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Risk modeling for Breast-Specific outcomes, CVD risk, and overall mortality in Alliance Clinical Trials of Breast Cancer

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Many of the factors that increase a person's risk of first cancers also increase a person's risk of second cancers and overall morality, but most models used at time of diagnosis do not incorporate these factors

Summary of Prediction Models used to calculate Age-specific Absolute BC Risk

Model	Family History	Mutations	Polygenes	Risk Factors
Claus	Multigenerational	No	No	No
Gail/BCRAT	**First-Degree**	**No**	**No**	**Yes**
BRCAPRO	**Multigenerational**	***BRCA1/2***	**No**	**No**
IBIS	**Multigenerational**	***BRCA1/2***	**No**	**Yes**
BOADICEA	Multigenerational	*BRCA1/2*	Yes	No

Model Performance

Calibration (Accuracy)

Reflects how well the model predictions agree with outcome prevalences within subgroups of the population.

Measurement: Hosmer-Lemeshow goodness of fit statistics

Discrimination (Precision)

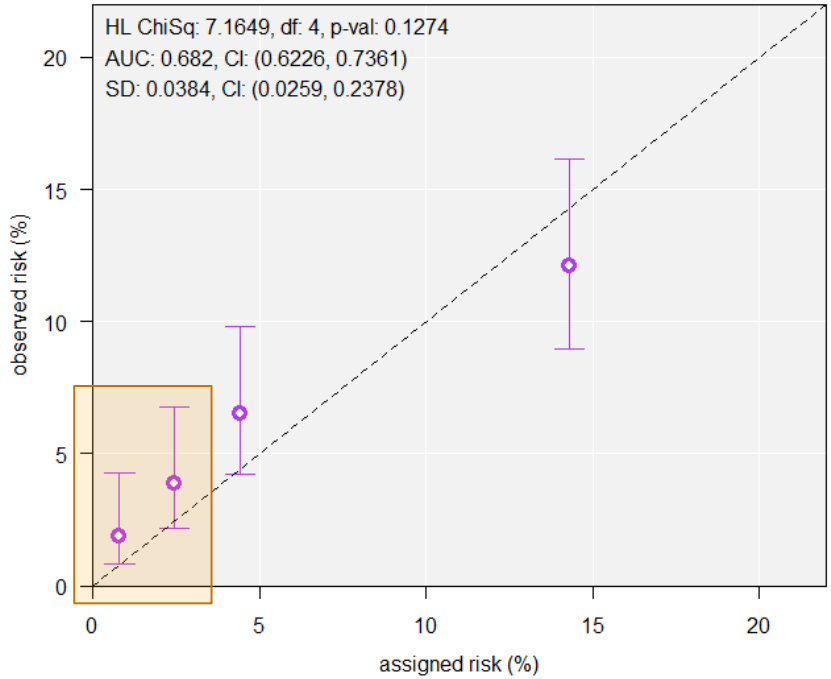
Reflects ability to discriminate those with different true risks

Measurement: Concordance (also called the C-statistic or area under the received operating characteristic (ROC) curve (AUC)),

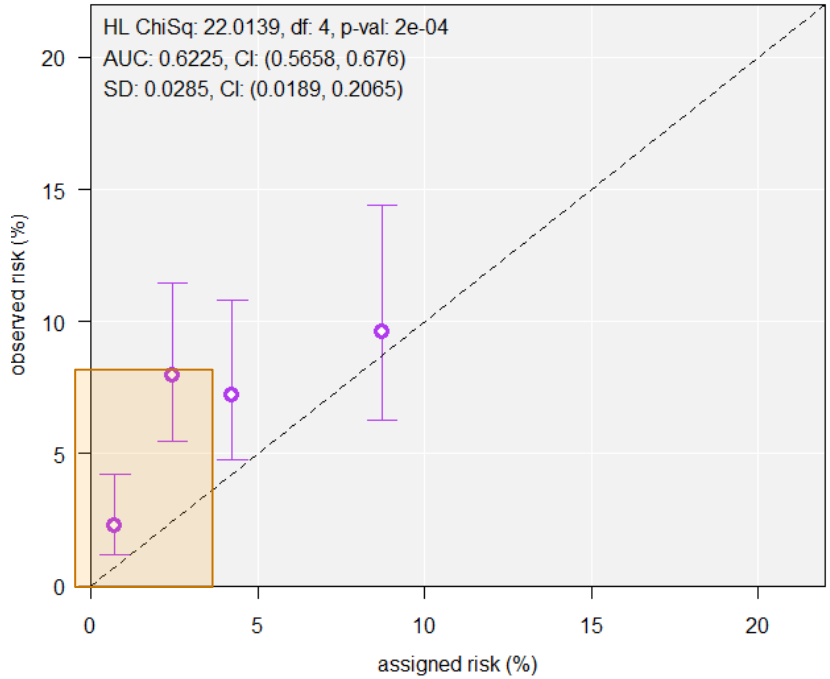
case risk percentiles, net reclassification index

Model with Pedigree Data (IBIS) Performed Better Even in Average Risk Women

The IBIS model



The Gail/BCRAT model



IBIS mean 10 year risk = 5.59%, BCRAT mean 10 year risk 3.18%
Range of difference in 10 year risk (0.001-79.5%)

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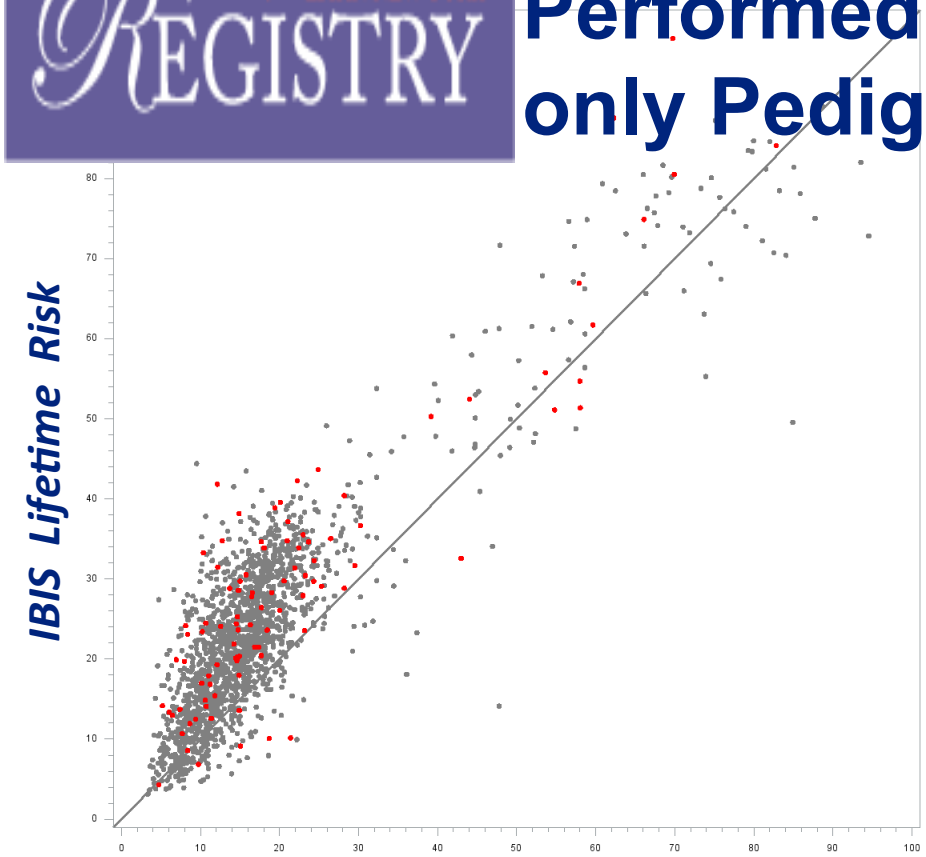
Quante AS, Whittemore AS, Shriver T, Strauch K, Terry MB
Breast Cancer Research 2012

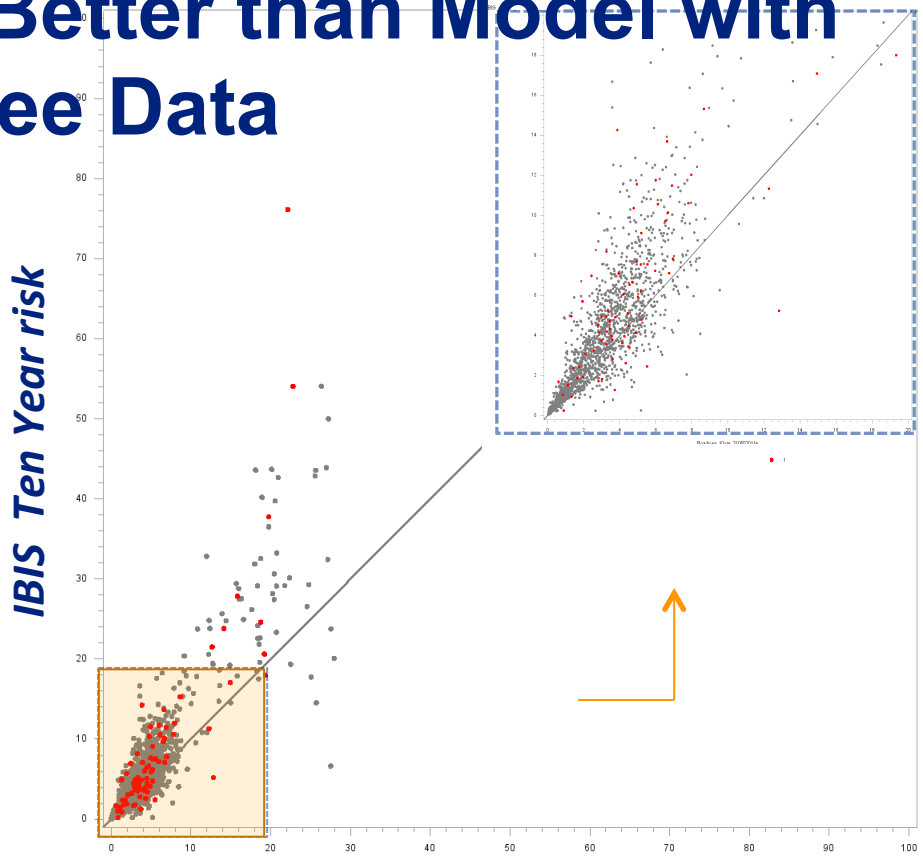
Summary of Breast Cancer Risk Assessment Models

Model	Family History	Mutations	Polygenes	Risk Factors
Claus	Multigenerational	No	No	No
Gail/BCRAT	**First-Degree**	**No**	**No**	**Yes**
BRCAPRO	**Multigenerational**	***BRCA1/2***	**No**	**No**
IBIS	**Multigenerational**	***BRCA1/2***	**No**	**Yes**
BOADICEA	Multigenerational	*BRCA1/2*	Yes	No

Model with Non-Genetic (IBIS) Performed Better than Model with only Pedigree Data

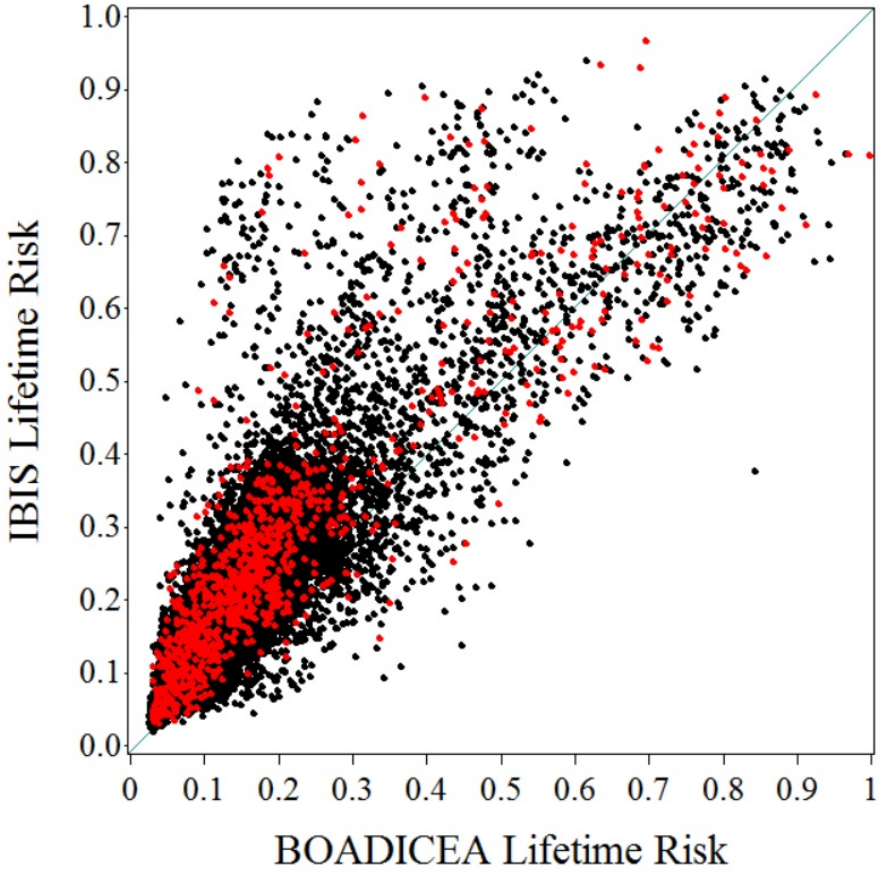


BOADICEA Lifetime Risk



BOADICEA Ten Year Risk

Quante AS, Whittemore AS, Shriver T, Hopper JL, Strauch K, Terry MB. J Natl Cancer Inst. 2015


IBIS Lifetime Risk
BOADICEA Lifetime Risk
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
0
0.1
0.2
0.3
0.4
0.5
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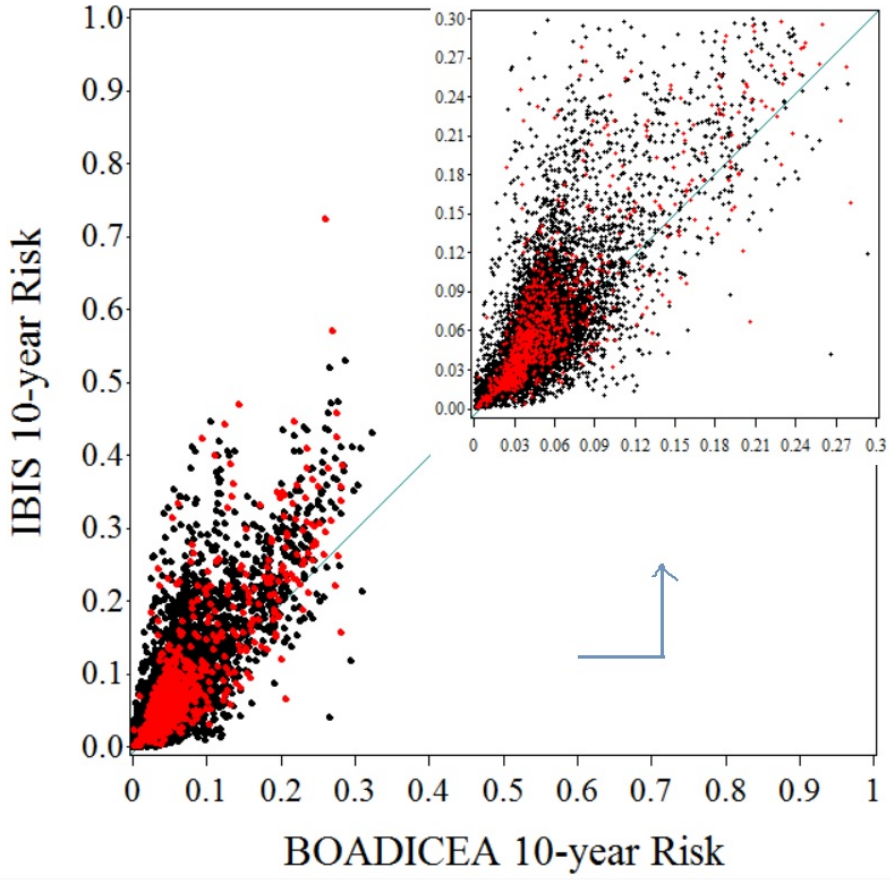
0.9
1


IBIS 10-year Risk
BOADICEA 10-year Risk
0.0
0.1
0.2
0.3
0.4
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0.03
0.06
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0.12
0.15
0.18
0.21
0.24
0.27
0.3

Accuracy and discrimination both important – different metrics

Useful to compare these metrics across subgroups

Aim 1. To assess the improvement in terms of discrimination and calibration from the addition of modifiable risk factors (e.g. physical activity, body mass index, and reproductive factors) on recurrence and contralateral breast outcomes in individuals with breast cancer compared with standard molecular and clinical markers. Examine whether the improvement in discrimination and calibration differs by race and ethnicity.

Aim 2. To assess whether the discrimination and calibration differ between a risk model that incorporates detailed treatment data along with molecular markers and clinical data versus a smaller model that just incorporates molecular markers and clinical data. Examine whether there are differences in discrimination and calibration from the removal of treatment data by race and ethnicity.

Aim 3: To assess the discrimination and calibration from standard models of cardiovascular disease risk in women diagnosed with breast cancer. Examine whether the discrimination differ by race and ethnicity.

CVD models

Framingham Heart Study

began in 1948, ages 28 - 62, healthy at baseline

Endpoints: stroke, myocardial infarction (MI), coronary heart disease, atherosclerosis, and congestive heart failure.

Risk factors: age, gender, systolic blood pressure, cholesterol (HDL and total), cigarette smoking, diabetes

Systematic Coronary Risk Evaluation (SCORE) Model European population, cardiovascular mortality only, 45-64 Weibull proportional hazards model, 10 year risk

SCOREOP (Older Persons): 65+, Cox PH, 5 and 10 yr

Coronary Risk in Elderly (CORE) Model: U.S. cohort, ages 65+, Fine and Gray model

Breast Cancer Models

Created to aid clinicians and patients in making informed decisions about treatment options.

Nottingham Prognostic Index (NPI) (1982) Adjuvant! Online (2001)

Kattan Nomogram (2004)

Oxford/Options Model (2010)

PREDICT Model (2010, 2012)

CancerMath (2011)

Poor performance for <35 or >75 years old

Choice of statistical method is very variable across models. Endpoints: recurrence, disease specific survival, overall survival Some account for competing deaths from other causes.

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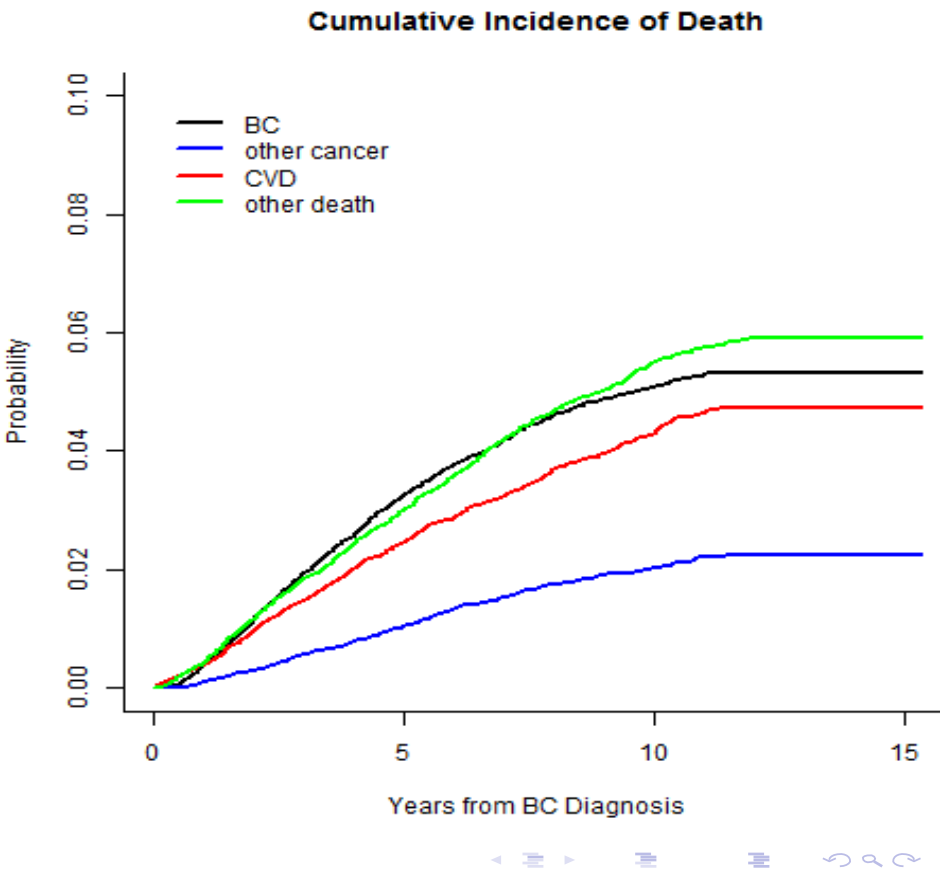
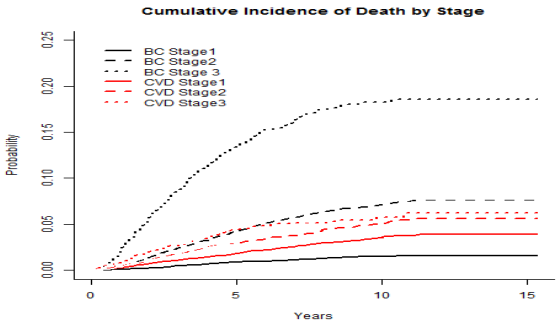
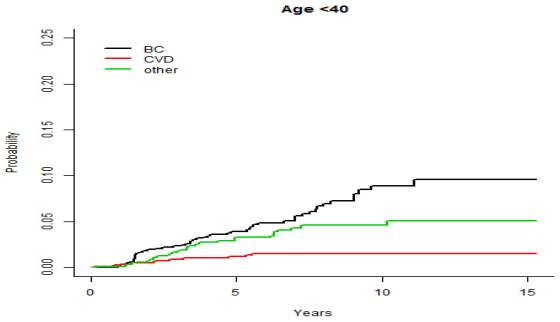
Cause of death	N(%), Median Time (months)
Breast Cancer	842 (5.3%) 40 (38 - 43)
CVD	696 (4.7%) 43 (40 - 46)
Other cancer	321 (2.3%) 51 (47 - 55)
All other	870 (5.9%) 45 (42 - 48)
Survivors	17,733 (81.8%) 7.2 years
>5 years >10 years	13,685 (66.9%) 5,106 (25.0%)

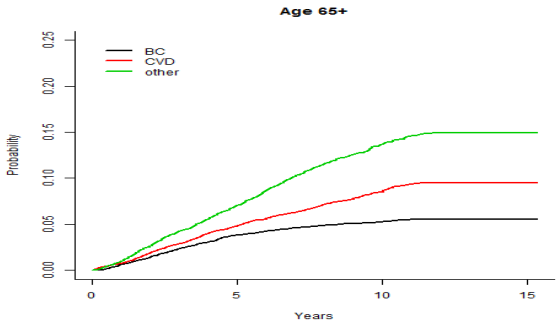


Risk Model	Time period predicts for	Sample size	Events	AUC (95% CI)
Framingham	2 years	10,211	304	0.70 (0.67, 0.73)
2000	4 years	9,529	596	0.74 (0.72, 0.76)
Framingham	5 years	8,236	699	0.71 (0.69, 0.73)
2001	10 years	1,976	952	0.64 (0.62, 0.67)
CORE	5 years	8,180	692	0.75 (0.73, 0.77)
	10 years	1,963	943	0.75 (0.73, 0.78)
Framingham	Continuous	11,019	966	0.62 (0.56, 0.68)
recalibrated	5 years	8,236	699	0.78 (0.76, 0.80)
	10 years	1,976	952	0.76 (0.74, 0.79)
Framingham 2008	10 years	4,478	3,734	0.66 (0.64, 0.68)
SCORE	10 years	1,308	188	0.73 (0.69, 0.78)
SCORE OP	10 years	1,300	184	0.76 (0.72, 0.80)

Stratified Analyses: Stage and Age







	N	BC death	CVD death	Other death	Censored
Stage 1	10,843	127 (1.6%)	294(3.9%)	551 (7.5%)	9871 (87.0%)
Stage 2	7,806	444 (7.6%)	316 (5.6%)	497 (8.6%)	6549 (78.2%)
Stage 3	1,813	271 (18.6%)	86 (6.2%)	143 (10.2%)	1313 (65.0%)
Total	**20,462**	**842 (5.3%)**	**696 (4.7%)**	**1191 (8.2%)**	**17733 (81.8%)**
Age<40	873	49 (9.5%)	11 (1.5%)	31 (5.1%)	782 (83.9%)
Age 40-50	4,003	163 (5.6%)	40 (1.3%)	85 (2.8%)	3715 (90.3%)
Age 50-65	7,936	283 (4.7%)	117 (1.9%)	250 (4.2%)	7286 (89.2%)
Age 65+	7,650	347 (5.5%)	528 (9.5%)	825 (14.9%)	5950 (70.1%)