

## SUPPLEMENTARY MATERIALS

### SUPPLEMENTARY METHODS

#### Model Creation

While our original intention was to create a single unified model for each cardiovascular outcome (heart failure, ischemic heart disease, and stroke), this was not methodologically feasible because prediction at a given age (e.g., 20y) could only use risk factor information available at that age and could not include information that became available afterwards. Therefore, separate models had to be created to predict the risk of each one of our three outcomes of interest by age 50y, based on the information available for individuals from ages 20y to 35y (in 5-year age intervals). Thus, this gave rise to 12 models (i.e., models for each of the 3 outcomes across age 20y, 25y, 30y, and 35y prediction time points).

The following variables were first selected *a priori* for statistical testing in our models: sex, age at diagnosis (5-year increments), and exposure (yes/no) to anthracyclines, alkylating agents, platinum agents, vinca alkaloids, and cranial, neck, chest, and abdominal radiotherapy. Cranial radiotherapy was included *a priori* for the stroke models only. Individuals with missing data relevant to each model were excluded. In developing models, we wanted to quantify the effects of the “time” variable (and absolute rates) which is nonparametrically modeled in Cox regression and therefore only expressible graphically. Thus, we chose to use piecewise exponential models which approximates Cox models. Using piecewise exponential regression adjusted for current age as a cubic spline, models were built to examine the relationships

between these independent variables and the outcomes (heart failure, ischemic heart disease, and stroke; including deaths from these outcomes). If an individual experienced  $>1$  of these 3 outcomes, we counted only their first event. Deaths from other causes were treated as competing risk events. Current age was handled by splitting the records at each age (as an integer) during follow-up. Backwards selection was then used to determine the most influential treatment predictors accounting for sex and age at diagnosis.<sup>1</sup> The least statistically significant variable with  $p \geq 0.05$  (as determined by the likelihood ratio test) was dropped and the reduced model refitted using the same rule until all remaining exposure variables were statistically significant ( $p < 0.05$ ). To estimate the performance of the prediction models, we performed 10-fold internal cross-validation of the variable selection process.<sup>2</sup> This method is identical to what we have published on previously.<sup>3,4</sup> We then added information regarding hypertension, dyslipidemia, and diabetes status at each prediction time point to these models. Based on how the CCSS survey items are collected for these three cardiovascular risk factors, there are no issues with missing data for these three risk factors.

### **Risk Score Creation**

Estimates of the regression coefficients associated with predictors (**Supplementary Table 1**) were then converted to integer risk scores for ease of summing in subsequent risk models (rate ratios  $<1.3$ , 1.3-1.9, 2.0-2.9, 3.0-4.9, and  $\geq 5.0$  corresponding to risk scores 0, 1, 2, 3, and 4, respectively; **Supplementary Table 2**) based on previously published methods.<sup>3,5,6</sup>

### **Risk Score Discriminatory/Predictive Power & Replication**

After randomly selecting half the overall cohort to be the discovery dataset, Cox regression with age as its time scale was used to estimate our risk scores' discriminatory / predictive power.<sup>7</sup> Specifically, we examined the area under the receiver operating characteristic curve (AUC) at age 50y and the concordance (C) statistic through age 50y.<sup>8</sup> The AUC( $t$ ) is the probability that a classifier will rank a randomly chosen case higher than a randomly chosen non-case on a given time  $t$ . C( $t$ ) statistics represents the weighted average of AUC from the study start time to time  $t$ . AUCs and C-statistics (at/through age 50y) for heart failure, ischemic heart disease, and stroke were then estimated for the remaining half of the cohort (i.e., replication dataset) based on the risk scores developed from the discovery dataset (**Supplementary Table 2**).

Given the number of models and the number of events available for each model, risk scores occasionally were not monotonic (i.e., both increasing and decreasing in value) across dose categories or across time points. Therefore, to improve the internal consistency of models for each outcome across time, we allowed risk scores to be adjusted by one point (heart failure, n=14 of 72 scores; ischemic heart disease, n=6 of 40 scores; stroke, n=13 of 81 scores) or rarely by two points (heart failure, n=4; stroke, n=1). To ensure that these changes did not alter the models' discriminatory or predictive power, the AUC and C-statistics were re-estimated in both the discovery and replication cohorts using these revised scores (**Table 3** in the main text).

### **Risk Group Creation**

Although other general population predictors are often based on the sum of individual risk scores,<sup>9-12</sup> given the relatively smaller number of cases we had available, estimates associated with individual risk scores were not always precise. Therefore, we collapsed risk scores into risk

groups predictive of “moderate” and “high” risk of heart failure, ischemic heart disease, or stroke.<sup>5</sup> As the performance of our risk score-based models appeared similar in the discovery and replication datasets, we combined the discovery and replication datasets to determine the most appropriate risk group categories. Specifically, the sum of individual risk scores were examined based on their absolute risks (cumulative incidence at age 50y treating death from other causes as a competing risk event)<sup>13</sup> and rate ratios compared with siblings (piecewise exponential regression, incorporating a generalized estimating equation modification to account for potential within-family correlation).<sup>14</sup> The risk groupings were designed such that each group ideally would be significantly distinct from both siblings as well as from each other per our regression models, and that the cumulative incidence of an event occurring in the high risk group by age 50y would be approximately 10% or greater (Table 4 in the main text).

## **Software**

R (version 3.3.2, R Foundation), specifically the function `risksetROC` (version 1.0.4), was used to calculate the AUC and C statistics. SAS (version 9.3, SAS Institute) was used for the piecewise exponential regression analyses. The codes used are available from the authors upon request.

## **References**

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**SUPPLEMENTARY TABLES**

**Supplementary Table 1.** Multivariable piecewise exponential models (rate ratios, 95% confidence intervals) for covariates associated with each cardiovascular outcome\*

Characteristic	Heart failure, Rate ratio (95%CI)				Ischemic heart disease, Rate ratio (95%CI)				Stroke, Rate ratio (95%CI)			
	Age 20y	Age 25y	Age 30y	Age 35y	Age 20y	Age 25y	Age 30y	Age 35y	Age 20y	Age 25y	Age 30y	Age 35y
Sex												
Male	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.57 (0.92-2.68)	1.60 (1.03-2.51)	1.92 (1.20-3.10)	1.77 (0.98-3.19)	1.05 (0.66-1.69)	1.44 (0.86-2.42)	0.94 (0.55-1.62)	1.93 (0.90-4.16)
Female	1.86 (1.23-2.82)	2.04 (1.29-3.25)	1.42 (0.84-2.40)	1.47 (0.72-3.03)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Age at diagnosis, y												
<5	0.84 (0.44-1.61)	3.73 (1.69-8.25)	3.37 (1.15-9.89)	2.64 (0.31-22.69)	0.56 (0.23-1.36)	0.41 (0.12-1.41)	0.73 (0.17-3.20)	0 (-)	1.89 (1.00-3.55)	2.11 (0.78-5.71)	1.49 (0.50-4.49)	1.09 (0.21-5.74)
5-9	1.44 (0.89-2.31)	2.25 (1.08-4.70)	0.90 (0.31-2.67)	0.50 (0.07-3.90)	1.14 (0.64-2.03)	1.20 (0.64-2.23)	0.89 (0.39-2.03)	0.84 (0.29-2.44)	1.27 (0.73-2.23)	2.25 (1.07-4.75)	1.37 (0.61-3.07)	1.44 (0.48-4.28)
10-14	-- <sup>†</sup>	1.82 (1.05-3.16)	1.28 (0.71-2.33)	1.01 (0.44-2.35)	-- <sup>†</sup>	0.65 (0.37-1.13)	0.74 (0.41-1.34)	0.44 (0.18-1.08)	-- <sup>†</sup>	0.96 (0.47-1.95)	1.24 (0.63-2.41)	0.77 (0.32-1.89)
≥15	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Alkylator	--	--	--	--	--	--	--	--	1.25 (0.63-2.47)	2.01 (0.93-4.34)	1.08 (0.54-2.19)	1.44 (0.53-3.93)
Anthracycline, mg/m <sup>2</sup>												
None	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	--	--	--	--	--	--	--	--
<100	1.09 (0.32-3.77)	2.19 (0.65-7.41)	0.89 (0.12-6.71)	0 (-)	--	--	--	--	--	--	--	--
100-249	3.67 (1.85-7.28)	4.55 (2.22-9.33)	1.71 (0.63-4.62)	2.11 (0.46-9.76)	--	--	--	--	--	--	--	--
≥250	11.54 (6.85-19.45)	8.29 (4.80-14.33)	4.14 (2.20-7.78)	5.02 (2.09-12.06)	--	--	--	--	--	--	--	--
Vinca alkaloid	--	--	--	--	--	--	--	--	0 (-)	0 (-)	0 (-)	1.35 (0.41-

Cranial radiation <sup>‡</sup> , Gy													4.41)
None	--	--	--	--	--	--	--	--	--	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
<20	--	--	--	--	--	--	--	--	--	1.11 (0.37- 3.30)	0.62 (0.14- 2.70)	0.71 (0.21- 2.41)	1.10 (0.24- 5.15)
20-29	--	--	--	--	--	--	--	--	--	1.16 (0.37- 3.30)	1.41 (0.44- 4.50)	1.67 (0.71- 3.92)	4.23 (1.42- 12.64)
30-49	--	--	--	--	--	--	--	--	--	5.42 (2.14- 13.69)	5.22 (1.87- 14.57)	2.17 (0.50- 9.52)	6.06 (1.24- 29.66)
≥50	--	--	--	--	--	--	--	--	--	12.78 (7.15- 22.83)	13.32 (7.14- 24.85)	6.15 (3.04- 12.47 )	6.80 (2.26- 20.48)
Chest radiation, Gy													
None	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
<5	1.36 (0.64-2.85)	1.40 (0.57- 3.43)	1.54 (0.51- 4.64)	0 (-)	1.86 (0.74- 4.67)	0.68 (0.16- 2.96)	1.22 (0.27-5.60)	0 (-)	0.66 (0.20- 2.17)	0.21 (0.03- 1.58)	0 (-)	0 (-)	
5-14	1.43 (0.55-3.70)	3.75 (1.42- 9.87)	1.40 (0.19- 10.61)	0 (-)	1.67 (0.39- 7.22)	2.91 (0.83- 10.18)	4.62 (1.07-19.90)	5.95 (0.61-57.65)	0.65 (0.09- 4.87)	1.05 (0.13- 8.24)	0.82 (0.11- 6.40)	1.20 (0.15- 9.71)	
15-34	2.56 (1.43-4.57)	1.86 (0.89- 3.90)	2.97 (1.34- 6.54)	1.11 (0.23- 5.25)	1.94 (0.88- 4.27)	3.04 (1.48- 6.24)	5.35 (2.31-12.40)	5.94 (1.33-26.59)	0.85 (0.41- 1.77)	0.79 (0.33- 1.91)	0.62 (0.24- 1.59)	0.33 (0.07- 1.45)	
≥35	6.76 (3.89-11.76)	8.71 (4.83- 15.71)	5.81 (2.89- 11.67)	6.30 (2.47- 16.09)	5.86 (3.13- 10.97)	7.42 (4.18- 13.17)	10.07 (5.00-20.28)	19.14 (5.86-62.50)	1.52 (0.85- 2.74)	1.57 (0.86- 2.85)	1.30 (0.68- 2.48)	1.42 (0.60- 3.35)	
Cardiovascular risk factors													
Diabetes	3.78 (0.91-15.73)	2.11 (0.29- 15.41)	0 (-)	3.35 (0.75- 14.95)	4.40 (1.0- 18.9)	6.94 (1.61- 29.96)	2.48 (0.34-18.22)	1.84 (0.23-14.50)	0 (-)	0 (-)	0 (-)	4.63 (1.03- 20.80)	
Dyslipidemia	2.94 (0.67-12.84)	0 (-)	0 (-)	0 (-)	0 (-)	1.49 (0.19- 11.50)	0.68 (0.09-5.00)	1.48 (0.34-6.55)	1.85 (0.43- 7.95)	1.30 (0.17- 9.89)	3.51 (1.20- 10.21)	2.01 (0.55- 7.37)	
Hypertension	5.66 (2.54-12.61)	1.06 (0.26- 4.38)	0.74 (0.18- 3.07)	1.44 (0.33- 6.22)	4.59 (1.59- 13.26)	2.20 (0.78- 6.21)	1.47 (0.53-4.07)	3.56 (1.46-8.68)	1.45 (0.34- 6.19)	0.87 (0.12- 6.47)	4.30 (2.00- 9.26)	1.81 (0.58- 5.63)	

\*Other characteristics assessed but not found to be predictive, and therefore not shown included platinum-based agents, neck radiation, and abdominal radiation. CI -= confidence interval. Abbreviation: Ref, referent group.

†Due to small numbers, diagnosis age 10-14 and ≥15 combined as the referent group.

‡Cranial radiation exposure was only considered for the stroke outcome models.





**Supplementary Table 2.** Original integer risk scores for survivors across 5-year age categories associated with cardiovascular outcomes and corresponding prediction models at/through age 50 years\*

Characteristic	Heart failure				Ischemic heart disease				Stroke			
	Age 20y	Age 25y	Age 30y	Age 35y	Age 20y	Age 25y	Age 30y	Age 35y	Age 20y	Age 25y	Age 30y	Age 35y
Sex												
Male	0	0	0	0	1	1	1	1	0	1 <sup>†</sup>	0	1
Female	1	2 <sup>†</sup>	1	1	0	0	0	0	0	0	0	0
Age at diagnosis, y												
<5	0 <sup>†</sup>	3 <sup>†</sup>	3 <sup>†</sup>	2	--	--	--	--	1	2 <sup>†</sup>	1	0 <sup>†</sup>
5-9	1	2 <sup>†</sup>	0	0	--	--	--	--	0 <sup>†</sup>	2 <sup>†</sup>	1	1
10-14	0	1 <sup>†</sup>	0	0	--	--	--	--	0	0	0	0
≥15	0	0	0	0	--	--	--	--	0	0	0	0
Alkylator									0	2 <sup>†</sup>	0 <sup>†</sup>	1
Anthracycline, mg/m <sup>2</sup>												
None	0	0	0	0	--	--	--	--	--	--	--	--
<100	0	2 <sup>†</sup>	0	0	--	--	--	--	--	--	--	--
100-249	3	3	1 <sup>†</sup>	2	--	--	--	--	--	--	--	--
≥250	4	4	3 <sup>†</sup>	4	--	--	--	--	--	--	--	--
Vinca alkaloid	--	--	--	--	--	--	--	--	0	0	0	1 <sup>†</sup>
Cranial radiation <sup>‡</sup> , Gy												
None	--	--	--	--	--	--	--	--	0	0	0	0
<20	--	--	--	--	--	--	--	--	0	0	0	0
20-29	--	--	--	--	--	--	--	--	0	1	1	3
30-49	--	--	--	--	--	--	--	--	4	4	2 <sup>†</sup>	4
≥50	--	--	--	--	--	--	--	--	4	4	4	4
Chest radiation, Gy												
None	0	0	0	0	0	0	0	0	0	0	0	0
<5	1	1	1	0	1	0	0	0	0	0	0	0
5-14	1	3 <sup>†</sup>	1	0	1	2	3	4	0	0	0	0
15-34	2	1 <sup>†</sup>	2	0 <sup>†</sup>	1	3	4	4	0	0	0	0
≥35	4	4	4	4	4	4	4	4	1	1	1	1
Cardiovascular risk factors												
Diabetes	3	2	0 <sup>†</sup>	3 <sup>†</sup>	3	4 <sup>†</sup>	2	1	0	0	0 <sup>†</sup>	3
Dyslipidemia	2 <sup>†</sup>	0 <sup>†</sup>	0	0	0	1	0 <sup>†</sup>	1	1	1	3 <sup>†</sup>	2
Hypertension	4 <sup>†</sup>	0 <sup>†</sup>	0 <sup>†</sup>	1	3 <sup>†</sup>	2	1 <sup>†</sup>	3 <sup>†</sup>	1	0 <sup>†</sup>	3 <sup>†</sup>	1 <sup>†</sup>

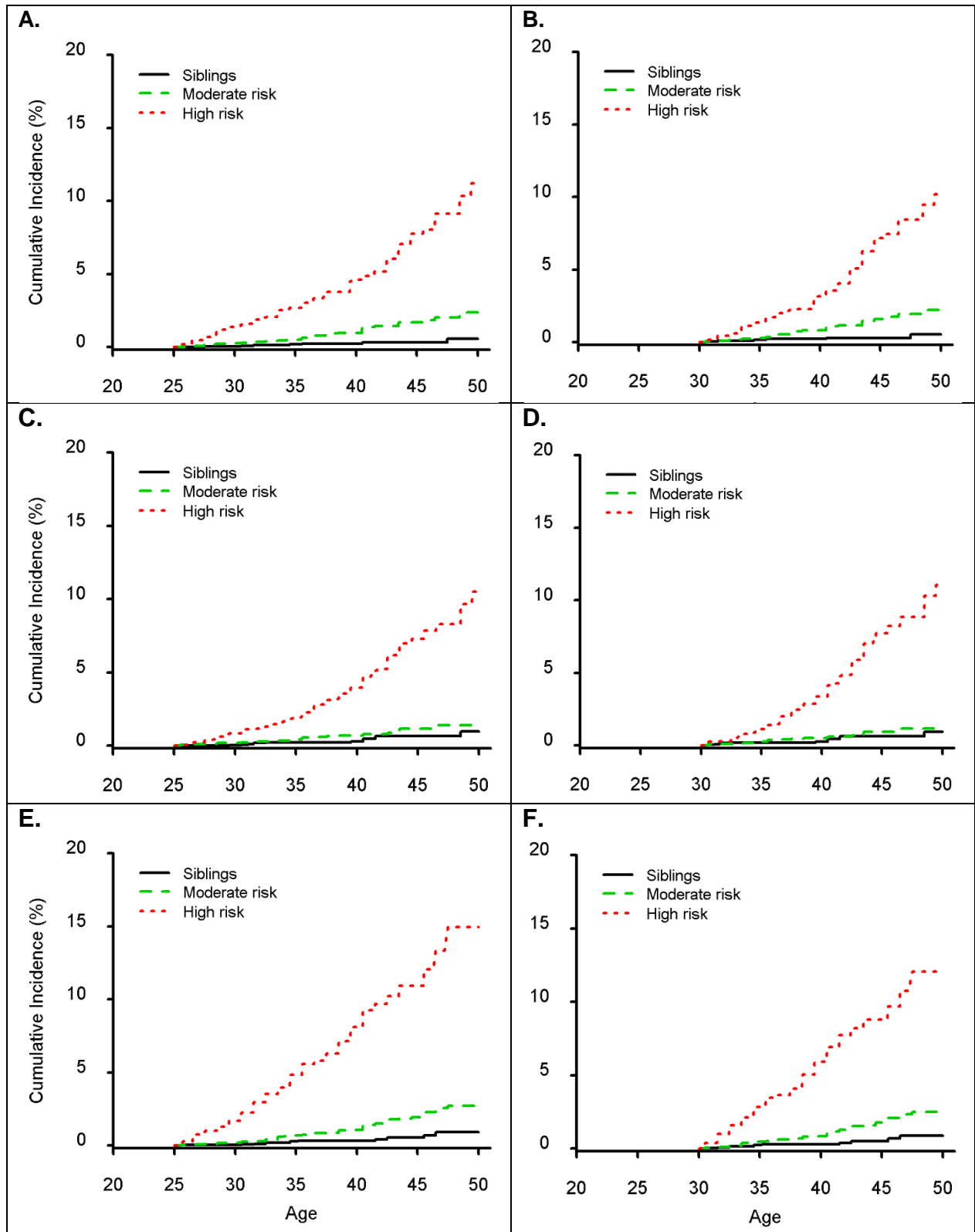
Discovery cohort												
AUC, age 50y	0.75	0.72	0.64	0.68	0.69	0.71	0.71	0.73	0.70	0.68	0.58	0.59
C-statistic, age 50y	0.76	0.73	0.65	0.69	0.68	0.72	0.73	0.74	0.73	0.71	0.61	0.61
Replication cohort												
AUC, age 50y	0.74	0.70	0.70	0.65	0.69	0.70	0.72	0.70	0.73	0.61	0.61	0.70
C-statistic, age 50y	0.76	0.71	0.74	0.66	0.68	0.72	0.74	0.72	0.74	0.64	0.68	0.72

\*Risk scores 0, 1, 2, 3, and 4, correspond to rate ratios (see Supplementary Table 1) <1.3, 1.3-1.9, 2.0-2.9, 3.0-4.9, and  $\geq$ 5.0, respectively. Abbreviations: –, characteristic not applicable to a given model; AUC, area under the receiver operating characteristic curve; C, concordance.

†Risk scores that were subsequently adjusted to improve models' internal consistency, either across age time points and/or dose categories.

‡Cranial radiation exposure was only considered for the stroke outcome models.

## SUPPLEMENTARY FIGURE



**Supplementary Figure 1. Cumulative incidence of cardiovascular outcomes stratified by prediction risk status.** Incidence curves for heart failure (A, B), ischemic heart disease (C, D), and stroke (E, F) among participants age 25y (left column; 13,362 survivors and 3,796 siblings) and age 30y (right column; 8,980 survivors and 2,923 siblings) at time of prediction.