**eAppendix 1: R code for the application of the Aalen additive hazards model**

**Step 1 – loading the data set**

We assume that data are saved as comma separated values in a plain text file (named “rsetht.csv”) with column headings in the first row. The data are loaded into the R variable “SIC” by the following command:

SIC <- read.csv ('C:\\...\\rsetht.csv')

**Step 2 – Fitting the Aalen additive hazards model**

The functions required for estimating the Additive hazards model are included in the package “timereg”. Before using the package for the first time it must be installed using the menu Packages -> Install packages. Once installed the package can be loaded by the command :

library(timereg)

The model can now be fitted using the “aalen” function. The name “aalen” refers to a specific version of the additive hazards model, in which all effects are assumed age-dependent, but the R function includes the whole class of Additive hazards models. The output from the function (i.e. the model fit) must be saved to an R variable from which for instance parameter estimates can be extracted. Therefore we fit the model using this command:

fit.HT\_ALC <- aalen(Surv(AGEIN\_Y, AGEOUT\_Y, BRSTC) ~

const(factor(HT\_ALC)) + (factor(EDU)) + (factor(PA)) + (factor(PARI)) + (factor(BMI)) + (factor(SMOKING)) + (factor(COHORT)), data=SIC, start.time=50)

where the first argument to the “Surv”-function is age at entry into the study, the second argument is event time (age at censoring/event), and the third argument indicates event (=1) or censoring (=0). The explanatory variables are listed to the right of the “~” symbol. The wrapper “const” preceding the “HT\_ALC” variable instructs R to estimate an age-invariant effect of that variable, which is analogues to assuming a constant hazards ratio in a Cox model. The effects of the remaining covariates are allowed to vary over time. The wrapper “factor” indicates that the variables are categorical. The argument “start.time=50” indicates that only person-time after the age of 50 should be included in the analysis.

Next, parameter estimates can be extracted by the command:

summary(fit.HT\_ALC)

**eAppendix 2: Cohort specific estimates**

**BMI and hormone therapy use combined**

*Diet, Cancer and Health Study:* Additional breast cancer cases per 100,000 person-years according to BMI and hormone therapy use combined. Adjusted for age, cohort origin, educational level, alcohol consumption, smoking, parity and physical activity

*Copenhagen City Heart Study:* Additional breast cancer cases per 100,000 person-years according to BMI and hormone therapy use combined. Adjusted for age, cohort origin, educational level, alcohol consumption, smoking, parity and physical activity

Alcohol consumption and hormone therapy use combined

*Diet, Cancer and Health Study:* Additional breast cancer cases per 100,000 person-years according to alcohol consump­tion and hormone therapy use combined. Adjusted for age, cohort origin, educational level, BMI, smoking, parity and physical activity

***Copenhagen City Heart Study:*** Additional breast cancer cases per 100,000 person-years according to alcohol consump­tion and hormone therapy use combined. Adjusted for age, cohort origin, educational level, BMI, smoking, parity and physical activity

**eAppendix3: Results from the Cox Proportional Hazards Model**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Combined Effects of Hormone Therapy Use and BMI and Hormone Therapy use and Alcohol Con­sump­tion on Postmenopausal Breast Cancer, the Social Inequality in Cancer Study, Denmark, 1981–2008. | | | | | | | | |
|  | |  | Hazard ratios and 95% CIb | | | | | |
|  | |  | **Hormone therapy** | | | | |  |
|  | |  | **Nonusers**  (n=617) | |  | **Current users**  (n=523) | |  |
| **BMIa** | |  | *HR* | *(95% CI)* |  | *HR* | *(95% CI)* |  |
|  | *Normalweight* |  | 1 | *(reference)* |  | 2.11 | (1.84 to 2.42) |  |
|  | *Overweight* |  | 1.19 | (1.03 to 1.38) |  | 1.72 | (1.45 to 2.05) |  |
|  | *Obese* |  | 1.21 | (1.00 to 1.47) |  | 2.15 | (1.66 to 2.79) |  |
| *Test for interactionc* | |  | *P = 0.004* | | | | |  |
| **Alcohol consumption** | |  |  | |  |  | |  |
|  | *< 1* *drinks/week* |  | 1 | *(reference)* |  | 2.00 | (1.56 to 2.57) |  |
|  | *1*–*6 drinks/week* |  | 1.19 | (0.99 to 1.44) |  | 1.91 | (1.56 to 3.21) |  |
|  | *7+ drinks/week* |  | 1.32 | (1.08 to 1.60) |  | 2.62 | (2.15 to 3.21) |  |
| *Test for interactiond* | |  | *P = 0.11* | | | | |  |

**aDefined as: normalweight** <25 kg/m2; overweight = 25–29.9 kg/m2; obese = 30+ kg/m2.

bAdjusted for age, cohort origin, educational level, parity, BMI (analysis of alcohol consumption), alcohol consumption (analysis of BMI), smoking and physical activity.

c*P* for interaction between hormone therapy use and BMI.

*dP* for interaction between hormone therapy use and alcohol consumption.

All estimates met the proportional hazards assumption.

**eAppendix4: Overview of previous studies on hormone therapy use combined with high BMI and hormone therapy combined with alcohol consumption in relation to postmenopausal breast cancer**

**High BMI and hormone therapy use:**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| *Reference* | *Study size* | *Presented analyses* | *Effect measure* | *Main findings regarding BMI/hormone therapy use interactions (95% CI’s)* |
| Beral (1997)1 | 52,758 cases  108,411 controls | Stratified analyses of duration of HT use according to BMI and *P* for interaction | RR | In current/recent HT users with long durations of use vs. never users:  RR=1.52 (1.36–1.68) for BMI < 25 kg/m2  RR=1.02 (0.81–1.23) for BMI ≥ 25 kg/m2  *P* = 0.001 |
| Magnusson (1999)2 | 3,345 cases  3,454 controls | Stratified analyses of BMI according to HT and *P* for interaction | OR | In current/recent HT users with 1-60 months of use vs. never users:  OR=1.9 (1.3–2.8) for BMI < 22 kg/m2  OR=1.3 (1.1–1.7) for BMI 22–27 kg/m2  OR=1.1 (0.8–1.4) for BMI > 27 kg/m2  *P* = 0.02  Similar findings for longer durations of use |
| Schairer (2000)3 | 46,355 women  (2,082 cases) | Stratified analyses of HT use type according to BMI and *P* for interaction | RR | Increase in RR per year of HT use (vs. never use):  RR=0.03 (0.01–0.03) for BMI < 24.5 kg/m2  RR= -0.01 (-0.02–0.17) for BMI ≥ 24.5 kg/m2  *P* = 0.002 |
| Morimoto (2002)4 | 85,917 women  1,030 cases | Stratified analyses of BMI according to HT and *P* for interaction | RR | Obese women (BMI >31.1) vs. lean (BMI ≤ 22.6):  RR=2.5 (1.6–3.9) in never HT users  RR=1.0 (0.7–1.3) in ever HT users  *P* = 0.001 |
| Ursin (2002)5 | 1,897 cases  1,637 matched controls | Stratified analyses of BMI according to HT use type and *P* for interaction | OR | BMI > 24.56 vs. BMI ≤ 24.56:  OR=1.12 (1.03–1.22) per 5 years use of HT (all types)  OR=1.06 (0.96–1.18) per 5 years use of HT (all types)  *P* = 0.35 |
| Lahmann (2004)6 | 103,344 women (postmeno­pausal)  1,405 cases | Combined effects of HT use and BMI | RR | Combinations of HT/BMI vs. non-HT use/BMI < 25):  *Among nonusers:*  RR=1.28 (1.11–1.48) for BMI 25–29.9  RR=1.28 (1.06–1.54) for BMI ≥30.0  *In HT users:*  RR=2.04 (CI: 1.74–2.39) for BMI <25  RR=1.93 (1.58–2.35) for BMI 25–29.9  RR=1.39 (0.95–2.03) for BMI ≥30.0 |
| Feigelson (2004)7 | 62,756 women  1,934 cases | Stratified analyses of BMI according to HT and *P* for interaction | RR | BMI 30–35 vs. BMI < 22:  RR=1.35 (1.04–1.76) in non-HT users  RR=0.56 (0.40–0.80) in current HT users  *P* < 0.001 |
| Li (2006)8 | 975 cases  1,007 controls | Stratified analyses of BMI according to HT and of HT use type according to BMI (and *P* for interaction) | OR | BMI ≥ 30 vs. BMI < 25:  OR=1.4 (0.9–2.1) in never HT users  OR=1.2 (0.8–1.9) in users of HT unopposed estrogen  OR=0.9 (0.5–1.7) in users of HT EPT  *P* = 0.65 |
| Gertig (2006)9 | 13,444 women  (336 cases) | Stratified analyses of HT use type according to BMI and *P* for interaction | RR | Recent vs. never user of HT:  RR=1.6 (1.1­–2.5) for BMI < 25  RR=1.5 (1.0­–2.4) for BMI 25–29.9  RR=1.4 (0.8­–2.5) for BMI 30+  *P* = 0.96 |
| Modugno (2006)10 | 200 cases and 200 matched controls | Stratified analyses of BMI according to HT | OR | 3rd tertile BMI vs. 1st tertile BMI:  OR=3.3 (1.4-8.4) in non-HT users  OR=1.5 (0.7-3.2) in HT users |
| Wu (2007)11 | 1,277 cases  1,160 controls | Combined effects of HT use and weight adjusted for height  *P* for interaction | OR | Risk of BC (reference group weight <50 kg and non-HT use)  OR=1.4 (0.9-2.2) for weight >61.3  OR=1.1 (0.6-2.1) for EPT use  OR=2.2 (1.1-4.4) for weight >61.3 combined with EPT use  *P* = 0.75 |
| Brinton (2008)12 | 126,638 women  (3,657 cases) | Stratified analyses of HT use type according to BMI  *P* for interaction | RR | User >10 years (EPT) vs. non-user of HT:  RR=2.75 for BMI < 25  RR=1.79 for BMI 25–29.9  RR=1.99 for BMI 30+  *P* = 0.01 |
| Ritte (2012)13 | 144,223 women (postmeno­pausal)  (8,325 cases) | Combined effects of HT use and BMI  *P* for interaction | RR | Risk of ER+/PR+ tumors (reference group BMI < 22.5 and never HT use)  RR=1.75 (*P* < 0.05) for BMI ≥25.9  RR=2.42 (*P* < 0.05) for current HT users  RR=2.39 (*P* < 0.05) for BMI ≥25.9 and HT users  *P* < 0.001 |
| Canchola (2012)14 | 52,642 women  (2,321) | Combined effects of HT use and BMI and *P* for interaction | RR | Risk of ER+/PR+ tumors (reference group BMI < 25 and non-HT use)  RR=1.32 (0.96–1.82) in BMI ≥30  RR=1.92 (1.55–2.38) in EPT hormone users  RR=2.14 (1.59–2.89) in BMI ≥30 and EPT users  *P* = 0.43 |
| White (2012)15 | 82,971  (3,030) | Stratified analyses of BMI according to HT and *P* for interaction | RR | BMI ≥ 30 vs. BMI 20–25:  RR=1.14 (0.97–1.35) in current HT users  RR=1.60 (1.27–2.01) in former HT users  RR=1.60 (1.36–1.87) in never HT users  *P* = 0.0008 |
| John (2013)16 | 1,389 cases  1,644 controls | Restricted to non-HT users | OR | In non-HT users:  OR=0.94 (0.74-1.21) for BMI ≥30 vs. <25 |

Abbreviations: BC, breast cancer; CI, confidence interval; EPT, estrogen/progestin therapy; HT, hormone therapy; OR, odds ratio; RR, relative risk; vs, versus

**Alcohol consumption and hormone therapy use:**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| *Reference* | *Study size* | *Presented analyses* | *Effect measure* | *Main findings regarding alcohol/hormone therapy use interactions (95% CI’s)* |
| Gapstur (1995)17 | 37,105 women  (939) | Combined effects of HT use (ever/never) and alcohol and *P* for interaction | RR | Risk of ER+/PR+ tumors (reference group alcohol = 0 grams per day and never HT use):  RR=1.0 (0.7–1.5) for alcohol ≥4 g/day  RR=1.1 (0.9–1.5) for EPT ever users  RR=1.8 (1.3–2.5) for alcohol ≥4 g/day and EPT ever users  *P* = 0.03 |
| Smith-Warner (1998)18 | 322,647  (4,335 cases) | Stratified analyses of alcohol consumption according to HT use and *P* for interaction | RR | Risk of BC for 10-g/day increment in alcohol intake:  RR=1.09 (1.03–1.14) for never HT users  RR=1.09 (1.00–1.18) for past HT users  RR=1.06 (0.98–1.16) for current HT users  *P* = 0.80 |
| Ursin (2002)5 | 1,897 cases  1,637 matched controls | Stratified analyses of alcohol consumption according to HT use and *P* for interaction | OR | Alcohol consumption < 1/week vs. ≥ 1/week:  OR=1.07 (0.98–1.18) per 5 years use of HT (all types)  OR=1.12 (1.02–1.23) per 5 years use of HT (all types)  *P* = 0.45 |
| Chen (2002)19 | 44,187 women  (1,722 cases) | Combined effects of HT use and alcohol | RR | Risk of BC for combinations of HT use and alcohol consumption (reference group never use of HT and alcohol intake 0 g/day:  RR=1.31 (1.05–1.66) for HT use ≥5 years  RR=1.28 (0.97–1.69) for alcohol ≥ 20 g/day  RR=1.99 (1.41–2.79) for HT use ≥5 years and alcohol ≥ 20 g/day |
| Tjønneland (2003)20 | 23,778 women  (425 cases) | Stratified analyses of alcohol consumption according to HT use and *P* for interaction | RR | Risk of BC for 10-g/day increment in alcohol intake:  RR=1.07 (0.97–1.18) for never HT users  RR=1.20 (1.07–1.36) for past HT users  RR=1.07 (1.00–1.16) for current HT users  *P* = 0.40 |
| Suzuki (2005)21 | 51,847 women  (1,188 cases) | Combined effects of HT use (ever/never) and alcohol and *P* for interaction | RR | Risk of BC for combinations of HT use and alcohol consumption (reference group never use of HT and non-drinkers):  RR=0.90 (0.67–1.22) for ever use of HT  RR=1.31 (0.94–1.81) for alcohol ≥ 10 g/day  RR=1.72 (1.30–2.28) for ever use of HT and alcohol ≥ 10 g/day  *P* = 0.11 |
| Gertig (2006)9 | 13,444 women  (336 cases) | Stratified analyses of HT use type according to alcohol consumption and *P* for interaction | RR | Never vs. recent user of HT:  RR=1.3 (0.9­–2.1) for nondrinker  RR=1.2 (0.7­–1.9) for alcohol <10g/day  RR=2.4 (1.5­–3.9) for alcohol ≥10g/day  *P* = 0.32 |
| Zhang (2007)22 | 38,454 women  (1,484 cases) | Stratified analyses of alcohol consumption according to HT use and *P* for interaction | RR | Risk of BC for 10-g/day increment in alcohol intake:  RR=1.00 (0.86–1.15) for never HT users  RR=0.93 (0.74–1.18) for past HT users  RR=1.15 (1.06–1.26) for current HT users  *P* = 0.09 |
| Nielsen (2008)23 | 5,035 women  (267 cases) | Combined effects of HT use and alcohol and *P* for interaction | RR | Risk of BC for combinations of HT use and alcohol consumption (reference group no current use of HT and non-drinkers)\*:  RR=1.87 for HT use  RR=1.02 for alcohol > 10 drinks/day  RR=4.74 for use of HT and alcohol > 14 drinks/day  *P* = 0.11  (\*95% CI’s not presented in figure) |
| Lew (2009)24 | 184,418 women  (5,461 cases) | Stratified analyses of alcohol consumption according to HT use and *P* for interaction | RR | Alcohol consumption >35 g/day vs. 0 g/day:  RR=1.31 (1.04–1.64) for never users of HT  RR=1.22 (0.73–2.03) for past users of HT  RR=1.40 (1.14–1.71) for current users of HT  *P* = 0.10 |
| Li (2010)25 | 87,724 women  (2,944 cases) | Stratified analyses of alcohol consumption according to HT use | RR | Risk of ER+PR+ ductal carcinomas per drink per day:  RR=1.12 (0.96–1.31) for current users of estrogens  RR =0.97 (0.83–1.14) for current users of EPT  RR =0.97 (0.83–1.14) for current users of EPT  RR =1.06 (0.92–1.21) for never users of HT  RR =1.09 (0.87–1.37) for former users of HT  Risk of ER+PR+ lobular carcinomas per drink per  day:  RR =1.17 (0.96–1.43) for current users of estrogens  RR =1.04 (0.84–1.28) for current users of EPT  RR =1.17 (1.04–1.32) for never users of HT  RR =1.26 (1.02–1.56) for former users of HT |
| Horn-Ross (2012)26 | 40,680 women  (660 cases) | Combined effects of HT use and alcohol and *P* for interaction | RR | Risk of BC for combinations of HT use and alcohol consumption (reference group never use of HT and non-drinkers):  RR=1.34 (0.91–1.97) for current use of HT  RR=1.52 (0.94–2.47) for alcohol ≥ 20 g/day  RR=2.11 (1.41–3.15) for current use of HT and alcohol ≥ 20 g/day  *P* = 0.38 |

Abbreviations: BC, breast cancer; CI, confidence interval; EPT, estrogen/progestin therapy; ER+, estrogen receptor positive; g/day, grams per day; HT, hormone therapy; OR, odds ratio; PR+, progesterone receptor positive; RR, relative risk; vs, versus

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