

PLCO Trial

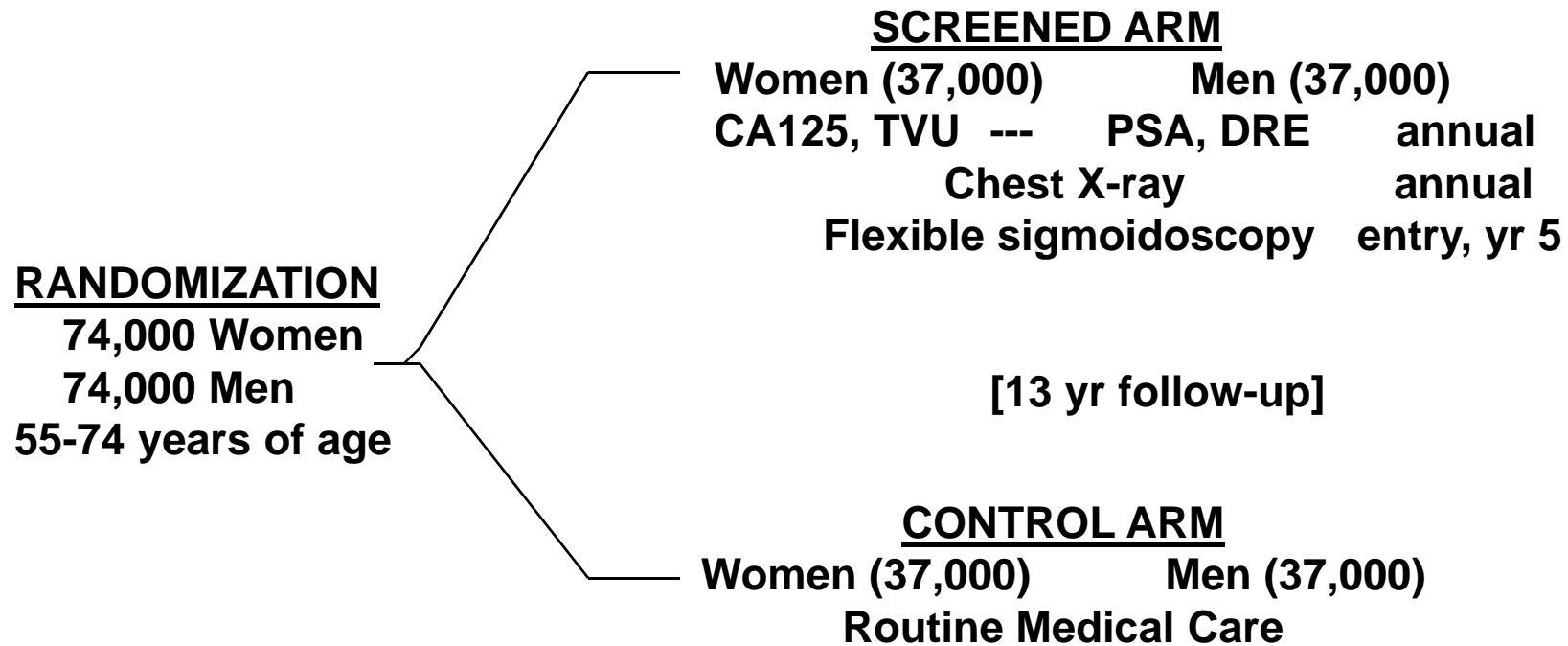
Philip Prorok
National Cancer Institute

Society for Clinical Trials
May 21, 2012

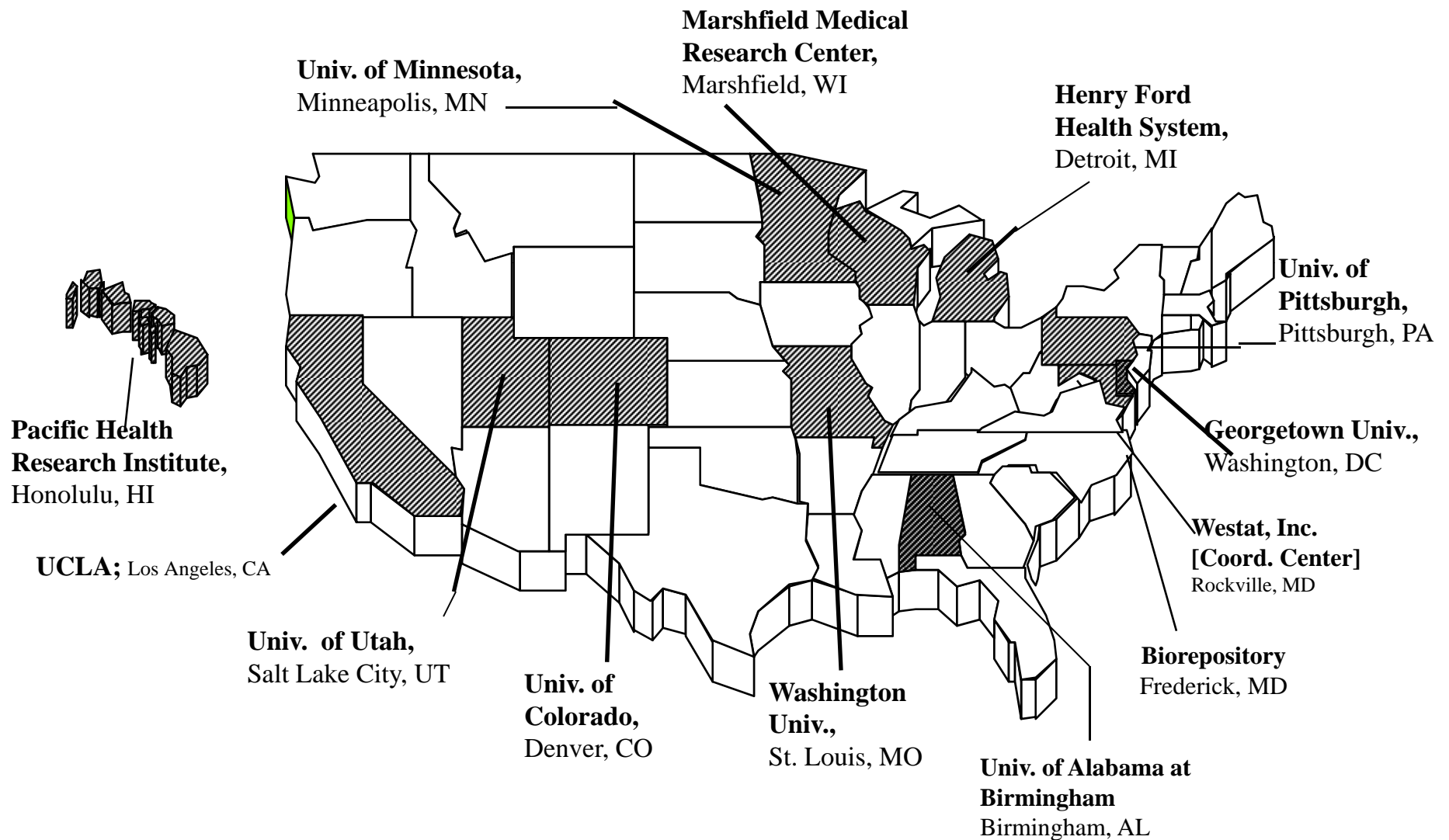
PLCO Trial

Evaluation of Screening for
Prostate, **L**ung, **C**olorectal
and **O**varian Cancer

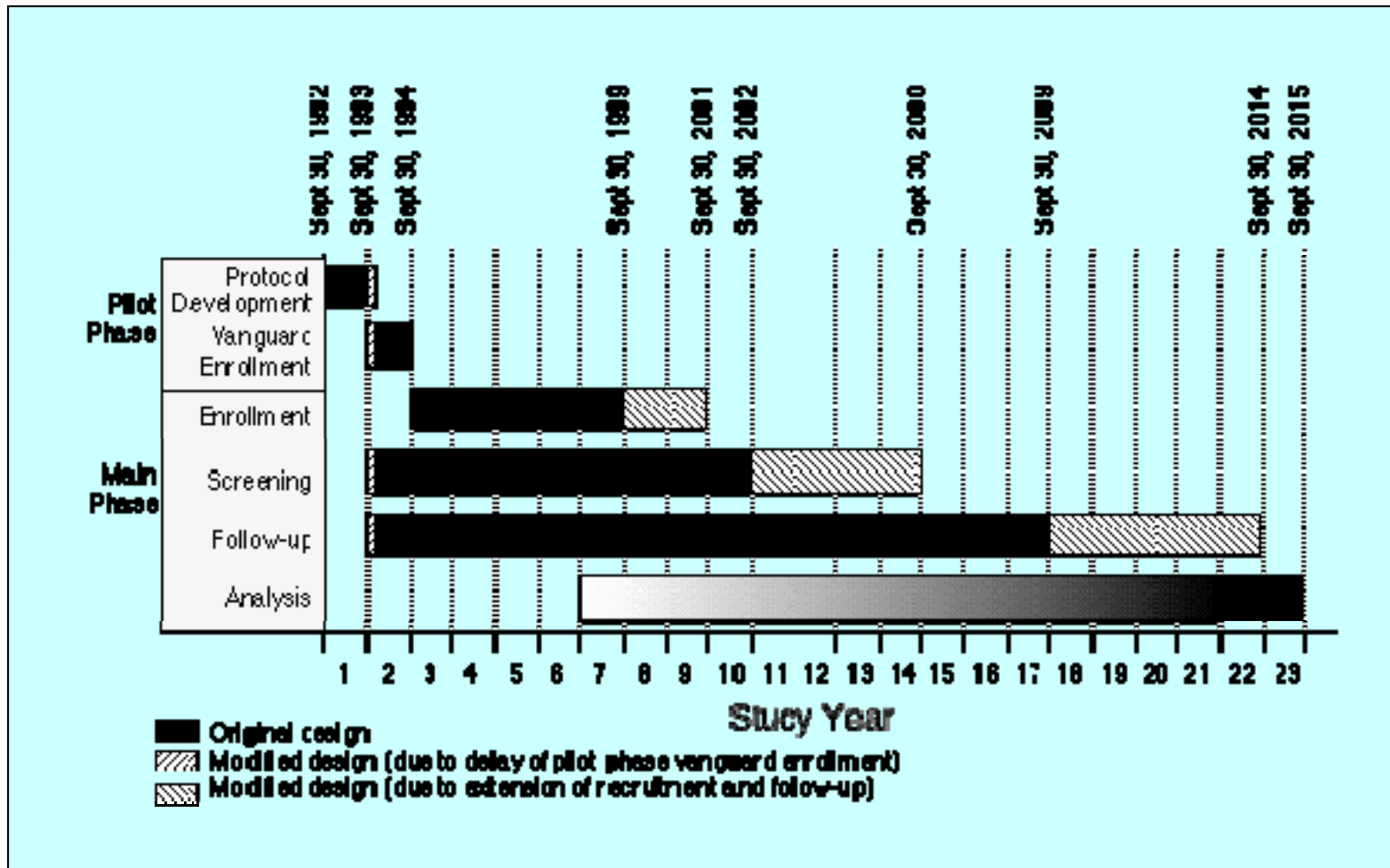
PLCO Trial Protocol



Trial Screening Centers



PLCO Trial Timeline



Participant Demographics

	<i>Intervention Arm</i>		<i>Control Arm</i>		<i>Total</i>	
	<i>N</i>	<i>%</i>	<i>N</i>	<i>%</i>	<i>N</i>	<i>%</i>
<i>All</i>	77445	100.0	77455	100.0	154900	100.0
<i>Sex</i>						
<i>Female</i>	39105	50.5	39111	50.5	78216	50.5
<i>Male</i>	38340	49.5	38344	49.5	76684	49.5
<i>Age, y</i>						
<i>55-59</i>	25851	33.4	25839	33.4	51690	33.4
<i>60-64</i>	23783	30.7	23771	30.7	47554	30.7
<i>65-69</i>	17457	22.5	17473	22.6	34930	22.6
<i>70-74</i>	10354	13.4	10372	13.4	20726	13.4
<i>Race or ethnic group</i>						
<i>White, Non-Hispanic</i>	66874	86.4	65708	84.8	132582	85.6
<i>Black, Non-Hispanic</i>	3883	5.0	3825	4.9	7708	5.0
<i>Hispanic</i>	1421	1.8	1397	1.8	2818	1.8
<i>Asian</i>	2791	3.6	2785	3.6	5576	3.6
<i>Other</i>	2476	3.2	3740	4.8	6216	4.0
<i>Education Level</i>						
<i>< High school</i>	5620	7.3	5461	7.1	11081	7.2
<i>High School</i>	17272	22.3	17122	22.1	34394	22.2
<i>Some college</i>	25935	33.5	25585	33.0	51520	33.3
<i>College graduate</i>	26659	34.4	25915	33.5	52574	33.9
<i>Unknown</i>	1959	2.5	3372	4.4	5331	3.4

Table L.3.3: Compliance For ASU and/or BQ Due By December 31, 2010 as of August 31, 2011.

		<i>Randomization Group</i>				<i>Total</i>	
		<i>Control</i>		<i>Intervention</i>			
		<i># Exp.</i>	<i>%</i>	<i># Exp.</i>	<i>%</i>	<i># Exp.</i>	<i>%</i>
BQ	Totals	77455	96.0	77445	97.6	154900	96.8
ASU	Totals	923943	92.7	925527	93.3	1849470	93.0
	T1	76390	92.2	76414	93.4	152804	92.8
	T2	75842	90.3	75870	92.0	151712	91.1
	T3	75209	91.1	75256	92.2	150465	91.6
	T4	74514	92.3	74583	92.4	149097	92.3
	T5	73720	92.9	73835	93.3	147555	93.1
	T6	72869	94.3	73004	94.1	145873	94.2
	T7	71945	94.8	72092	94.9	144037	94.8
	T8	70919	95.0	71022	95.5	141941	95.2
	T9	69757	95.2	69850	95.6	139607	95.4
	T10	67293	95.3	67448	95.7	134741	95.5
	T11	60415	95.1	60469	95.6	120884	95.3
	T12	49112	95.0	49183	95.3	98295	95.1
	T13	38693	94.8	38904	95.1	77597	94.9
	T14	26810	74.3	26939	75.2	53749	74.8
	T15	14439	74.5	14535	74.9	28974	74.7
	T16	5816	92.5	5924	92.4	11740	92.4
T17	200	89.0	199	92.0	399	90.5	

Cumulative Deaths from Prostate Cancer in PLCO by Arm: Deaths Grouped in One-Week Intervals

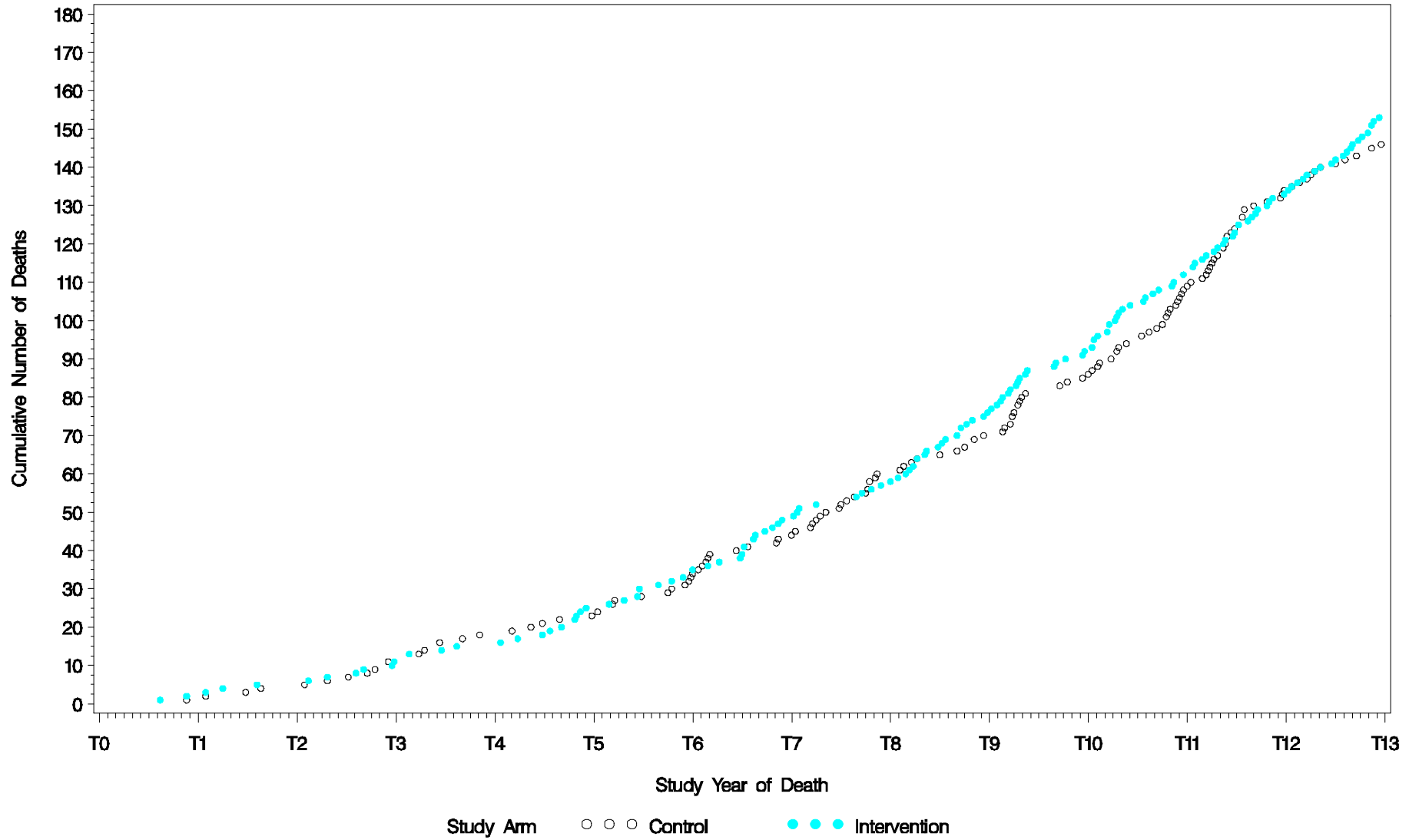
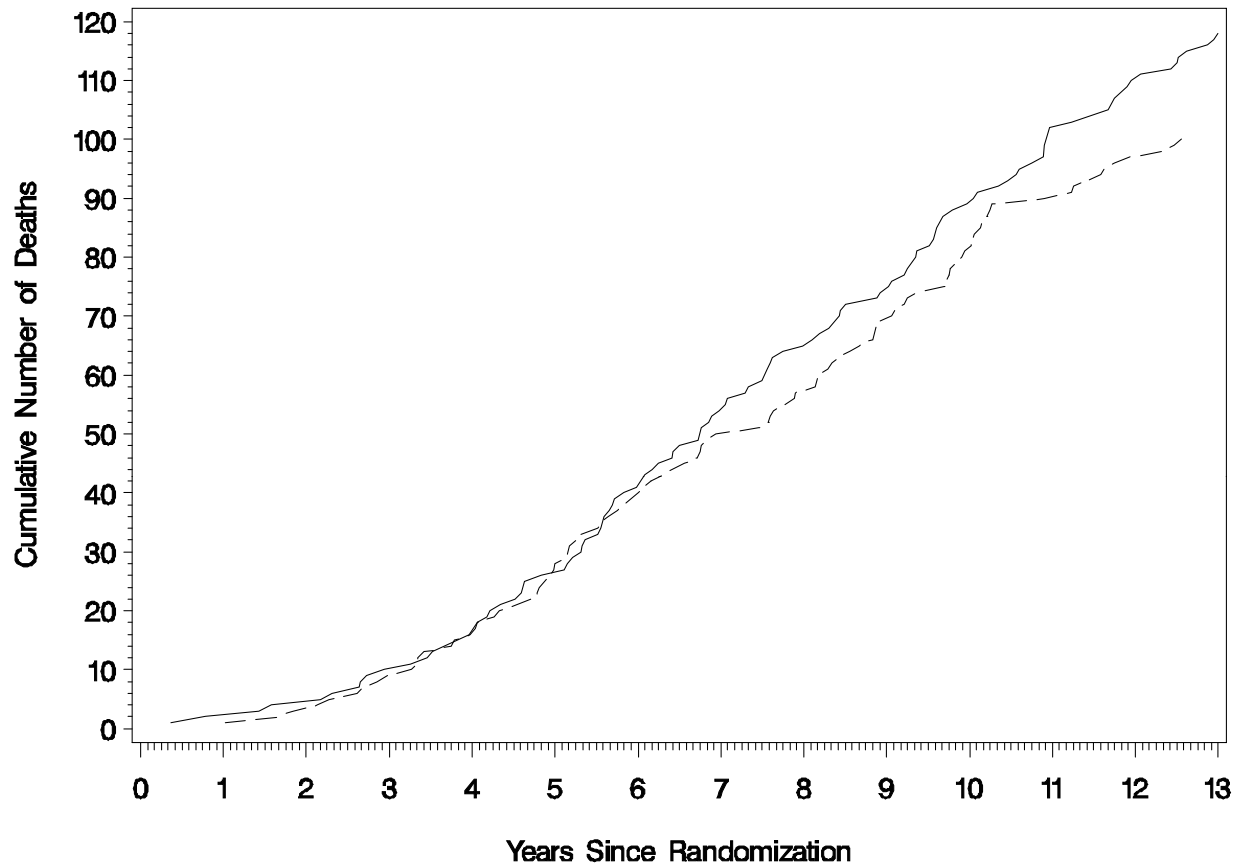
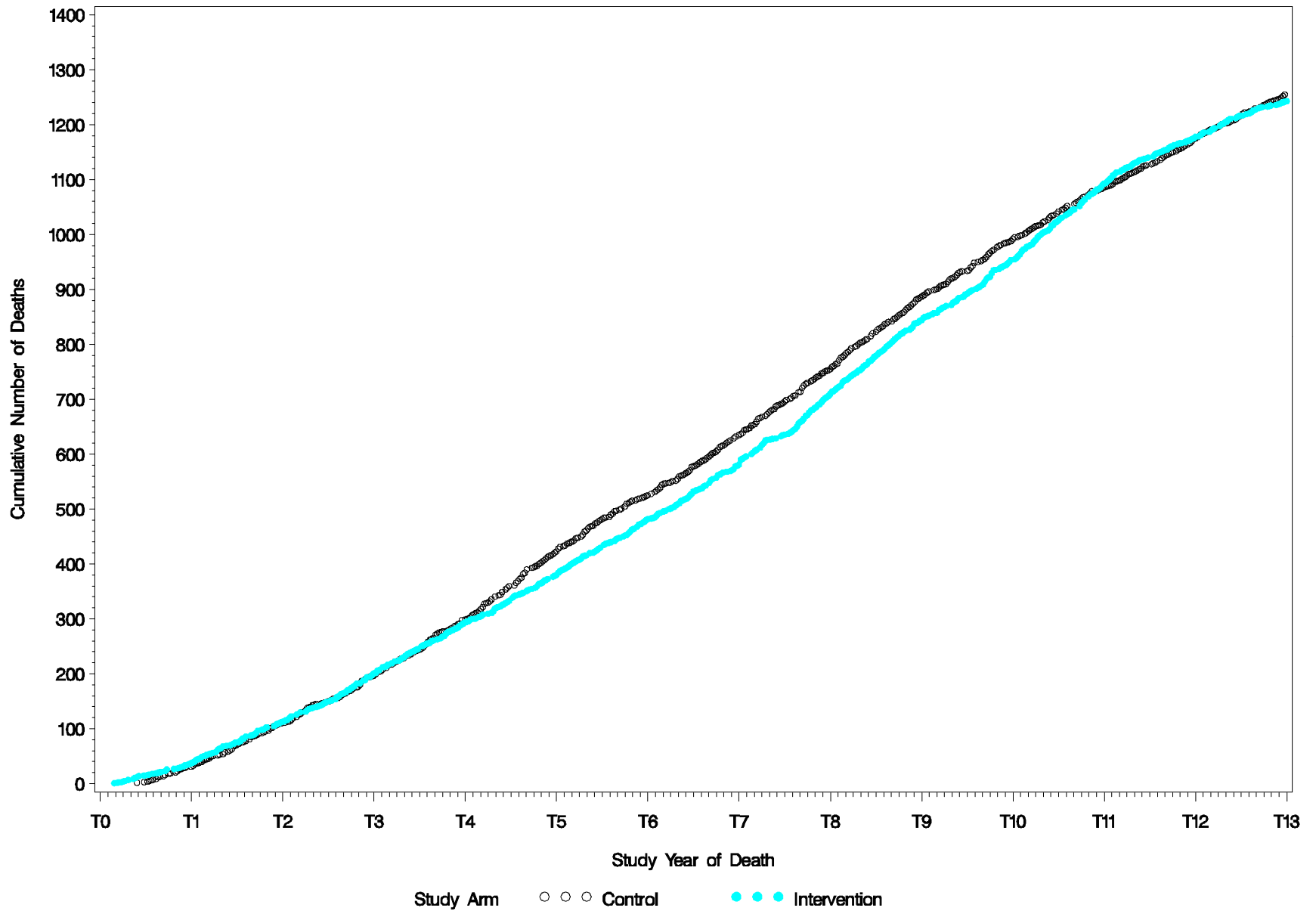


Figure 2B. Cumulative Deaths From Ovarian Cancer By Trial Arm

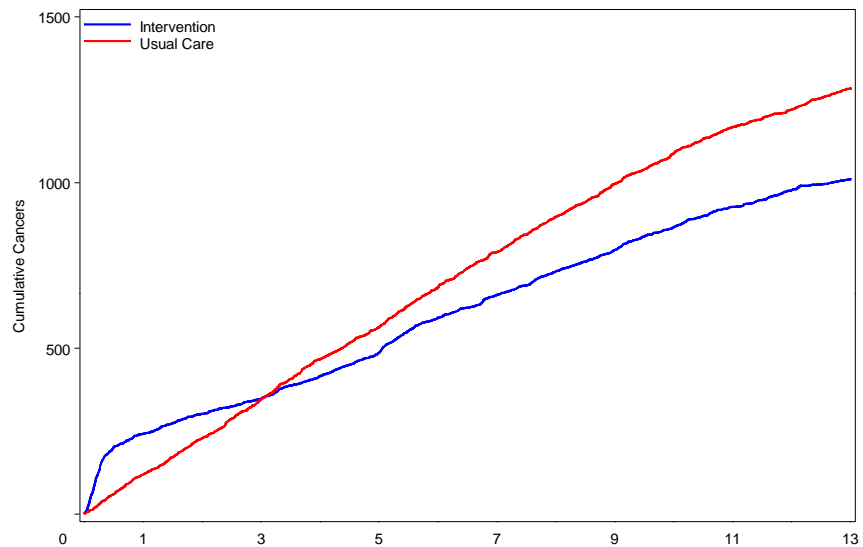


Study Arm		Years Since Randomization												
		1	2	3	4	5	6	7	8	9	10	11	12	13
Intervention	Cumulative Deaths	2	4	10	16	26	41	54	65	74	89	102	110	118
	Cumulative Person-Years	34210	68283	102191	135892	169354	202565	235475	267952	299372	327722	350870	368802	381574
Usual Care	Cumulative Deaths	0	3	9	16	28	40	50	57	69	82	90	97	100
	Cumulative Person-Years	34260	68388	102344	136097	169617	202874	235836	268380	299903	328329	351557	369603	382502

Cumulative Deaths from Lung Cancer in PLCO by Arm: Deaths Grouped in One-Week Intervals

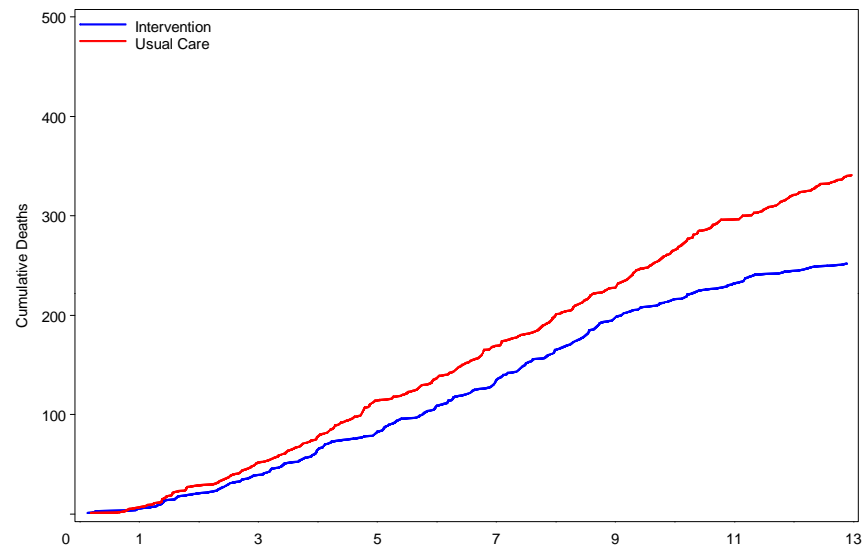


Overall Colorectal Cancer Incidence by Year



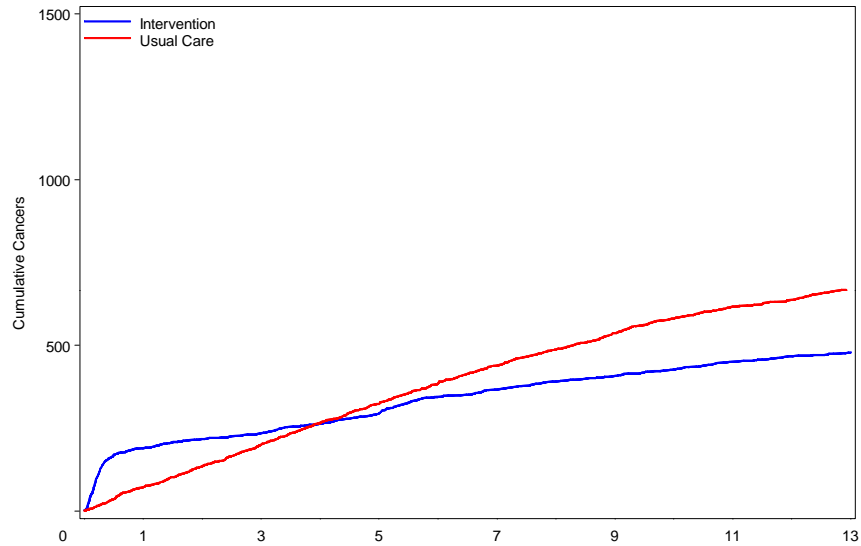
	Years Since Randomization							
	0	1	3	5	7	9	11	13
Intervention								
Cancers	242	347	487	659	797	927	1012	
Person-years	76520	227007	373895	516773	654740	772625	848403	
Usual Care								
Cancers	119	344	564	790	998	1169	1287	
Person-years	76592	227438	374467	517055	654447	771744	847103	

Overall Colorectal Cancer Mortality by Year



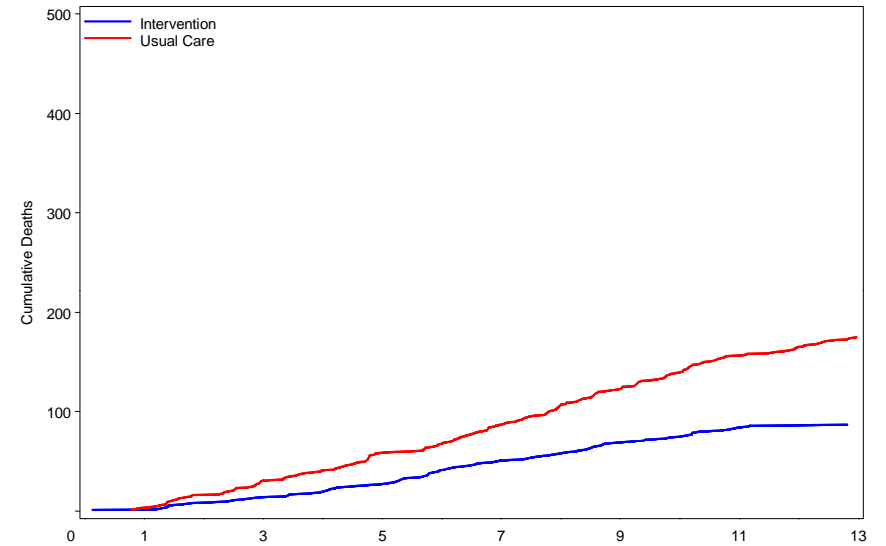
	Years Since Randomization							
	0	1	3	5	7	9	11	13
Intervention								
Deaths	6	39	83	135	198	232	252	
Person-years	77276	230295	380730	528006	670832	793203	871930	
Usual Care								
Deaths	6	51	114	169	228	296	341	
Person-years	77288	230354	380731	527828	670526	792674	871275	

Distal Colorectal Cancer Incidence by Year



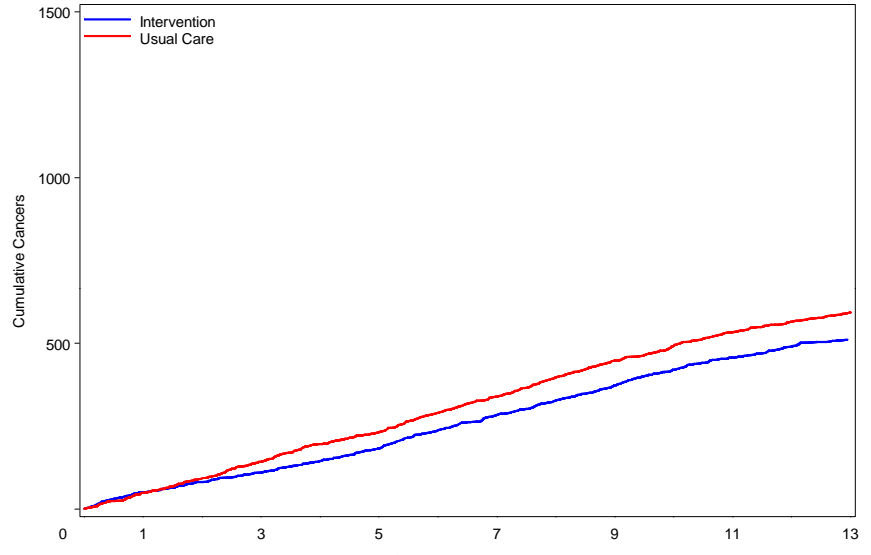
	Years Since Randomization						
	1	3	5	7	9	11	13
Intervention							
Cancers	190	234	295	367	407	450	479
Person-years	76520	227007	373895	516773	654740	772625	848403
Usual Care							
Cancers	71	200	324	439	538	617	669
Person-years	76592	227438	374467	517055	654447	771744	847103

Distal Colorectal Cancer Mortality by Year



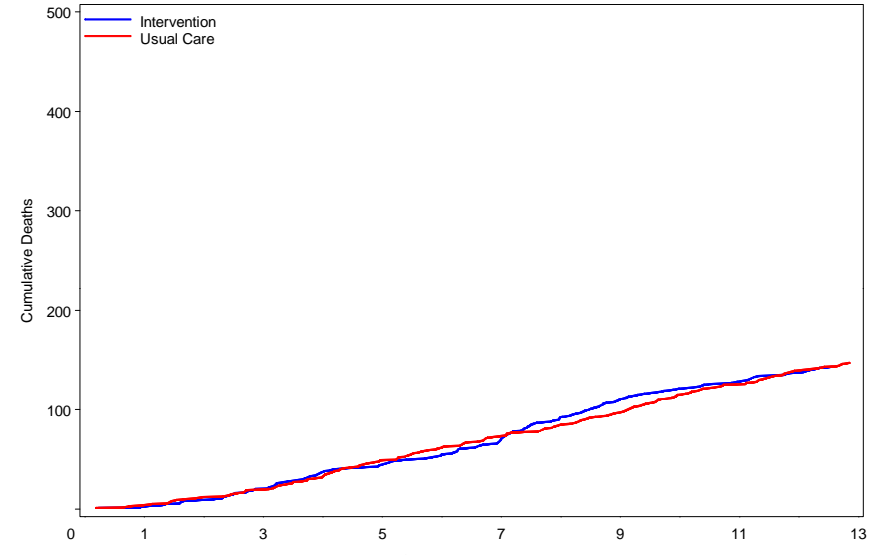
	Years Since Randomization						
	1	3	5	7	9	11	13
Intervention							
Deaths	1	14	27	51	69	84	87
Person-years	77276	230295	380730	528006	670832	793203	871930
Usual Care							
Deaths	3	30	58	87	123	156	175
Person-years	77288	230354	380731	527828	670526	792674	871275

Proximal Colorectal Cancer Incidence by Year



	Years Since Randomization							
	0	1	3	5	7	9	11	13
Intervention								
Cancers	0	50	109	183	282	374	458	512
Person-years	76520	227007	373895	516773	654740	772625	848403	
Usual Care								
Cancers	0	48	142	232	339	448	534	595
Person-years	76592	227438	374467	517055	654447	771744	847103	

Proximal Colorectal Cancer Mortality by Year



	Years Since Randomization							
	0	1	3	5	7	9	11	13
Intervention								
Deaths	0	3	20	45	71	111	128	143
Person-years	77276	230295	380730	528006	670832	793203	871930	
Usual Care								
Deaths	0	3	19	49	73	96	125	147
Person-years	77288	230354	380731	527828	670526	792674	871275	

Sample Size Calculation

The number of study participants required in the control group for a one-sided α -level test with power $1-\beta$ to detect a $(1-r)$ x100% mortality reduction is

$$N_C = D / \{ (Q_1 + fQ_2) R_C Y \}$$

where

$$D = \{ (Q_1 + f Q_2) Z_{1-\alpha} - \sqrt{Q_1 Q_2} (1+f) Z_\beta \}^2 / f(Q_1 - Q_2)^2$$

$$f = N_S / N_C$$

N_S = number of participants in the screened group

R_C = average annual disease-specific death rate in controls

Y = trial duration

$$Q_1 = r + (1-r) P_C$$

$$Q_2 = r + (1-r) P_S$$

P_C = proportion of compliers in the control group

P_S = proportion of compliers in the screened group

Adjustment for Healthy Volunteer Effect

(Bias results in fewer than expected events
based on national rates)

- Morrison, Moss
 - Start with “cancer-free, symptom free” population
 - Estimate incidence of new cases
 - Estimate deaths among new cases
- Empirical
 - Use observed control group death rates — HIP, lung, colon trials
 - Let R_N = death rate from national data
 - For a 10 year study, the adjusted control group death rate is
$$R_C = \{(1/4 R_N \times 2) + (1/2 R_N \times 3) + (R_N \times 5)\} / 10$$
 - Gives slightly larger sample size than that used by Morrison, Moss

Healthy Volunteer Effect in the PLCO Trial

	PLCO Trial (%)		National Health Interview Survey (%)	
	Men	Women	Men	Women
Smoking Status				
Current smoker	12	10	21	18
Regular Physical Activity				
	85	84	56	52
Education				
Less than high school	8	7	23	24
High school/post-high school	51	63	52	60
College degree	41	30	25	16
Medical Diagnosis				
Cancer	2	7	8	10
Diabetes	9	7	14	13
CAHD, stroke	15	7	19	10
Hypertension	34	34	42	44

(P Pinsky, Am J Epi, 2007)

Standardized Mortality Ratio in PLCO Participants

	Standardized mortality ratio	95% confidence interval
All non-PLCO causes	43	42-44
Cardiovascular	37	35-38
Digestive	34	30-38
Respiratory	34	31-36
Diabetes	28	24-31
Injuries and poisoning	64	58-70
All non-prostate, lung, colorectal or ovarian cancers	56	54-59

(P Pinsky, Am J Epi, 2007)

Sample Size Calculation

The number of study participants required in the control group for a one-sided α -level test with power $1-\beta$ to detect a $(1-r)$ x100% mortality reduction is

$$N_C = D / \{ (Q_1 + fQ_2) R_C Y \}$$

where

$$D = \{ (Q_1 + f Q_2) Z_{1-\alpha} - \sqrt{Q_1 Q_2} (1+f) Z_\beta \}^2 / f(Q_1 - Q_2)^2$$

$$f = N_S / N_C$$

N_S = number of participants in the screened group

R_C = average annual disease-specific death rate in controls

Y = trial duration

$$Q_1 = r + (1-r) P_C$$

$$Q_2 = r + (1-r) P_S$$

P_C = proportion of compliers in the control group

P_S = proportion of compliers in the screened group

Noncompliance

- Adjust for noncompliance in design
- Monitor noncompliance during trial
- Use “Cuzick method” to adjust, but requires individual level data
- Recommendation: collect individual participant level compliance data in all trial arms

COMPLIANCE (%)

	Design	Observed
<i>Compliance</i>		
DRE	90	86
PSA	90	85
CA125	90	80
TVU	85	80
SIG	85	84/54
XRAY	85	83
<i>Contamination</i>		(1% Sample)
DRE	20	44
PSA	20	45
CA125	10	3
TVU	10	4
SIG	15	47
XRAY	40	11

Treatment Reporting

- Screening trials should present data showing the distribution of treatment approaches comparing trial arms within each disease prognostic category (ex. cancer stage)
- Essential for interpreting trial results and separating screening effect (if there is any) from treatment effect

Figure L.8.1: Primary Treatment for Non-Small Cell Lung Cancers by Clinical Stage as of August 31, 2011.

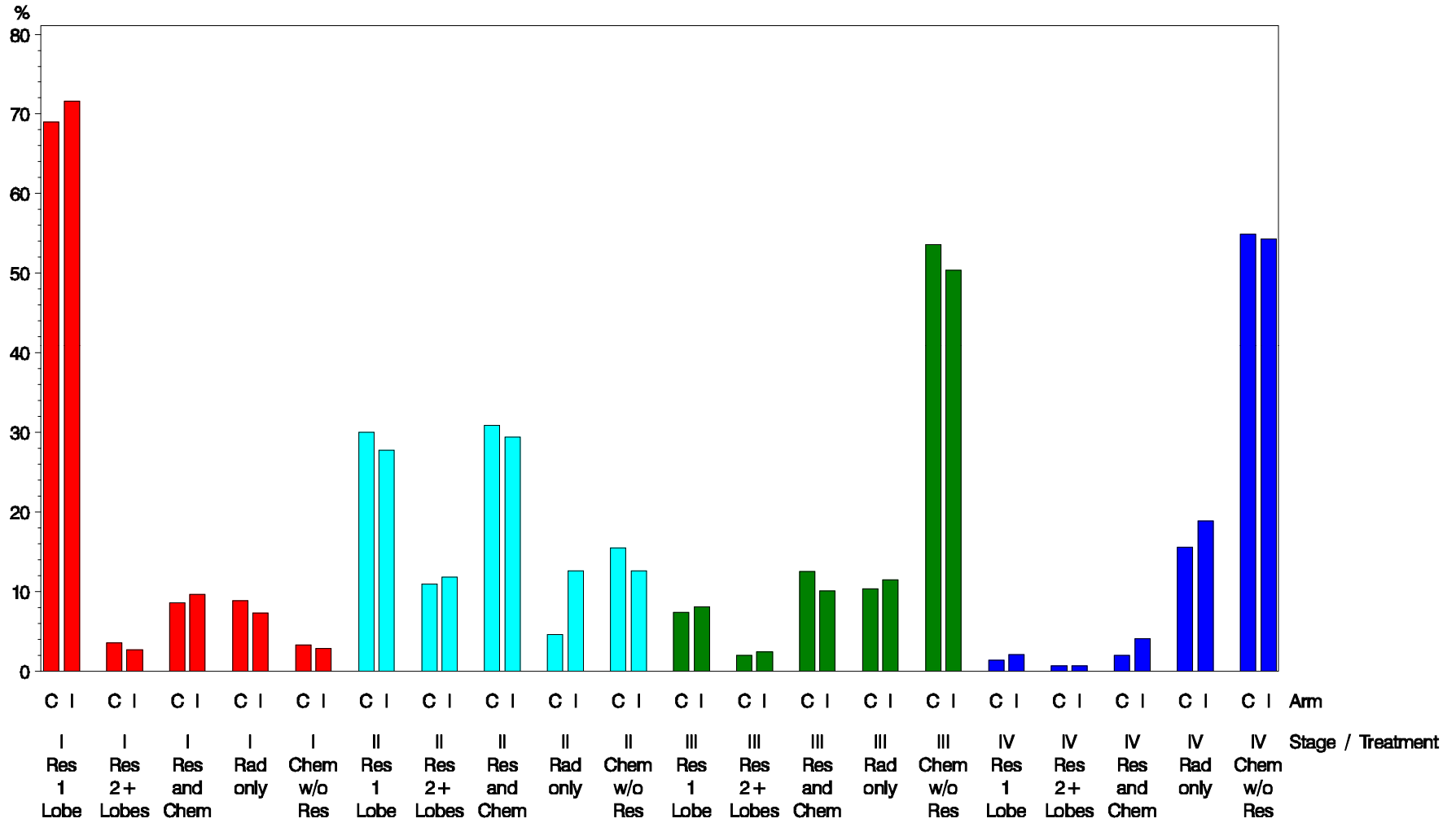
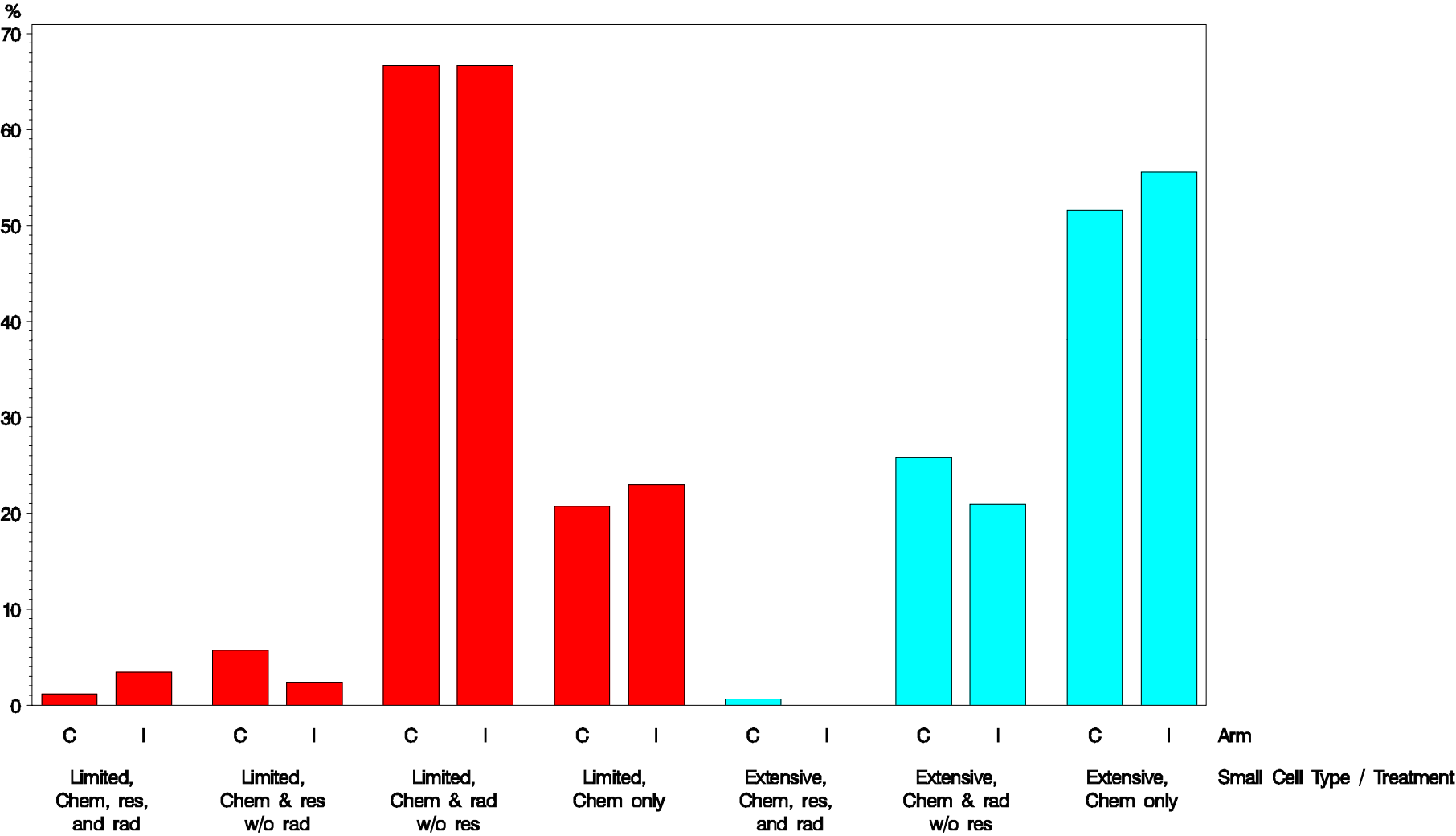


Figure L.8.2: Primary Treatment for Small Cell Lung Cancers as of August 31, 2011.



Screening Harms

False Positives

Overdiagnosis

Overdiagnosis

Definiton: the diagnosis as a result of screening of cancer cases that , in the absence of screening, would not have presented clinically during the person's lifetime

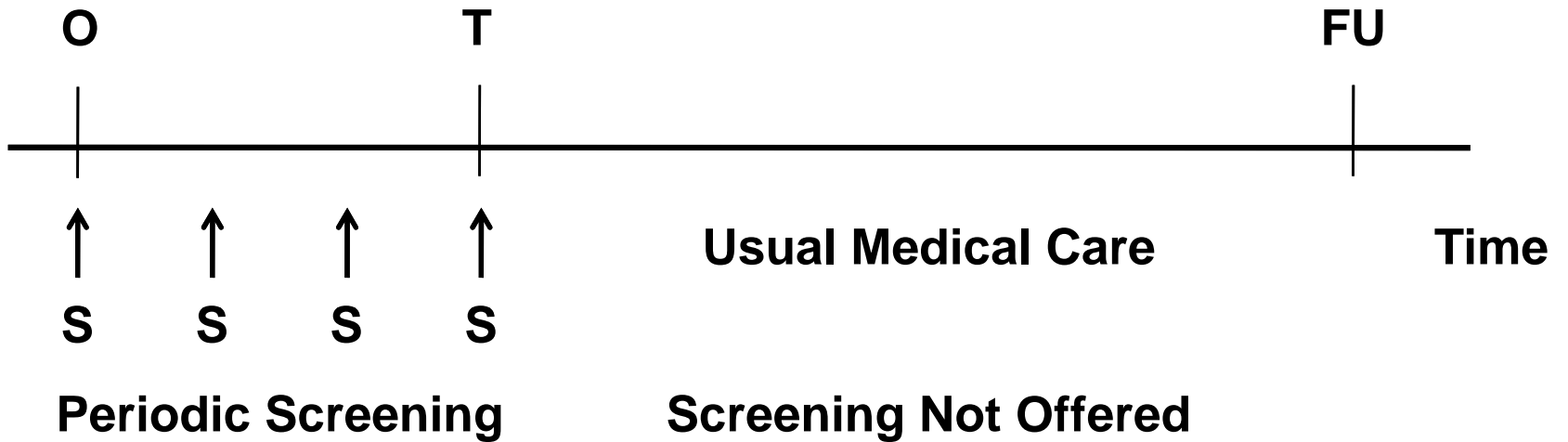
Appears to be the rule rather than the exception in cancer screening

Leads to unnecessary treatment - morbidity, mortality

Observed in screening for neuroblastoma, prostate, cervix, breast , lung , ovary

STOP SCREEN DESIGN

Intervention Arm



Control Arm

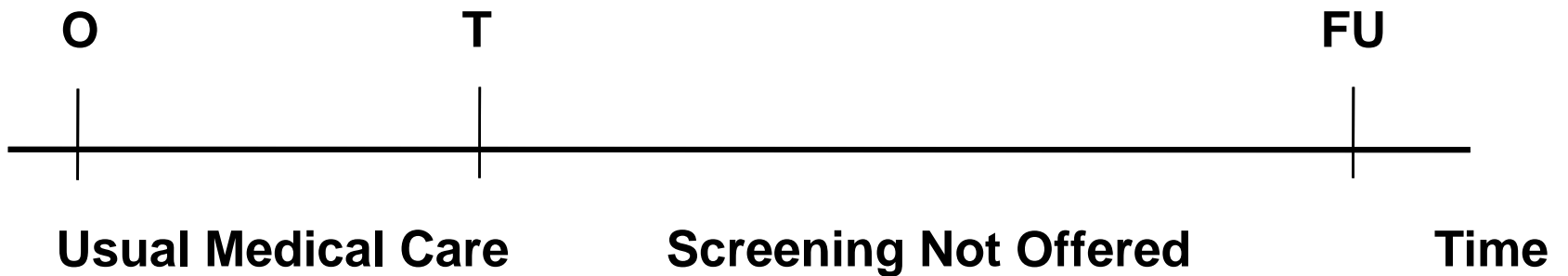
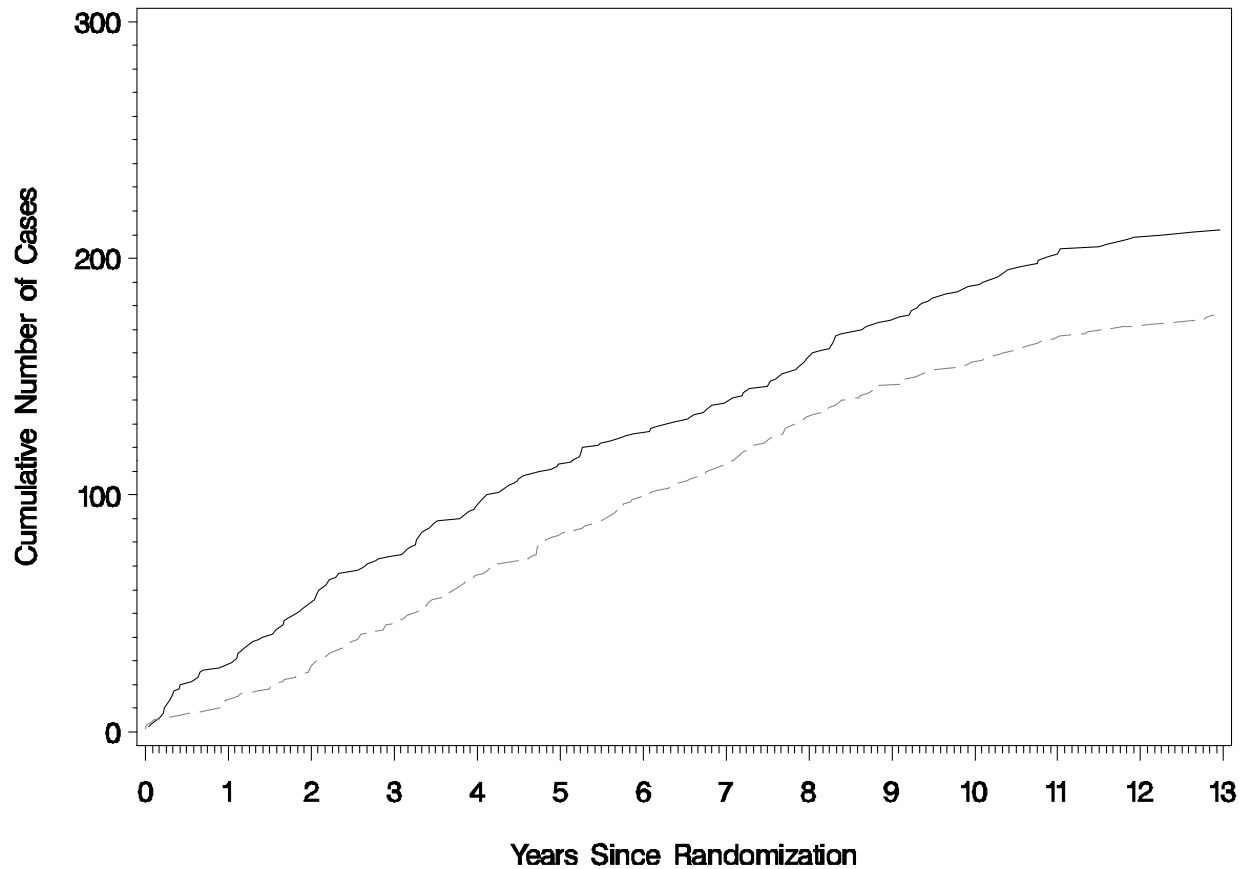


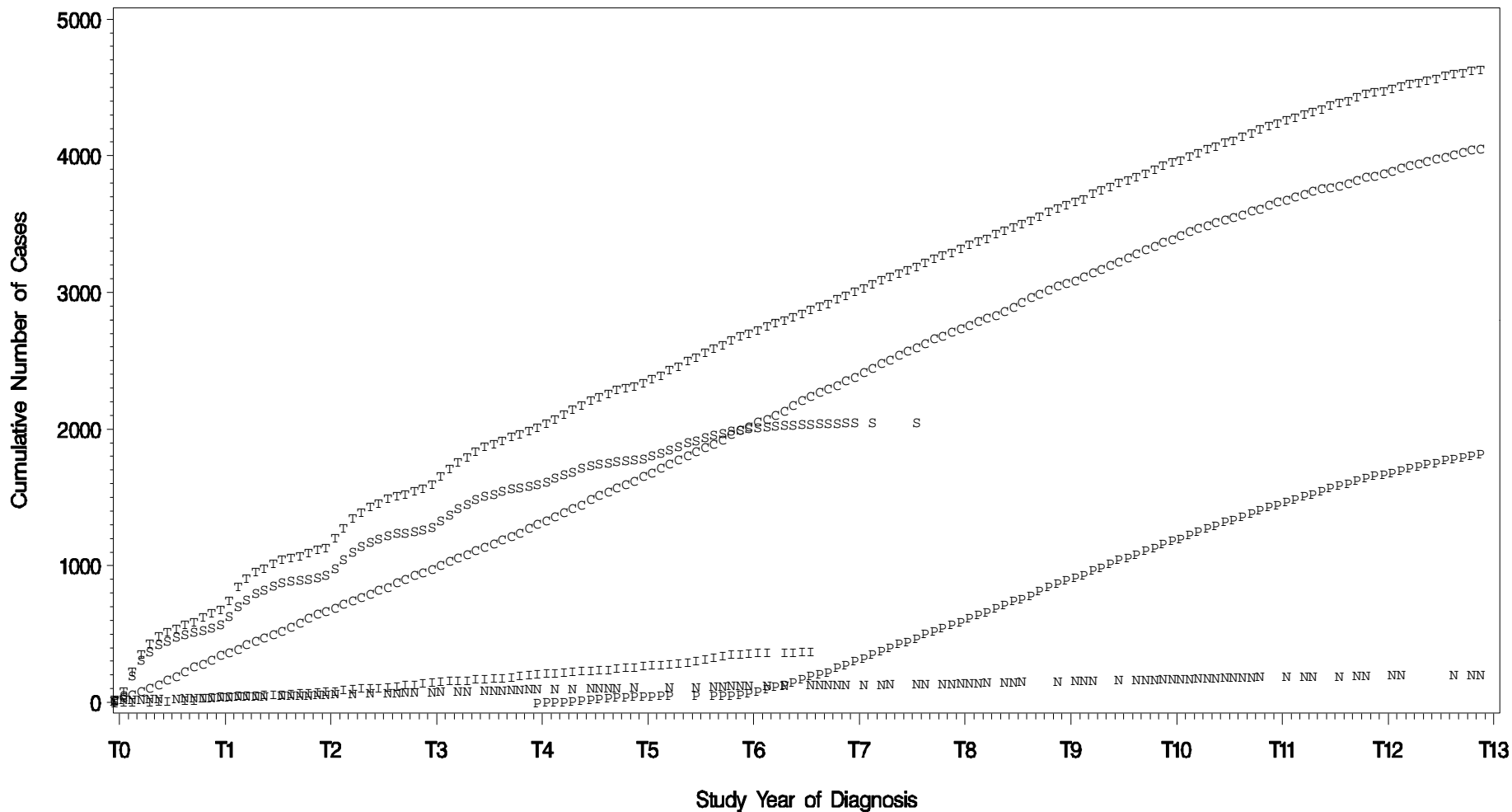
Figure 2A. Cumulative Cases Of Ovarian Cancer By Trial Arm



Study Arm ——— Intervention (I) - - - Usual Care (UC)

		<i>Years Since Randomization</i>												
		<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>	<i>6</i>	<i>7</i>	<i>8</i>	<i>9</i>	<i>10</i>	<i>11</i>	<i>12</i>	<i>13</i>
<i>Study Arm</i>														
<i>Intervention</i>	<i>Cumulative Cancers</i>	28	54	74	95	113	126	139	159	174	188	202	209	212
	<i>Cumulative Person-Years</i>	33908	67517	100777	133698	166273	198513	230393	261831	292223	319627	341975	359375	371833
<i>Usual Care</i>	<i>Cumulative Cancers</i>	13	27	45	66	83	99	113	133	146	156	167	171	176
	<i>Cumulative Person-Years</i>	33994	67771	101279	134498	167380	199906	232046	263732	294424	322113	344734	362347	374976

Cumulative Prostate Cancer Cases in PLCO by Interval Status: Diagnoses Grouped in One-Week Intervals



Stage: N N N Never Screened P P P Post Screening I I I Interval
 S S S Screening DX T T T Total Intervention C C C Control