Supplementary Online Content

Chlebowski RT, Aragaki AK, Anderson GL, et al. Association of low-fat dietary pattern with breast cancer overall survival: a secondary analysis of the Women's Health Initiative randomized clinical trial. *JAMA Oncol*. Published online May 24, 2018. doi:10.1001/jamaoncol.2018.1212

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable. Characteristics of Invasive Breast Cancers (N=1764) by Randomly Assigned Group in the Women's Health Initiative Dietary Modification Trial During the Intervention Period

Characteristic	Intervention (N=671) No. (%)	Comparison (N=1093) No. (%)	*P* Value[a]
Histology			
Ductal	435 (65.0)	711 (65.3)	
Lobular	64 (9.6)	98 (9.0)	.78
Ductal and lobular	84 (12.6)	151 (13.9)	
Other	86 (12.9)	128 (11.8)	
ER status			
Positive	521 (84.0)	850 (83.9)	.95
Negative	99 (16.0)	163 (16.1)	
PR status			
Positive	439 (71.7)	669 (67.1)	.05
Negative	173 (28.3)	328 (32.9)	
ER/PR status			
ER+PR+	429 (71.5)	651 (66.6)	
ER+PR-	85 (14.2)	184 (18.8)	.05
ER-PR-	86 (14.3)	142 (14.5)	
HER2 overexpression	90 (18.8)	134 (17.6)	.61
Triple-negative tumor	40 (8.5)	74 (9.9)	.43
Stage			
Local	492 (74.8)	812 (75.5)	.75
Regional or distant	166 (25.2)	264 (24.5)	
Grading			
Well differentiated	170 (28.6)	287 (29.4)	
Moderately differentiated	241 (40.6)	416 (42.6)	.36
Poorly differentiated	183 (30.8)	273 (28.0)	
Tumor size, cm			
<1	170 (28.0)	305 (30.9)	
1-<2	287 (47.3)	405 (41.0)	.91
>=2	150 (24.7)	277 (28.1)	
Number of positive lymph nodes			
None	449 (75.0)	739 (75.8)	
1 to 3	112 (18.7)	167 (17.1)	.97
≥ 4	38 (6.3)	69 (7.1)	

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

[a] *P* values are based on χ^2 tests of association for most tumor characteristics. Trend tests were used for ordinal tumor characteristics: grading, tumor size, and number of positive lymph nodes

eFigure Legends

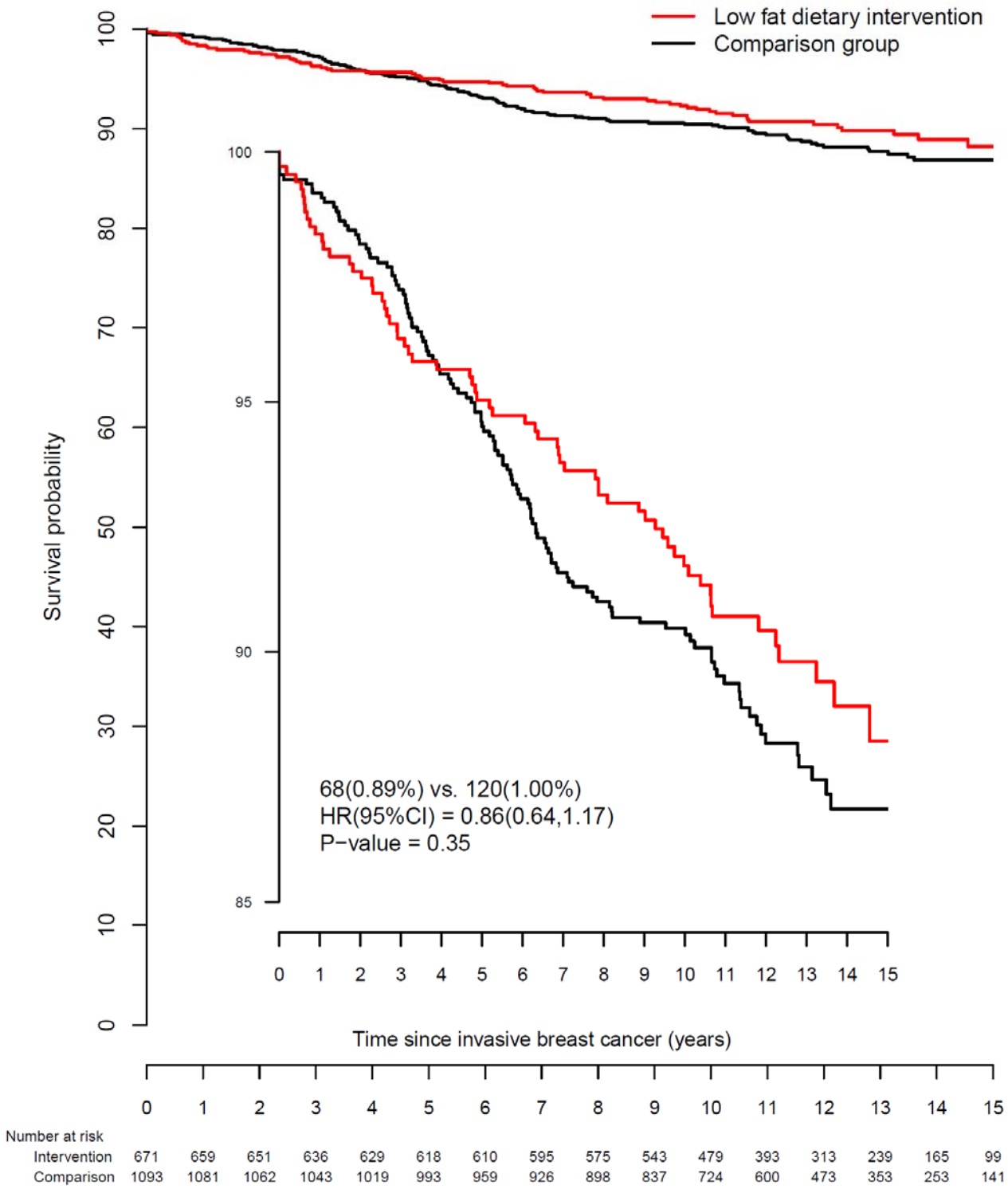
eFigure 1. Dietary modification influence on breast cancer specific survival (breast cancer followed by death from the cancer). Kaplan-Meier estimates for breast cancer specific survival (survival from diagnosis with death from breast cancer) among the 1,764 breast cancer cases diagnosed during the dietary intervention period, measured from cancer diagnosis and followed through September, 2013. Summary statistics are from a Cox model stratified by age at diagnosis, randomization status in the hormone therapy trials, and study period (intervention period, post-intervention period extension I, or post-intervention period extension II; time-dependent). The p-value corresponds to a two-sided score (log-rank) test. Percentages are annualized. HR = hazard ratio; CI = confidence interval.

eFigure 2. Time on dietary intervention preceding or following an invasive breast cancer among participants randomized to the intervention (n=671). The amount of time elapsed during the dietary intervention period that preceded (blue) or followed (red) a diagnosis of an invasive breast cancer among women that were randomized to the intervention group. Participants were ranked by time elapsed from randomization to breast cancer diagnosis. The figure illustrates that participants that had more time on intervention before cancer, typically had less time on intervention after cancer, and visa-versa. Quartiles for time preceding (following) cancer diagnosis are indicated by the blue (red) hashmarks.

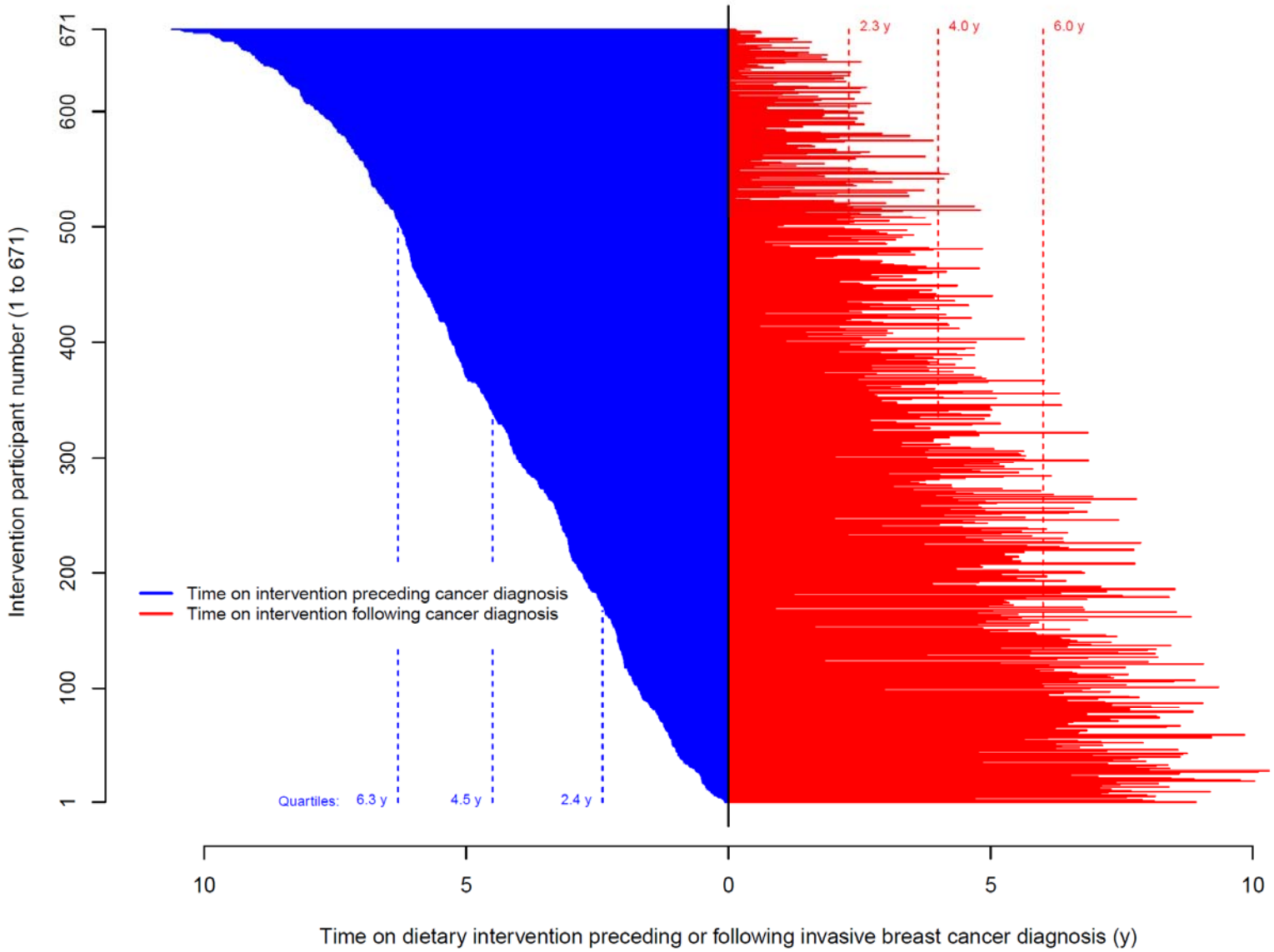
eFigure 3. Temporal analyses of the dietary modification influence on breast cancer overall survival during the intervention period. Estimated dietary intervention effects on breast cancer overall survival (breast cancer followed by death from any cause) measured from diagnosis during the intervention period (left panel), and complementary analysis that used an alternate time metric, time from randomization, for overall survival of the same cohort, during the intervention period (right panel). Overall hazard ratios (HR) and 95% CIs (black line and gray-shaded region, respectively) are shown for the effect of the dietary versus control group for the intervention period using these alternate time metrics. A reference line (dotted black) at unity corresponds to no differential risk between randomization groups, where an HR < 1 favors the intervention group. Linear time-varying HRs, 95%CIs (red lines), and significance levels are also displayed. To demonstrate that these linear time-varying HRs adequately summarize the data, the two time metrics are partitioned, by tertile of time from diagnosis (left panel) or time from randomization (right panel), and the corresponding HRs (95%CIs; solid blue lines and blue-shaded regions, respectively), are presented. Tests of the time-varying linear HR was significant (P = 0.02) during the intervention period for time since diagnosis, and non-significant (P = .42) using time from randomization; longer dietary exposure has the stronger influence after breast cancer diagnosis (left panel vs. right panel). Percentages are annualized. HR = hazard ratio; CI = confidence interval.

eFigure 4. Schematic for dietary intervention effects on breast cancer and subsequent survival. Schematic illustrates the overall influence of the dietary intervention, versus comparison group, on incidence of invasive breast cancer and subsequent death from all-causes. The summary statistics are from a Cox model that accommodates multiple events by using event-specific time-dependent strata. A participant is not considered at risk for all-cause mortality until diagnosis of an invasive breast cancer. At the end of the intervention period, participants that did not have an invasive breast cancer are censored. The p-value corresponds to a 2 degree-of-freedom score (log-rank) test of whether the dietary intervention has no effect on (1) invasive breast cancer risk and/or (2) subsequent breast cancer overall survival. A robust sandwich estimate for variance-covariance matrix was used to account for within person correlation due to multiple events.

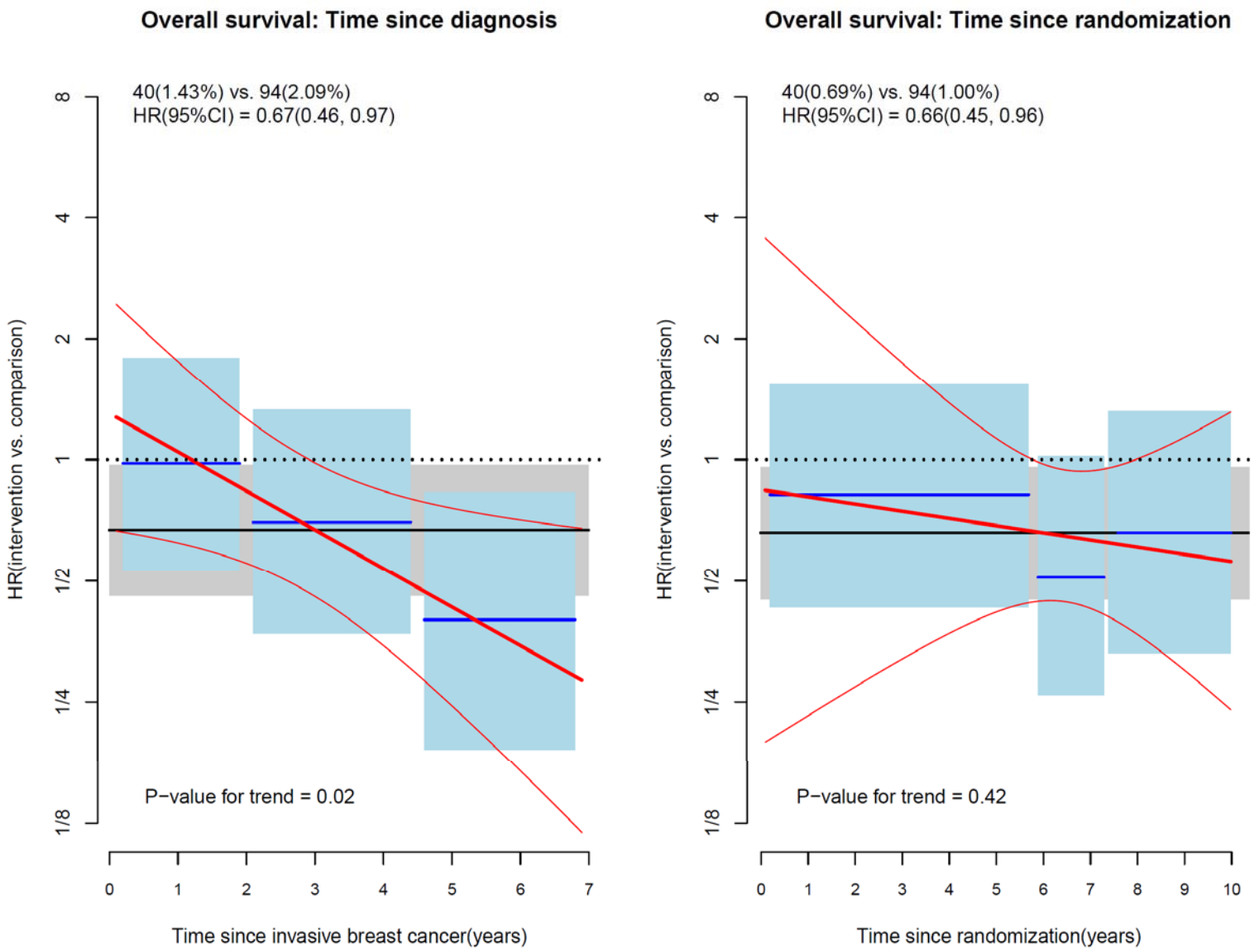
eFigure 1



eFigure 2

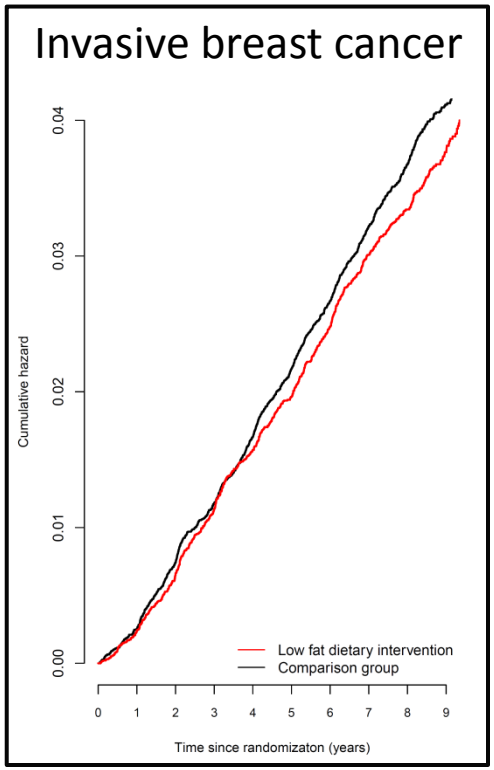


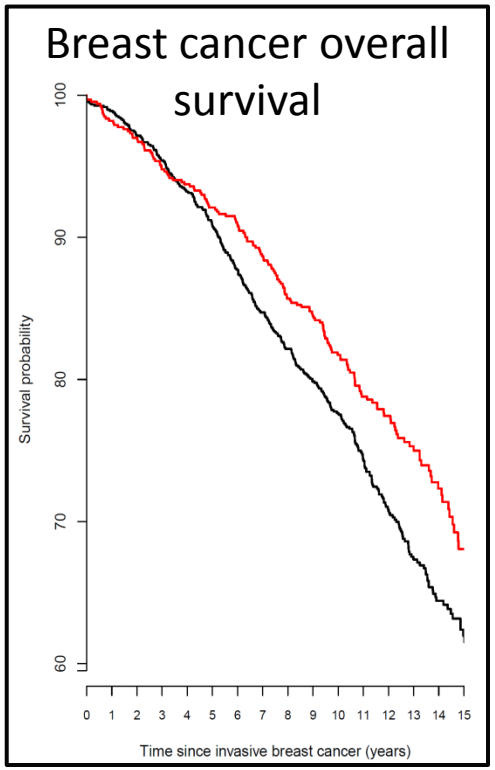
eFigure 3



eFigure 4

Randomization to the WHI dietary modification trial





	No. Randomized	No. (%) of Cancers	No. (%) of Deaths after Cancer
Intervention:	19,541	671(0.42)	174(2.29)
Comparison:	29,294	1093(0.46)	342(2.85)
HR(95%CI):		0.92(0.84, 1.01)	0.78(0.65, 0.94)

P-value = 0.006