

Serum selenium, selenoprotein P levels and glutathione peroxidase 3 activity as predictors of mortality and recurrence following breast cancer: a multicentre cohort study

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Supplementary Material

Supplementary Table 1 Se biomarkers in relation to tumour characteristics

Characteristic	Selenium Q					Selenoprotein P Q					Glutathione Peroxidase 3 Q				
	1, N = 400	2, N = 399	3, N = 399	4, N = 399	5, N = 399	1, N = 400	2, N = 399	3, N = 399	4, N = 399	5, N = 399	1, N = 400	2, N = 399	3, N = 399	4, N = 399	5, N = 399
Age (years)	68 (58)	66 (54)	63 (51)	62 (53)	61 (53)	65 (54)	63 (49)	63 (52)	64 (56)	64 (57)	67 (55)	64 (54)	64 (54)	63 (53)	63 (53)
	- (78)	- (72)	- (69)	- (69)	- (68)	- (75)	- (72)	- (70)	- (69)	- (69)	- (76)	- (71)	- (70)	- (69)	- (69)
Menopausal Status															
Pre-menopausal	56 (14)	73 (19)	90 (23)	79 (20)	67 (17)	76 (19)	106 (27)	83 (21)	63 (16)	37 (9.3)	67 (17)	78 (20)	70 (18)	76 (19)	74 (19)
Post-menopausal	325 (83)	302 (77)	292 (74)	298 (76)	307 (78)	305 (77)	267 (68)	293 (75)	316 (80)	343 (86)	304 (78)	298 (76)	311 (78)	303 (77)	308 (78)
Uncertain	12 (3.1)	18 (4.6)	14 (3.5)	17 (4.3)	22 (5.6)	14 (3.5)	21 (5.3)	16 (4.1)	15 (3.8)	17 (4.3)	20 (5.1)	18 (4.6)	17 (4.3)	15 (3.8)	13 (3.3)
Laterality															
Left	218 (55)	219 (55)	196 (49)	187 (47)	218 (55)	218 (55)	205 (51)	209 (52)	194 (49)	212 (53)	213 (53)	206 (52)	201 (50)	213 (53)	205 (51)
Right	182 (46)	180 (45)	203 (51)	212 (53)	181 (45)	182 (46)	194 (49)	190 (48)	205 (51)	187 (47)	187 (47)	193 (48)	198 (50)	186 (47)	194 (49)
Size (mm)	17 (12)	16 (11)	16 (11)	15 (11)	16 (11)	17 (12)	15 (11)	15 (11)	16 (11)	16 (11)	17 (12)	15 (11)	15 (11)	16 (11)	15 (11)
	- (25)	- (22)	- (22)	- (22)	- (22)	- (23)	- (22)	- (23)	- (22)	- (22)	- (24)	- (22)	- (21)	- (23)	- (22)
Lymph Nodes															
>=4	38 (10)	42 (11)	27 (7.0)	34 (8.9)	34 (8.8)	36 (9.4)	35 (9.2)	31 (7.9)	39 (10)	34 (8.9)	31 (8.0)	36 (9.4)	36 (9.5)	39 (10)	33 (8.6)
1-3	91 (24)	88 (23)	97 (25)	89 (23)	96 (25)	95 (25)	86 (23)	109 (28)	76 (20)	95 (25)	97 (25)	87 (23)	87 (23)	93 (24)	97 (25)
No Involvement	243 (64)	249 (65)	254 (65)	247 (65)	247 (64)	243 (63)	253 (66)	245 (63)	257 (68)	242 (63)	249 (65)	254 (66)	245 (65)	246 (64)	246 (64)
Submicrometastasis	8 (2.1)	6 (1.6)	10 (2.6)	10 (2.6)	8 (2.1)	9 (2.3)	8 (2.1)	5 (1.3)	8 (2.1)	12 (3.1)	9 (2.3)	7 (1.8)	9 (2.4)	9 (2.3)	8 (2.1)
(Missing)	20	14	11	19	14	17	17	9	19	16	14	15	22	12	15
NHG															
I	76 (20)	79 (20)	62 (16)	71 (18)	95 (24)	78 (21)	75 (19)	66 (17)	79 (20)	85 (22)	80 (21)	73 (19)	76 (19)	74 (19)	80 (21)
II	176 (46)	188 (48)	189 (49)	184 (47)	181 (46)	178 (47)	160 (41)	196 (51)	198 (50)	186 (47)	180 (47)	192 (50)	186 (48)	185 (48)	175 (45)
III	130 (34)	121 (31)	138 (35)	135 (35)	114 (29)	123 (32)	151 (39)	126 (32)	117 (30)	121 (31)	123 (32)	122 (32)	129 (33)	130 (33)	134 (34)
(Missing)	18	11	10	9	9	21	13	11	5	7	17	12	8	10	10
Ki67 Expression															
Low	44 (44)	40 (37)	48 (54)	45 (52)	49 (52)	44 (43)	43 (42)	45 (47)	48 (49)	46 (57)	51 (50)	48 (53)	39 (43)	34 (37)	54 (54)
High	55 (56)	68 (63)	41 (46)	42 (48)	46 (48)	59 (57)	59 (58)	50 (53)	49 (51)	35 (43)	52 (50)	43 (47)	52 (57)	59 (63)	46 (46)
(Missing)	301	291	310	312	304	297	297	304	302	318	297	308	308	306	299
Histological Type															
Ductal	317 (79)	330 (83)	311 (78)	313 (78)	326 (82)	313 (78)	327 (82)	325 (81)	315 (79)	317 (80)	330 (82)	306 (77)	324 (81)	311 (78)	326 (82)
Lobular	55 (14)	46 (12)	58 (15)	58 (15)	43 (11)	51 (13)	47 (12)	52 (13)	56 (14)	54 (14)	44 (11)	56 (14)	49 (12)	60 (15)	51 (13)
Other	24 (6.0)	18 (4.5)	22 (5.5)	22 (5.5)	19 (4.8)	26 (6.5)	22 (5.5)	19 (4.8)	21 (5.3)	17 (4.3)	19 (4.8)	29 (7.3)	22 (5.5)	22 (5.5)	13 (3.3)
Ductal+ Lobular/Other	4 (1.0)	4 (1.0)	8 (2.0)	6 (1.5)	10 (2.5)	10 (2.5)	2 (0.5)	3 (0.8)	7 (1.8)	10 (2.5)	7 (1.8)	8 (2.0)	4 (1.0)	5 (1.3)	8 (2.0)
HER2 Positive	59 (15)	40 (10)	57 (15)	47 (12)	45 (11)	50 (13)	53 (13)	49 (12)	48 (12)	48 (12)	47 (12)	57 (14)	44 (11)	49 (12)	51 (13)
ER Positive	325 (81)	345 (87)	345 (86)	339 (85)	356 (89)	334 (84)	334 (84)	349 (88)	341 (86)	352 (88)	341 (85)	347 (87)	340 (85)	342 (86)	340 (85)
PGR Positive	267 (67)	290 (73)	289 (72)	287 (72)	301 (76)	279 (70)	289 (73)	295 (74)	285 (72)	286 (72)	283 (71)	290 (73)	288 (72)	284 (72)	289 (72)

Median (IQR); n (%)

Supplementary Table 2 Adjusting the fully adjusted Cox regression models of Se, SELENOP and GPx3 quintiles for type of treatment one by one regarding overall survival.

Characteristic	+ Breast Surgery Method		+ Axillary Surgery Method		+ Endocrine Treatment		+ Cytotoxic Treatment		+ Immuno Treatment		+ Radio Treatment	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Selenium Quintiles												
1	—	—	—	—	—	—	—	—	—	—	—	—
2	0.65	0.47 to 0.88	0.62	0.45 to 0.85	0.63	0.46 to 0.87	0.63	0.46 to 0.87	0.63	0.46 to 0.87	0.66	0.48 to 0.90
3	0.54	0.39 to 0.75	0.52	0.37 to 0.73	0.53	0.38 to 0.74	0.54	0.38 to 0.75	0.54	0.39 to 0.75	0.54	0.39 to 0.75
4	0.48	0.33 to 0.68	0.47	0.33 to 0.67	0.47	0.33 to 0.67	0.47	0.33 to 0.67	0.47	0.33 to 0.68	0.48	0.34 to 0.69
5	0.44	0.29 to 0.65	0.42	0.28 to 0.63	0.42	0.28 to 0.63	0.43	0.29 to 0.64	0.43	0.29 to 0.64	0.44	0.29 to 0.66
Selenoprotein P Quintiles												
1	—	—	—	—	—	—	—	—	—	—	—	—
2	0.54	0.39 to 0.75	0.55	0.39 to 0.77	0.54	0.39 to 0.76	0.54	0.39 to 0.76	0.53	0.38 to 0.75	0.54	0.39 to 0.76
3	0.60	0.43 to 0.83	0.60	0.43 to 0.83	0.60	0.43 to 0.83	0.59	0.43 to 0.82	0.60	0.44 to 0.84	0.61	0.44 to 0.85
4	0.47	0.33 to 0.67	0.46	0.32 to 0.66	0.46	0.32 to 0.66	0.46	0.32 to 0.66	0.45	0.31 to 0.64	0.47	0.33 to 0.68
5	0.51	0.36 to 0.73	0.51	0.36 to 0.74	0.51	0.36 to 0.73	0.52	0.36 to 0.74	0.52	0.36 to 0.74	0.53	0.37 to 0.75
GPx3 Quintiles												
1	—	—	—	—	—	—	—	—	—	—	—	—
2	0.76	0.56 to 1.03	0.79	0.58 to 1.07	0.76	0.56 to 1.03	0.76	0.56 to 1.03	0.77	0.57 to 1.05	0.78	0.58 to 1.06
3	0.45	0.31 to 0.65	0.42	0.29 to 0.62	0.43	0.30 to 0.63	0.44	0.30 to 0.63	0.43	0.30 to 0.62	0.45	0.31 to 0.65
4	0.59	0.42 to 0.84	0.60	0.42 to 0.85	0.59	0.42 to 0.84	0.60	0.42 to 0.85	0.61	0.43 to 0.86	0.60	0.42 to 0.85
5	0.53	0.37 to 0.76	0.53	0.37 to 0.77	0.52	0.36 to 0.75	0.52	0.36 to 0.74	0.52	0.36 to 0.75	0.53	0.37 to 0.76

HR = Hazard Ratio, CI = Confidence Interval

Fully Adjusted Model, N=1996. Missing values in adjustment factors were imputed via multiple imputation. Model includes Age, Menopausal Status, ER Expression, PGR Expression, HER2 Expression, Nottingham Histologic Grade, Histologic Type, Number of Lymph Nodes involved, Mode of Diagnosis, Tumour Size [mm] + Treatment options.

Supplementary Table 3 Adjusting the fully adjusted Cox regression models of Se, SELENOP and GPx3 quintiles for type of treatment one by one regarding recurrence free survival.

Characteristic	+ Breast Surgery Type		+ Axillary Surgery Type		+ Endocrine Treatment		+ Cytotoxic Treatment		+ Immuno Treatment		+ Radio Treatment	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Selenium Quintiles												
1	—	—	—	—	—	—	—	—	—	—	—	—
2	0.88	0.56 to 1.38	0.86	0.55 to 1.36	0.88	0.56 to 1.39	0.87	0.55 to 1.37	0.88	0.56 to 1.38	0.88	0.56 to 1.38
3	0.68	0.42 to 1.11	0.66	0.41 to 1.07	0.67	0.41 to 1.08	0.68	0.42 to 1.11	0.70	0.43 to 1.14	0.68	0.42 to 1.09
4	0.64	0.39 to 1.05	0.65	0.40 to 1.07	0.65	0.40 to 1.06	0.64	0.39 to 1.05	0.64	0.39 to 1.06	0.64	0.39 to 1.04
5	0.87	0.54 to 1.41	0.88	0.55 to 1.43	0.86	0.53 to 1.39	0.89	0.55 to 1.44	0.88	0.54 to 1.42	0.87	0.54 to 1.40
Selenoprotein P Quintiles												
1	—	—	—	—	—	—	—	—	—	—	—	—
2	1.15	0.73 to 1.80	1.16	0.74 to 1.83	1.19	0.75 to 1.87	1.15	0.73 to 1.80	1.14	0.73 to 1.79	1.15	0.73 to 1.81
3	0.93	0.58 to 1.50	0.94	0.59 to 1.52	0.92	0.57 to 1.48	0.91	0.57 to 1.46	0.95	0.59 to 1.53	0.94	0.58 to 1.51
4	0.73	0.44 to 1.22	0.74	0.44 to 1.23	0.73	0.44 to 1.21	0.72	0.43 to 1.20	0.71	0.42 to 1.18	0.72	0.43 to 1.21
5	0.80	0.48 to 1.33	0.80	0.48 to 1.34	0.81	0.48 to 1.35	0.81	0.48 to 1.35	0.82	0.49 to 1.36	0.80	0.48 to 1.33
GPx3 Quintiles												
1	—	—	—	—	—	—	—	—	—	—	—	—
2	0.71	0.46 to 1.12	0.74	0.47 to 1.15	0.71	0.45 to 1.11	0.71	0.45 to 1.11	0.73	0.47 to 1.14	0.72	0.46 to 1.13
3	0.68	0.43 to 1.08	0.65	0.41 to 1.04	0.63	0.40 to 1.00	0.68	0.43 to 1.08	0.65	0.41 to 1.03	0.67	0.42 to 1.06
4	0.48	0.29 to 0.79	0.49	0.30 to 0.81	0.48	0.29 to 0.79	0.50	0.30 to 0.82	0.50	0.30 to 0.82	0.48	0.29 to 0.79
5	0.58	0.36 to 0.94	0.59	0.36 to 0.95	0.57	0.35 to 0.93	0.57	0.35 to 0.93	0.57	0.35 to 0.92	0.58	0.36 to 0.93

HR = Hazard Ratio, CI = Confidence Interval

Fully Adjusted Model, N=1996. Missing values in adjustment factors were imputed via multiple imputation. Model includes Age, Menopausal Status, ER Expression, PGR Expression, HER2 Expression, Nottingham Histologic Grade, Histologic Type, Number of Lymph Nodes involved, Mode of Diagnosis, Tumour Size [mm] + Treatment options.

Supplementary Table 4 Overall survival with complete cases.

Characteristic	At Risk	Death	Univariate ^a		Age Adjusted ^b		Fully Adjusted ^c	
	N	N	HR	95% CI	HR	95% CI	HR	95% CI
Selenium Quintiles								
1	400	119	—	—	—	—	—	—
2	399	62	0.48	0.35 to 0.65	0.59	0.44 to 0.81	0.70	0.50 to 0.98
3	399	53	0.40	0.29 to 0.55	0.53	0.38 to 0.74	0.54	0.38 to 0.76
4	399	43	0.32	0.22 to 0.45	0.46	0.32 to 0.66	0.43	0.29 to 0.63
5	399	33	0.24	0.17 to 0.36	0.37	0.25 to 0.55	0.42	0.27 to 0.65
Total	1,996	310						
Selenium per SD increase			0.59	0.52 to 0.66	0.71	0.63 to 0.81	0.70	0.61 to 0.80
SELENOP Quintiles								
1	400	106	—	—	—	—	—	—
2	399	55	0.47	0.34 to 0.65	0.53	0.38 to 0.73	0.54	0.38 to 0.77
3	399	60	0.51	0.37 to 0.70	0.61	0.44 to 0.83	0.60	0.42 to 0.85
4	399	43	0.36	0.26 to 0.52	0.42	0.30 to 0.61	0.59	0.41 to 0.84
5	399	46	0.39	0.27 to 0.55	0.46	0.32 to 0.65	0.44	0.29 to 0.65
Total	1,996	310						
SELENOP per SD increase			0.65	0.58 to 0.73	0.71	0.63 to 0.80	0.75	0.66 to 0.85
GPx3 Quintiles								
1	400	105	—	—	—	—	—	—
2	399	72	0.64	0.48 to 0.87	0.80	0.59 to 1.08	0.77	0.56 to 1.07
3	399	40	0.34	0.24 to 0.49	0.45	0.31 to 0.65	0.47	0.32 to 0.70
4	399	50	0.44	0.31 to 0.61	0.60	0.43 to 0.85	0.59	0.40 to 0.87
5	399	43	0.37	0.26 to 0.53	0.53	0.37 to 0.76	0.53	0.36 to 0.78
Total	1,996	310						
GPx3 per SD increase			0.65	0.58 to 0.73	0.76	0.68 to 0.85	0.76	0.67 to 0.86

HR = hazard ratio, CI = confidence interval

^a Crude model, N=1996. No missing values.

^b Age adjusted model, N=1996. No missing values. Adjusted for age at diagnosis of breast cancer.

^c Fully Adjusted Model, N=1798.

Supplementary Table 5 Recurrence free survival with complete cases.

Characteristic	At Risk	Recurrence	Univariate ^a		Age Adjusted ^b		Fully Adjusted ^c	
	N	N	HR	95% CI	HR	95% CI	HR	95% CI
Selenium Quintiles								
1	400	43	—	—	—	—	—	—
2	399	36	0.78	0.50 to 1.22	0.80	0.52 to 1.25	0.93	0.57 to 1.51
3	399	29	0.61	0.38 to 0.98	0.64	0.40 to 1.02	0.66	0.40 to 1.11
4	399	27	0.56	0.35 to 0.91	0.59	0.36 to 0.96	0.64	0.38 to 1.08
5	399	32	0.67	0.42 to 1.05	0.70	0.44 to 1.11	0.87	0.52 to 1.46
Total	1,996	167						
Selenium per SD increase			0.90	0.77 to 1.06	0.92	0.78 to 1.08	0.95	0.80 to 1.13
SELENOP Quintiles								
1	400	37	—	—	—	—	—	—
2	399	43	1.10	0.71 to 1.71	1.13	0.73 to 1.75	1.25	0.78 to 2.01
3	399	34	0.84	0.53 to 1.35	0.87	0.54 to 1.38	0.88	0.52 to 1.48
4	399	26	0.65	0.39 to 1.07	0.66	0.40 to 1.08	0.89	0.53 to 1.51
5	399	27	0.67	0.41 to 1.10	0.67	0.41 to 1.11	0.75	0.43 to 1.31
Total	1,996	167						
SELENOP per SD increase			0.84	0.71 to 0.99	0.84	0.71 to 1.00	0.89	0.75 to 1.05
GPx3 Quintiles								
1	400	47	—	—	—	—	—	—
2	399	35	0.71	0.46 to 1.09	0.73	0.47 to 1.13	0.69	0.43 to 1.11
3	399	32	0.62	0.40 to 0.98	0.64	0.41 to 1.01	0.69	0.43 to 1.12
4	399	25	0.49	0.30 to 0.80	0.51	0.31 to 0.83	0.42	0.24 to 0.72
5	399	28	0.55	0.34 to 0.88	0.57	0.35 to 0.91	0.59	0.35 to 0.97
Total	1,996	167						
GPx3 per SD increase			0.81	0.68 to 0.95	0.83	0.70 to 0.98	0.83	0.70 to 0.98

HR = hazard ratio, CI = confidence interval

^a Crude model, N=1996. No missing values.

^b Age adjusted model, N=1996. No missing values. Adjusted for age at diagnosis of breast cancer.

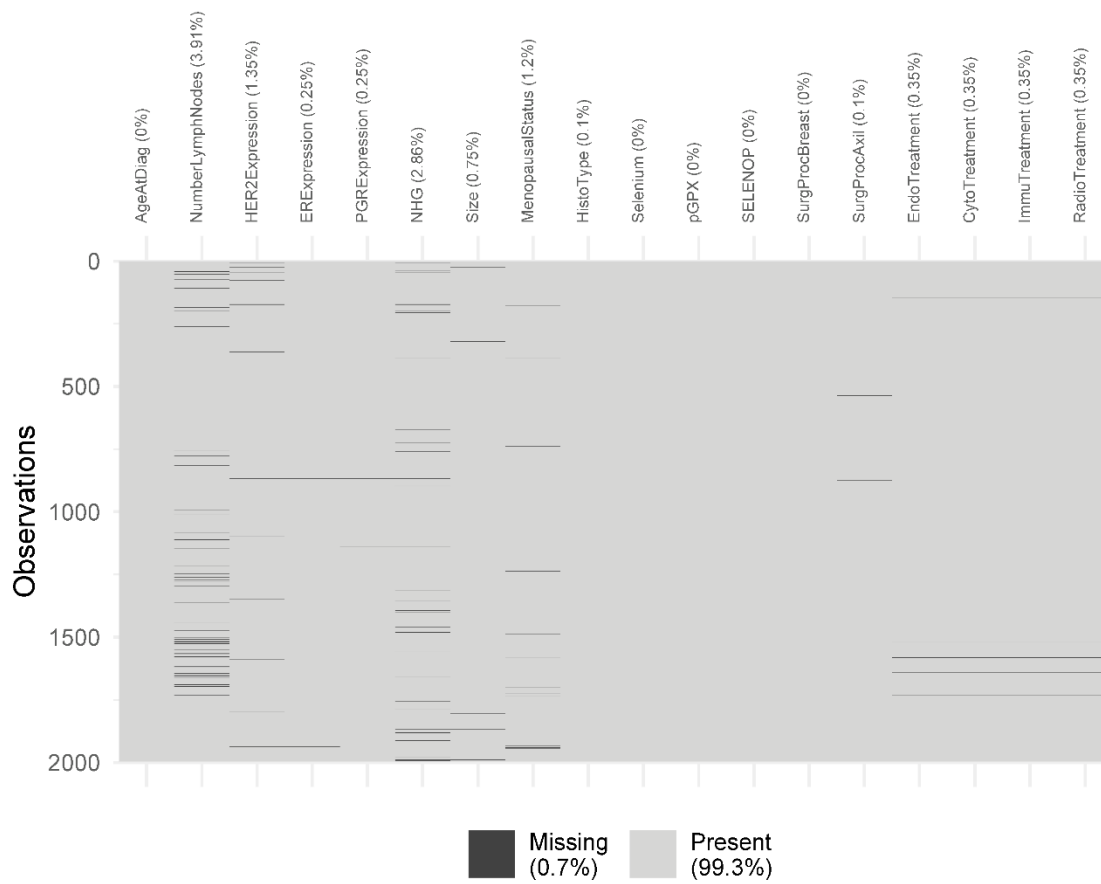
^c Fully Adjusted Model, N=1798.

Supplementary Table 6 Overall and recurrence free survival excluding male breast cancer cases.

Characteristic	Overall Survival ^a		Recurrence Free Survival ^a	
	HR	95% CI	HR	95% CI
Selenium Quintiles				
1	—	—	—	—
2	0.63	0.46, 0.87	0.86	0.55, 1.36
3	0.53	0.38, 0.75	0.67	0.41, 1.08
4	0.47	0.32, 0.67	0.62	0.38, 1.02
5	0.41	0.28, 0.62	0.85	0.53, 1.37
Selenium per SD increase	0.71	0.63, 0.81	0.96	0.82, 1.13
SELENOP Quintiles				
1	—	—	—	—
2	0.55	0.40, 0.77	1.16	0.74, 1.82
3	0.60	0.43, 0.84	0.93	0.58, 1.50
4	0.46	0.32, 0.67	0.71	0.43, 1.19
5	0.51	0.35, 0.73	0.79	0.47, 1.32
SELENOP per SD increase	0.74	0.65, 0.83	0.85	0.72, 1.00
GPx3 Quintiles				
1	—	—	—	—
2	0.74	0.54, 1.01	0.71	0.45, 1.11
3	0.43	0.30, 0.62	0.64	0.41, 1.02
4	0.59	0.42, 0.84	0.47	0.29, 0.78
5	0.51	0.36, 0.74	0.56	0.35, 0.91
GPx3 per SD increase	0.75	0.66, 0.84	0.82	0.70, 0.96

HR = Hazard Ratio, CI = Confidence Interval

^a Fully Adjusted Model, N=1988. 8 male breast cancer cases excluded. Missing values in adjustment factors were imputed via multiple imputation. Model includes Age, Menopausal Status, Mode of Diagnosis, ER Expression, PGR Expression, HER2 Expression, Nottingham Histologic Grade, Histologic Type, Number of Lymph Nodes involved, and Tumour Size [mm]



Supplementary Fig 1. Missing data among the variables included in the analyses.