

Table 1. Distribution of baseline characteristics across tertiles of OPG adjusted for age and sex (n=6279). Continuous variables are reported as mean with 95% confidence interval and categorical values as percentage. The Tromsø Study (1994-2008)

	OPG tertiles			p (trend)
	T1 0.46-2.78 ng/ml	T2 2.79-3.55 ng/ml	T3 3.56-25.81 ng/ml	
Number of subjects	2093	2093	2093	
Age (years)*	53.6 (53.2-54.0)	61.5 (61.2-61.9)	66.7 (66.3-67.1)	<0.001
Sex (% men)†	58.5	48.2	41.6	<0.001
Never smoking (%)	31.3	30.0	35.3	
Former smoker (%)	36.6	37.8	33.0	
Current smoker (%)	32.1	32.3	31.7	
Body mass index (kg/m ²)	26.4 (26.2-26.6)	26.1 (25.9-26.2)	25.6 (25.5-25.8)	<0.001
Systolic BP (mm Hg)	142 (141-143)	144 (143-145)	149 (148-150)	<0.001
Diastolic BP (mm Hg)	82 (82-83)	83 (83-84)	84 (84-85)	<0.001
Total cholesterol (mmol/L)	6.63 (6.57-6.69)	6.81 (6.76-6.86)	6.73 (6.68-6.79)	0.025
HDL cholesterol (mmol/L)	1.48 (1.46-1.50)	1.53 (1.51-1.55)	1.57 (1.55-1.58)	<0.001
Triglycerides (mmol/L)	1.67 (1.63-1.72)	1.62 (1.58-1.66)	1.59 (1.55-1.64)	0.022
HbA1c (%)‡	5.40 (5.37-5.44)	5.45 (5.42-5.48)	5.56 (5.53-5.59)	<0.001
C-reactive protein (mg/L)	2.26 (1.95-2.56)	2.52 (2.24-2.80)	3.13 (2.83-3.44)	<0.001
Creatinine (µmol/L)	78.7 (78.0-79.5)	77.7 (77.0-78.4)	79.6 (78.8-80.4)	0.111
DM or HbA1c>6.1 (%)‡	4.8	5.4	9.0	<0.001
DM (selfreported) (%)	1.4	1.7	3.9	<0.001

*Adjusted for sex †adjusted for age. BP = Blood pressure; DM = Diabetes Mellitus

‡8 % missing, all other variables complete or <1% missing

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Table 2. Organ distribution (numbers with percentages in brackets) of incident cancer

(n=948) in the total population (n=6279). The Tromsø Study (1994-2008)

	N	%	OPG tertiles		
			T1	T2	T3
Gastrointestinal system	276	(29.1)	50	89	137
Respiratory system	167	(17.6)	44	64	59
Breast	76	(8.0)	30	26	20
Female genital organs	43	(4.5)	17	8	18
Prostate gland	178	(18.8)	42	75	61
Urinary system	83	(8.8)	20	33	30
Miscellaneous*	125	(13.2)			

*(peritoneum, connective tissue, thyroid, hematopoietic, unknown primary site)

Table 3. Hazard ratios (HR) with 95% confidence intervals (CI) for incident cancer across tertiles of osteoprotegerin (OPG) and per 1 standard deviation (SD) increase in OPG levels. The Tromsø Study (1994-2008)

OPG	Cancer (n)	Unadjusted HR (95% CI) (n=6279)	Model 1 HR (95% CI) (n=6279)	Model 2 HR (95% CI) (n=5717)	Model 3 HR (95% CI) (n=5717)
T1	234	1.00	1.00	1.00	1.00
T2	343	1.53 (1.30-1.81)	1.14 (0.96-1.36)	1.08 (0.90-1.30)	1.08 (0.90-1.30)
T3	371	1.85 (1.57-2.18)	1.13 (0.94-1.38)	1.04 (0.85-1.28)	1.05 (0.86-1.29)
<i>P (trend)</i>		<i><0.001</i>	<i>0.25</i>	<i>0.76</i>	<i>0.70</i>
Per 1 SD	948	1.20 (1.15-1.24)	1.06 (0.99-1.15)	1.02 (0.94-1.11)	1.03 (0.94-1.12)

Women		n=3174	n=3174	n=2899	n=2899
T1	106	1.00	1.00	1.00	1.00
T2	116	1.07 (0.83-1.40)	0.78 (0.59-1.02)	0.72 (0.54-0.96)	0.72 (0.54-0.96)
T3	149	1.53 (1.19-1.96)	0.90 (0.68-1.20)	0.85 (0.63-1.15)	0.85 (0.63-1.16)
<i>P (trend)</i>		<i>0.001</i>	<i>0.63</i>	<i>0.41</i>	<i>0.43</i>
Per 1 SD	371	1.22 (1.11-1.34)	1.01 (0.90-1.14)	0.98 (0.86-1.11)	0.98 (0.86-1.12)

Men		n=3105	n=3105	n=2818	n=2818
T1	127	1.00	1.00	1.00	1.00
T2	207	1.77 (1.42-2.21)	1.20 (0.95-1.51)	1.17 (0.91-1.49)	1.17 (0.91-1.49)
T3	243	2.49 (2.01-3.09)	1.25 (0.97-1.61)	1.18 (0.90-1.54)	1.19 (0.91-1.56)
<i>P (trend)</i>		<i><0.001</i>	<i>0.099</i>	<i>0.28</i>	<i>0.24</i>
Per 1 SD	577	1.21 (1.16-1.26)	1.10 (1.00-1.22)	1.06 (0.95-1.19)	1.07 (0.96-1.19)

1 SD OPG: total population 1.12 mg/ml, women 1.06 mg/ml, men 1.17 mg/ml

Model 1: Adjusted for age (and sex)

Model 2; Adjusted for age, (sex), smoking, systolic blood pressure, BMI, HDL cholesterol, CRP and diabetes mellitus or HbA1c >6.1 %

Model 3; As model 1 + ischemic stroke and/or myocardial infarction before baseline

Number of events in model 2 and 3: total population n=869, women n=343, men n=526

Table 4. Hazard ratios (HR) with 95% confidence intervals (CI) for incident cancer across tertiles of osteoprotegerin (OPG) and per 1 standard deviation (SD) increase in OPG levels. The Tromsø Study (1994-2008).

OPG	Cancer	Unadjusted HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Gastrointestinal*		n=6279	n=6279	n=5717	n=5717
T1	50	1.00	1.00	1.00	1.00
T2	89	1.85 (1.31-2.62)	1.29 (0.89-1.85)	1.36 (0.93-2.00)	1.36 (0.93-2.00)
T3	137	3.20 (2.31-4.42)	1.75 (1.20-2.54)	1.77 (1.18-2.65)	1.79 (1.19-2.67)
<i>P (trend)</i>		<0.001	0.002	0.004	0.004
Per 1 SD	276	1.25 (1.18-1.32)	1.15 (1.01-1.30)	1.14 (0.99-1.32)	1.15 (1.00-1.32)
Respiratory†		n=6279	n=6279	n=5717	n=5717
T1	44	1.00	1.00	1.00	1.00
T2	64	1.51 (1.03-2.21)	1.13 (0.75-1.70)	0.99 (0.65-1.51)	0.99 (0.65-1.51)
T3	59	1.56 (1.06-2.31)	0.98 (0.62-1.55)	0.89 (0.55-1.42)	0.89 (0.55-1.43)
<i>P (trend)</i>		0.026	0.87	0.60	0.60
Per 1 SD	167	1.20 (1.09-1.32)	1.09 (0.92-1.30)	1.09 (0.90-1.32)	1.09 (0.90-1.32)
Breast (women)‡		n=3174	n=3174	n=2899	n=2899
T1	30	1.00	1.00	1.00	1.00
T2	26	0.85 (0.50-1.44)	0.70 (0.40-1.21)	0.68 (0.38-1.21)	0.68 (0.38-1.22)
T3	20	0.72 (0.41-1.26)	0.52 (0.27-0.98)	0.54 (0.28-1.06)	0.55 (0.28-1.08)
<i>P (trend)</i>		0.24	0.043	0.07	0.08
Per 1 SD	76	0.86 (0.67-1.11)	0.72 (0.53-0.99)	0.73 (0.53-1.02)	0.74 (0.53-1.03)
Prostatic§		n=3105	n=3105	n=2818	n=2818
T1	42	1.00	1.00	1.00	1.00
T2	75	1.90 (1.30-2.77)	1.32 (0.89-1.97)	1.23 (0.81-1.88)	1.23 (0.81-1.87)
T3	61	1.82 (1.23-2.70)	0.97 (0.61-1.53)	0.85 (0.52-1.38)	0.86 (0.53-1.40)
<i>P (trend)</i>		0.003	0.71	0.36	0.40
Per 1 SD	178	1.12 (0.99-1.26)	0.85 (0.69-1.06)	0.82 (0.65-1.04)	0.82 (0.66-1.04)
Genital (women) 		n=3174	n=3174	n=2899	n=2899
T1	17	1.00	1.00	1.00	1.00
T2	8	0.46 (0.20-1.07)	0.33 (0.14-0.78)	0.19 (0.07-0.54)	0.19 (0.07-0.55)
T3	18	1.13 (0.58-2.19)	0.64 (0.29-1.39)	0.46 (0.20-1.07)	0.47 (0.20-1.09)
<i>P (trend)</i>		0.72	0.35	0.10	0.10
Per 1 SD	43	1.14 (0.85-1.52)	0.94 (0.65-1.35)	0.85 (0.57-1.28)	0.86 (0.56-1.29)
Urinary tract ¶		n=6279	n=6279	n=5717	n=5717
T1	20	1.00	1.00	1.00	1.00
T2	33	1.71 (0.98-2.97)	1.34 (0.74-2.41)	1.20 (0.65-2.22)	1.20 (0.65-2.21)
T3	30	1.71 (0.97-3.01)	1.16 (0.60-2.24)	0.91 (0.45-1.85)	0.91 (0.45-1.85)
<i>P (trend)</i>		0.067	0.75	0.72	0.73
Per 1 SD	83	1.22 (1.08-1.37)	1.17 (0.96-1.42)	1.10 (0.84-1.45)	1.10 (0.84-1.45)

1 SD OPG; total population 1.12 ng/ml, women 1.06 ng/ml, men 1.17 ng/ml

Model 1: adjusted for age (and sex)

Model 2: Adjusted for age, (sex), smoking, BMI, systolic blood pressure, HDL cholesterol, CRP diabetes mellitus or HbA1c >6.1 %

Model 3: As model 1 + ischemic stroke and/or myocardial infarction before baseline

Number of events model 2 and 3: *n=252, †n= 158, ‡n=72, §n=165, ||n=37, ¶n=74

Table 5. Hazard ratios with 95% confidence intervals (HR, 95% CI) of death of cancer calculated for OPG tertile groups and per SD (1.12 ng/ml) increase in OPG levels (n=6279).

The Tromsø Study (1994-2007).

OPG	Cancer (n)	Unadjusted HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
All cancers*		n=6279	n=6279	n=5717	n=5717
T1	69	1.00	1.00	1.00	1.00
T2	132	1.98 (1.48-2.65)	1.40 (1.03-1.90)	1.33 (0.97-1.83)	1.33 (0.96-1.83)
T3	186	3.12 (2.37-4.12)	1.77 (1.28-2.43)	1.61 (1.15-2.26)	1.63 (1.16-2.28)
<i>P (trend)</i>		<0.001	<0.001	0.005	0.004
Per 1 SD	387	1.27 (1.22-1.33)	1.24 (1.14-1.35)	1.24 (1.11-1.39)	1.25 (1.11-1.39)
Gastrointestinal†		n=6279	n=6279	n=5717	n=5717
T1	18	1.00	1.00	1.00	1.00
T2	45	2.58 (1.49-4.46)	1.70 (0.96-3.00)	1.77 (0.97-3.23)	1.77 (0.97-3.23)
T3	69	4.42 (2.63-7.42)	2.21 (1.23-3.99)	2.23 (1.19-4.19)	2.28 (1.21-4.28)
<i>P (trend)</i>		<0.001	0.008	0.015	0.012
Per 1 SD	132	1.28 (1.19-1.37)	1.22 (1.04-1.43)	1.24 (1.03-1.51)	1.26 (1.04-1.51)
Respiratory‡		n=6279	n=6279	n=5717	n=5717
T1	28	1.00	1.00	1.00	1.00
T2	39	1.43 (0.88-2.33)	1.10 (0.66-1.84)	1.03 (0.60-1.76)	1.03 (0.60-1.76)
T3	43	1.76 (1.09-2.83)	1.14 (0.65-2.00)	1.09 (0.61-1.96)	1.09 (0.61-1.96)
<i>P (trend)</i>		0.020	0.65	0.76	0.77
Per 1 SD	110	1.23 (1.11-1.35)	1.18 (0.99-1.39)	1.21 (0.98-1.50)	1.21 (0.98-1.50)

Model 1: adjusted for age (and sex)

Model 2: Adjusted for age, sex, smoking, BMI, systolic blood pressure, HDL cholesterol, CRP, diabetes mellitus or HbA1c >6.1 %

Model 3: As model 1 + ischemic stroke and/or myocardial infarction before baseline

Number of events model 2 and 3: *n=352, †n= 118, ‡n=103

Appendix table 1. Age- and sex-stratified hazard ratios (HR) with 95% confidence intervals (CI) for incident cancer across OPG tertile groups and per SD increase in OPG levels. The Tromsø Study (1994-2008).

OPG	Cancer	Unadjusted HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Women					
< 60 yrs		n=1264	n= 1264	n=1146	n=1146
T1	36	1.00	1.00	1.00	1.00
T2	32	0.86 (0.54-1.39)	0.60 (0.37-0.98)	0.53 (0.32-0.89)	0.53 (0.32-0.89)
T3	36	0.95 (0.60-1.51)	0.59 (0.37-0.96)	0.45 (0.26-0.77)	0.44 (0.26-0.75)
<i>P (trend)</i>		0.83	0.046	0.004	0.003
Per 1SD	104	1.02 (0.84-1.24)	0.86 (0.69-1.08)	0.75 (0.58-0.97)	0.73 (0.57-0.94)
Women					
≥ 60 yrs		n=1910	n=1910	n=1753	n=1753
T1	82	1.00	1.00	1.00	1.00
T2	89	1.11 (0.83-1.50)	1.05 (0.77-1.42)	1.03 (0.75-1.41)	1.03 (0.75-1.41)
T3	96	1.38 (1.02-1.85)	1.21 (0.88-1.66)	1.26 (0.90-1.77)	1.27 (0.90-1.78)
<i>P (trend)</i>		0.034	0.25	0.18	0.17
Per 1 SD	267	1.14 (1.02-1.28)	1.08 (0.95-1.23)	1.06 (0.93-1.22)	1.07 (0.93-1.23)
Men					
< 60 yrs		n=1390	n=1390	n=1246	n=1246
T1	35	1.00	1.00	1.00	1.00
T2	53	1.51 (0.99-2.32)	1.02 (0.66-1.57)	1.03 (0.65-1.64)	1.03 (0.65-1.64)
T3	87	2.79 (1.89-4.14)	1.64 (1.09-2.45)	1.48 (0.95-2.31)	1.48 (0.95-2.31)
<i>P (trend)</i>		<0.001	0.006	0.048	0.048
Per 1 SD	175	1.14 (1.07-1.22)	1.18 (1.04-1.35)	1.10 (0.90-1.34)	1.10 (0.90-1.34)
Men					
≥ 60yrs		n=1715	n=1715	n=1572	n=1572
1:	119	1.00	1.00	1.00	1.00
2:	142	1.23 (0.97-1.57)	1.14 (0.89-1.46)	1.11 (0.86-1.44)	1.11 (0.86-1.44)
3:	141	1.48 (1.16-1.90)	1.25 (0.96-1.64)	1.24 (0.93-1.64)	1.25 (0.94-1.65)
<i>P (trend)</i>		0.002	0.099	0.138	0.124
Per 1 SD	402	1.20 (1.08-1.33)	1.11 (0.99-1.25)	1.09 (0.97-1.23)	1.09 (0.97-1.23)

1 SD OPG: Men; < 60 years; 0.99 ng/ml, ≥ 60 years 1.14 ng/ml, women; < 60 years 0.81 ng/ml, ≥ 60 years 1.03 ng/ml

Model 1: Adjusted for age

Model 2: Adjusted for age, smoking, systolic blood pressure, BMI, HDL cholesterol, CRP diabetes mellitus or HbA1c >6.1 %

Model 3: As model 1 + ischemic stroke and/or myocardial infarction before baseline

Number of events in model 2 and 3: women: < 60 yrs n=94, ≥ 60 yrs n=249, men < 60 yrs n=153, ≥ 60 yrs n=373

Appendix table 2. Age stratified hazard ratios (HR) with 95% confidence intervals (CI) for incident breast cancer and gastrointestinal cancer across tertiles of osteoprotegerin (OPG) and per 1 standard deviation (SD)* increase in OPG levels. The Tromsø Study (1994-2008).

OPG	Cancer (n)	Unadjusted HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Breast (women)					
< 60 years[†]		n=1264	n=1264	n=1146	
T1	17	1.00	1.00	1.00	
T2	7	0.41 (0.17-0.98)	0.28 (0.12-0.69)	0.23 (0.09-0.61)	
T3	8	0.46 (0.20-1.08)	0.29 (0.12-0.69)	0.24 (0.10-0.61)	
<i>P (trend)</i>		0.051	0.004	0.002	
Per 1 SD	32	0.71 (0.47-1.07)	0.55 (0.35-0.88)	0.51 (0.31-0.83)	
Breast (women)					
≥ 60 years[‡]		n=1910	n=1910	n=1753	n=1753
T1	16	1.00	1.00	1.00	1.00
T2	14	0.90 (0.44-1.83)	0.88 (0.42-1.83)	0.90 (0.42-1.94)	0.91 (0.42-1.95)
T3	14	1.02 (0.50-2.08)	0.98 (0.45-2.14)	1.10 (0.49-2.46)	1.10 (0.49-2.47)
<i>P (trend)</i>		0.978	0.948	0.835	0.827
Per 1 SD	44	0.96 (0.70-1.31)	0.93 (0.66-1.32)	0.96 (0.67-1.36)	0.96 (0.67-1.38)
Gastrointestinal					
< 60 years[§]		n=2654	n=2654	n=2392	n=2392
T1	16	1.00	1.00	1.00	1.00
T2	15	0.93 (0.46-1.88)	0.64 (0.32-1.32)	0.74 (0.34-1.59)	0.74 (0.34-1.60)
T3	35	2.24 (1.24-4.05)	1.39 (0.75-2.59)	1.44 (0.72-2.89)	1.44 (0.72-2.90)
<i>P (trend)</i>		0.004	0.145	0.179	0.176
Per 1 SD	66	1.14 (1.03-1.27)	1.15 (0.92-1.43)	1.08 (0.80-1.46)	1.09 (0.80-1.49)
<i>P value</i>		0.015	0.214	0.625	0.576
Gastrointestinal					
≥ 60 years		n=3625	n=3625	n=3325	n=3325
T1	54	1.00	1.00	1.00	1.00
T2	68	1.29 (0.90-1.84)	1.20 (0.83-1.73)	1.20 (0.82-1.75)	1.20 (0.82-1.75)
T3	88	1.96 (1.40-2.75)	1.63 (1.13-2.37)	1.67 (1.14-2.47)	1.68 (1.14-2.48)
<i>P (trend)</i>		<0.0001	0.009	0.008	0.008
Per 1 SD	210	1.26 (1.11-1.43)	1.16 (1.00-1.34)	1.16 (1.00-1.35)	1.17 (1.00-1.36)

*1 SD OPG; total population; < 60 years 0.91 ng/ml, ≥ 60 years 1.09 ng/ml, women < 60 years 0.81 ng/ml, women ≥ 60 years 1.03 ng/ml

Model 1: adjusted for age (and sex)

Model 2: Adjusted for age, (sex), smoking, BMI, systolic blood pressure, HDL cholesterol, CRP, diabetes mellitus or HbA1c >6.1 %

Model 3: As model 1 + ischemic stroke and/or myocardial infarction before baseline

Number of events model 2 and 3: [†]n=30, [‡]n= 42, [§]n=57, ^{||}n=195

Appendix table 3. Hazard ratios with 95% confidence intervals (HR, 95% CI) of death of cancer calculated for OPG tertile groups and per SD (women; 1.06 ng/ml, men; 1.17 ng/ml) increase in OPG levels in women (n=3174) and men (n=3105). The Tromsø Study (1994-2007).

OPG	Cancer (n)	Unadjusted HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Women					
All cancers*		n=3174	n=3174	n=2899	n=2899
T1	34	1.00	1.00	1.00	1.00
T2	37	1.07 (0.67-1.70)	0.70 (0.43-1.13)	0.67 (0.41-1.11)	0.67 (0.41-1.12)
T3	70	2.25 (1.50-3.40)	1.11 (0.69-1.79)	1.07 (0.65-1.77)	1.07 (0.65-1.78)
<i>P (trend)</i>		<0.001	0.37	0.52	0.51
Per 1 SD	141	1.47 (1.29-1.68)	1.21 (1.02-1.43)	1.18 (0.98-1.42)	1.19 (0.98-1.44)
Gastrointestinal†		n=3174	n=3174	n=2899	n=2899
T1	9	1.00	1.00	1.00	1.00
T2	14	1.52 (0.66-3.52)	0.93 (0.39-2.21)	0.93 (0.38-2.26)	0.94 (0.39-2.28)
T3	32	3.91 (1.87-8.19)	1.72 (0.75-3.97)	1.96 (0.82-4.68)	1.97 (0.82-4.71)
<i>P (trend)</i>		<0.001	0.098	0.059	0.058
Per 1 SD	55	1.63 (1.34-1.98)	1.30 (1.02-1.68)	1.37 (1.05-1.74)	1.39 (1.06-1.83)
Men					
All cancers*		n=3105	n=3105	n=2818	n=2818
T1	41	1.00	1.00	1.00	1.00
T2	83	2.12 (1.46-3.09)	1.34 (0.90-1.98)	1.35 (0.89-2.03)	1.35 (0.89-2.04)
T3	122	3.71 (2.60-5.29)	1.66 (1.10-2.49)	1.55 (1.00-2.39)	1.57 (1.01-2.42)
<i>P (trend)</i>		<0.001	0.013	0.056	0.048
Per 1 SD	246	1.26 (1.20-1.32)	1.26 (1.14-1.39)	1.28 (1.11-1.47)	1.28 (1.11-1.47)
Gastrointestinal†		n=3105	n=3105	n=2818	n=2818
T1	13	1.00	1.00	1.00	1.00
T2	30	2.41 (1.26-4.63)	1.39 (0.71-2.75)	1.45 (0.70-3.02)	1.47 (0.71-3.04)
T3	34	3.22 (1.70-6.11)	1.23 (0.59-2.56)	1.15 (0.52-2.54)	1.19 (0.54-2.64)
<i>P (trend)</i>		<0.001	0.74	0.95	0.87
Per 1 SD	77	1.24 (1.13-1.37)	1.16 (0.91-1.48)	1.13 (0.85-1.50)	1.13 (0.86-1.50)

Model 1: adjusted for age

Model 2: Adjusted for age, smoking, BMI, systolic blood pressure, total cholesterol, CRP diabetes mellitus or HbA1c >6.1 %

Model 3: As model 1 + ischemic stroke and/or myocardial infarction before baseline

Number of events model 2 and 3: Women: all cancers n=128, GI n=51. Men: All cancers 224, GI cancer n=57.