,1.8)	0.1 (0,0.1)	1.1 (0.7,1.5)	2.9 (2,4.1)
after 50	HYS alone	no	66.4 (65,67.6)	5.5 (4.5,6.5)	1.5 (1.2,1.9)	1.6 (1.3,1.9)	0.6 (0.5,0.8)	0.7 (0.6,0.9)	2.8 (2.5,3.2)

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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).

```
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 = lc1 = lc2 = hf1 =
hf2 = tmp

svU1 = svU2 = chU1 = chU2 = stU1 = stU2 = bcU1 = bcU2 = ovU1 = ovU2 = ccU1 = ccU2 = lcU1
= lcU2 = hfU1 = hfU2 = tmp

svL1 = svL2 = chL1 = chL2 = stL1 = stL2 = bcL1 = bcL2 = ovL1 = ovL2 = ccL1 = ccL2 = lcL1
= lcL2 = 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)
```


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```
    st1[ii] = mean(ST1)
    st2[ii] = mean(ST2)

    stU1[ii] = quantile(ST1,probs = 0.975)
    stL1[ii] = quantile(ST1,probs = 0.025)
    stU2[ii] = quantile(ST2,probs = 0.975)
    stL2[ii] = quantile(ST2,probs = 0.025)

    bc1[ii] = mean(BC1)
    bc2[ii] = mean(BC2)

    bcU1[ii] = quantile(BC1,probs = 0.975)
    bcL1[ii] = quantile(BC1,probs = 0.025)
    bcU2[ii] = quantile(BC2,probs = 0.975)
    bcL2[ii] = quantile(BC2,probs = 0.025)

    ov1[ii] = mean(OV1)
    ov2[ii] = mean(OV2)

    ovU1[ii] = quantile(OV1,probs = 0.975)
    ovL1[ii] = quantile(OV1,probs = 0.025)
    ovU2[ii] = quantile(OV2,probs = 0.975)
    ovL2[ii] = quantile(OV2,probs = 0.025)

    cc1[ii] = mean(CC1)
    cc2[ii] = mean(CC2)

    ccU1[ii] = quantile(CC1,probs = 0.975)
    ccL1[ii] = quantile(CC1,probs = 0.025)
    ccU2[ii] = quantile(CC2,probs = 0.975)
    ccL2[ii] = quantile(CC2,probs = 0.025)

    lc1[ii] = mean(LC1)
    lc2[ii] = mean(LC2)

    lcU1[ii] = quantile(LC1,probs = 0.975)
    lcL1[ii] = quantile(LC1,probs = 0.025)
    lcU2[ii] = quantile(LC2,probs = 0.975)
    lcL2[ii] = quantile(LC2,probs = 0.025)

#     hf1[ii] = mean(HF1)
#     hf2[ii] = mean(HF2)

# sum(CVD2 > CVD1) / nsim

}

numc = 6
L = c(svL1,chL1,stL1,bcL1,ccL1,lcL1,svL2,chL2,stL2,bcL2,ccL2,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$typ = as.factor(c(rep(c("survival","death by CVD", "death by stroke","death by BC", "d
eath by CC","death by LC"),each = 11),
                    rep(c("survival","death by CVD", "death by stroke","death by BC","dea
th by CC","death by LC"),each = 11)))
df$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 0.06656 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
```


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```
## 34  0.01643 0.01385 0.01930 HYS alone     death by BC  45
## 35  0.01653 0.01380 0.01930 HYS alone     death by BC  46
## 36  0.01677 0.01425 0.01960 HYS alone     death by BC  47
## 37  0.01699 0.01400 0.01990 HYS alone     death by BC  48
## 38  0.01738 0.01480 0.02030 HYS alone     death by BC  49
## 39  0.01549 0.01285 0.01815 HYS alone     death by BC  50
## 40  0.01580 0.01330 0.01850 HYS alone     death by BC  51
## 41  0.01618 0.01355 0.01885 HYS alone     death by BC  52
## 42  0.01656 0.01405 0.01910 HYS alone     death by BC  53
## 43  0.01687 0.01400 0.01980 HYS alone     death by BC  54
## 44  0.01411 0.01160 0.01710 HYS alone     death by BC  55
## 45  0.00815 0.00620 0.01000 HYS alone     death by CC  45
## 46  0.00808 0.00625 0.01020 HYS alone     death by CC  46
## 47  0.00813 0.00620 0.01000 HYS alone     death by CC  47
## 48  0.00812 0.00630 0.01015 HYS alone     death by CC  48
## 49  0.00820 0.00635 0.01000 HYS alone     death by CC  49
## 50  0.00751 0.00580 0.00940 HYS alone     death by CC  50
## 51  0.00759 0.00555 0.00955 HYS alone     death by CC  51
## 52  0.00758 0.00590 0.00950 HYS alone     death by CC  52
## 53  0.00773 0.00600 0.00965 HYS alone     death by CC  53
## 54  0.00782 0.00600 0.00980 HYS alone     death by CC  54
## 55  0.00676 0.00480 0.00880 HYS alone     death by CC  55
## 56  0.02979 0.02550 0.03445 HYS alone     death by LC  45
## 57  0.02973 0.02564 0.03365 HYS alone     death by LC  46
## 58  0.02944 0.02535 0.03325 HYS alone     death by LC  47
## 59  0.02935 0.02550 0.03330 HYS alone     death by LC  48
## 60  0.02916 0.02585 0.03275 HYS alone     death by LC  49
## 61  0.02863 0.02479 0.03260 HYS alone     death by LC  50
## 62  0.02865 0.02455 0.03235 HYS alone     death by LC  51
## 63  0.02861 0.02490 0.03240 HYS alone     death by LC  52
## 64  0.02865 0.02499 0.03305 HYS alone     death by LC  53
## 65  0.02873 0.02470 0.03275 HYS alone     death by LC  54
## 66  0.02653 0.02270 0.03040 HYS alone     death by LC  55
## 67  0.52818 0.40671 0.60421 HYS + BSO        survival  45
## 68  0.54801 0.46230 0.60467 HYS + BSO        survival  46
## 69  0.56726 0.48981 0.61360 HYS + BSO        survival  47
## 70  0.58062 0.51479 0.62228 HYS + BSO        survival  48
## 71  0.59363 0.53703 0.63020 HYS + BSO        survival  49
## 72  0.62735 0.57508 0.65921 HYS + BSO        survival  50
## 73  0.63603 0.59491 0.66227 HYS + BSO        survival  51
## 74  0.64276 0.60928 0.66856 HYS + BSO        survival  52
## 75  0.64798 0.62265 0.66996 HYS + BSO        survival  53
## 76  0.65312 0.62879 0.67335 HYS + BSO        survival  54
## 77  0.68922 0.66048 0.71121 HYS + BSO        survival  55
## 78  0.16607 0.09459 0.27453 HYS + BSO    death by CVD  45
## 79  0.14627 0.08353 0.24121 HYS + BSO    death by CVD  46
## 80  0.12704 0.08184 0.20496 HYS + BSO    death by CVD  47
## 81  0.11168 0.07204 0.17436 HYS + BSO    death by CVD  48
## 82  0.10018 0.06237 0.15744 HYS + BSO    death by CVD  49
```


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```
## 83  0.08559 0.05433 0.13581 HYS + BSO    death by CVD  50
## 84  0.07676 0.04923 0.11881 HYS + BSO    death by CVD  51
## 85  0.06674 0.04665 0.09192 HYS + BSO    death by CVD  52
## 86  0.05823 0.04099 0.07905 HYS + BSO    death by CVD  53
## 87  0.05130 0.03469 0.06935 HYS + BSO    death by CVD  54
## 88  0.04424 0.02905 0.06510 HYS + BSO    death by CVD  55
## 89  0.03177 0.02169 0.04420 HYS + BSO death by stroke  45
## 90  0.03015 0.02105 0.04280 HYS + BSO death by stroke  46
## 91  0.02927 0.02145 0.03915 HYS + BSO death by stroke  47
## 92  0.02850 0.02130 0.03797 HYS + BSO death by stroke  48
## 93  0.02714 0.02000 0.03575 HYS + BSO death by stroke  49
## 94  0.02615 0.01930 0.03500 HYS + BSO death by stroke  50
## 95  0.02553 0.01810 0.03595 HYS + BSO death by stroke  51
## 96  0.02424 0.01610 0.03511 HYS + BSO death by stroke  52
## 97  0.02354 0.01520 0.03326 HYS + BSO death by stroke  53
## 98  0.02338 0.01459 0.03581 HYS + BSO death by stroke  54
## 99  0.02192 0.01304 0.03585 HYS + BSO death by stroke  55
## 100 0.01536 0.01115 0.02045 HYS + BSO     death by BC  45
## 101 0.01532 0.01130 0.01985 HYS + BSO     death by BC  46
## 102 0.01527 0.01130 0.02005 HYS + BSO     death by BC  47
## 103 0.01518 0.01140 0.01940 HYS + BSO     death by BC  48
## 104 0.01525 0.01145 0.01905 HYS + BSO     death by BC  49
## 105 0.01338 0.00985 0.01730 HYS + BSO     death by BC  50
## 106 0.01347 0.00990 0.01755 HYS + BSO     death by BC  51
## 107 0.01360 0.01010 0.01775 HYS + BSO     death by BC  52
## 108 0.01364 0.01005 0.01765 HYS + BSO     death by BC  53
## 109 0.01381 0.00990 0.01805 HYS + BSO     death by BC  54
## 110 0.01150 0.00750 0.01595 HYS + BSO     death by BC  55
## 111 0.00780 0.00510 0.01140 HYS + BSO     death by CC  45
## 112 0.00811 0.00525 0.01145 HYS + BSO     death by CC  46
## 113 0.00847 0.00600 0.01185 HYS + BSO     death by CC  47
## 114 0.00884 0.00610 0.01220 HYS + BSO     death by CC  48
## 115 0.00905 0.00640 0.01220 HYS + BSO     death by CC  49
## 116 0.00873 0.00600 0.01200 HYS + BSO     death by CC  50
## 117 0.00917 0.00635 0.01240 HYS + BSO     death by CC  51
## 118 0.00964 0.00680 0.01305 HYS + BSO     death by CC  52
## 119 0.01025 0.00680 0.01430 HYS + BSO     death by CC  53
## 120 0.01099 0.00725 0.01546 HYS + BSO     death by CC  54
## 121 0.01014 0.00610 0.01540 HYS + BSO     death by CC  55
## 122 0.04256 0.02944 0.06066 HYS + BSO     death by LC  45
## 123 0.04110 0.02975 0.05605 HYS + BSO     death by LC  46
## 124 0.03916 0.02750 0.05276 HYS + BSO     death by LC  47
## 125 0.03755 0.02790 0.04950 HYS + BSO     death by LC  48
## 126 0.03627 0.02680 0.04825 HYS + BSO     death by LC  49
## 127 0.03469 0.02590 0.04616 HYS + BSO     death by LC  50
## 128 0.03329 0.02429 0.04390 HYS + BSO     death by LC  51
## 129 0.03205 0.02390 0.04130 HYS + BSO     death by LC  52
## 130 0.03175 0.02300 0.04341 HYS + BSO     death by LC  53
```


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```
## 131 0.03045 0.02210 0.03975 HYS + BSO     death by LC  54
## 132 0.02763 0.01845 0.04005 HYS + BSO     death by LC  55
```

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

```
## reorder levels

foo <- df$typ
u <- levels(foo)
v <- c(1,2,5,4,3,6)
V <- v[foo]
bar <- reorder(foo, V)
df$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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```
#ptop = ptop + theme_classic() + labs(x="age at surgery", y = "") + scale_x_continuous(br
eaks = c(45,50,55))
#ptop = ptop + theme_classic() + labs(x="age at surgery", y = "") + scale_x_continuous(br
eaks=NULL)
ptop = ptop + labs(x="", y = "") + scale_x_continuous(breaks=c(45,50,55))


pbot = ggplot(data = df[part2,], 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[part2,],type == "HYS alone"), aes(ymin = L, ymax = U, fill =
type), alpha = 0.5) +
geom_ribbon(data = subset(df[part2,],type == "HYS + BSO"), aes(ymin = L, ymax = U, fill =
type), alpha = 0.5) +
facet_wrap(.~typ,nrow = 1) + ylim(0,.75)


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

ptop/pbot
```


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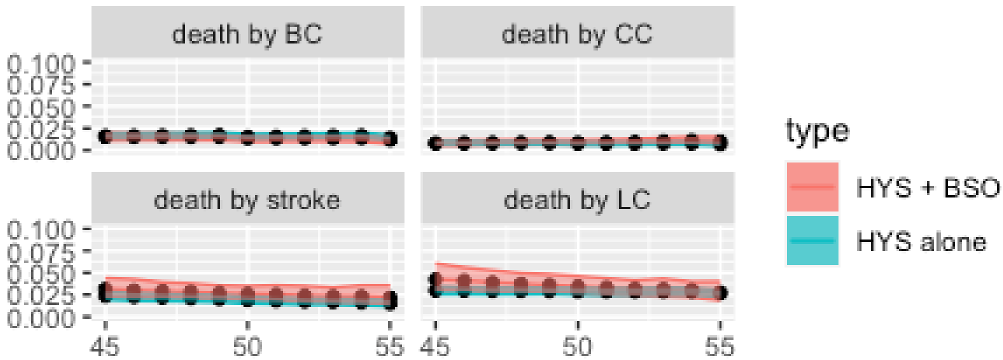

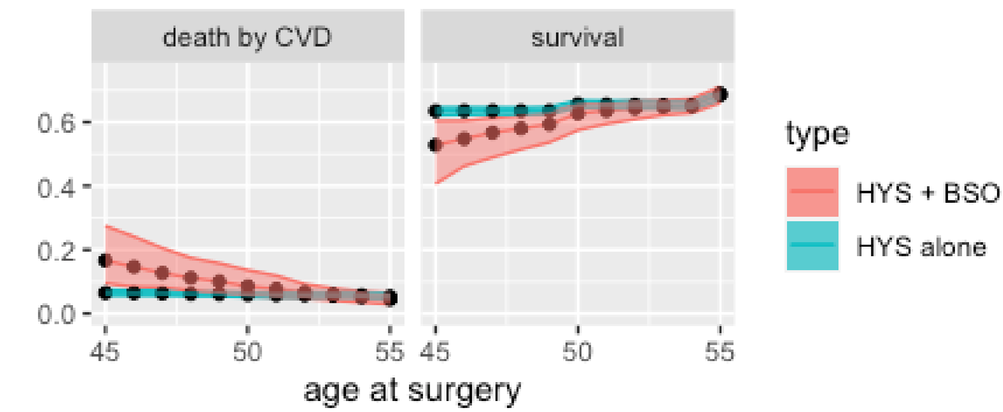


```r
ggsave("band-multi.pdf" )

## Saving 5 x 4 in image
```

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)

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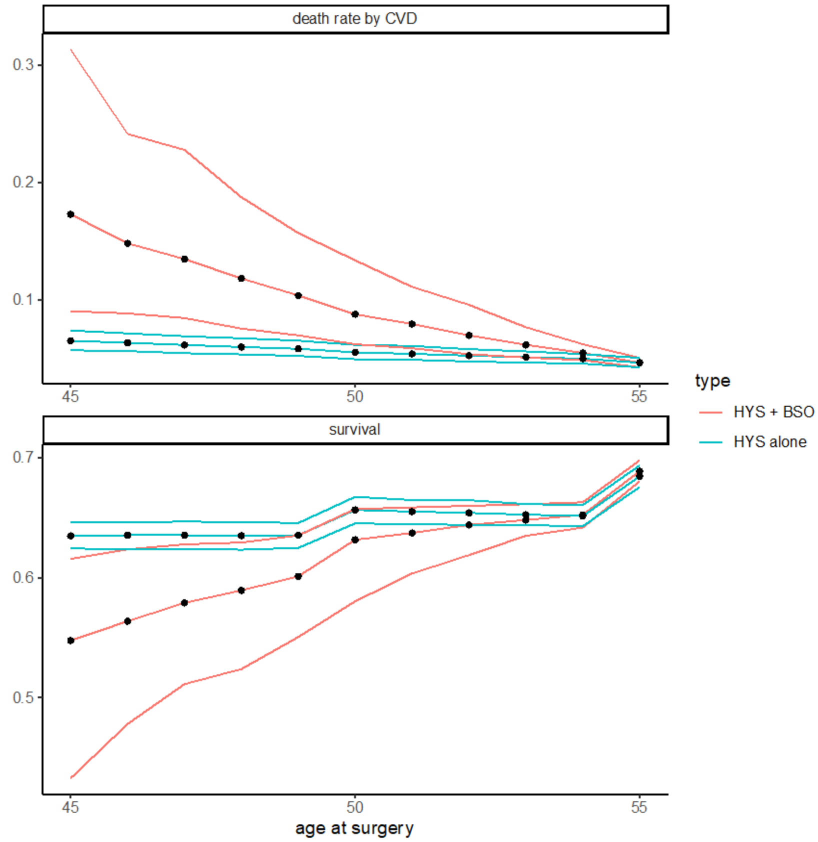

Control Figure 1: Results of a supporting control computation for comparison analogous to Fig 2 (main), but in which we have removed any factors for which prior work does not establish a nonsignificant hazard ratio.

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)

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