Plasma testosterone in the general population, cancer prognosis and cancer risk: a prospective cohort study

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Background: Testosterone is an important anabolic hormone in humans and *in vitro* testosterone stimulates growth of lung and colon cancer cells. We tested the hypothesis that plasma testosterone associate with increased risk of cancer and with increased risk of early death after cancer.

Materials and methods: Plasma testosterone was measured in 8771 20- to 94-year-old men and women who participated in a prospective study of the general population. Participants were included in 1981–1983 and followed for a median of 22 years (range: 0–30 years).

Results: During follow-up, 1140 men and 809 women developed cancer. For risk of early death after cancer, for men, after adjustment for age at diagnosis, tumour stage at diagnosis, and time since blood-sampling, the hazard ratio was 1.30 [95% confidence interval (CI) 1.03–1.65] for the 2nd quintile, 1.31 (1.02–1.67) for the 3rd quintile, 1.52 (1.19–1.93) for the 4th quintile, and 1.52 (1.20–1.91) for the 5th quintile, versus the 1st quintile. For women, corresponding hazard ratios were 1.09 (0.81–1.46), 1.17 (0.86–1.59), 1.03 (0.76–1.39), and 1.80 (1.32–2.46). For risk of cancer, multifactorially adjusted hazard ratios for risk of any cancer were 1.07 (95% CI 0.98–1.18) and 1.06 (0.93–1.22) for men and women, respectively, when testosterone doubled. For both men and women, a doubling of testosterone was not associated with risk of any cancer type.

Conclusions: In this prospective study of 8771 men and women from the general population followed for >30 years, increased levels of testosterone were associated with a 30%–80% increased risk of early death after cancer, but unchanged risk of incident cancer.

Key words: testosterone, cancer, survival, human, prospective cohort

introduction

Testosterone is the most important androgen in humans and affects the development of many different tissues and organs [1]. Testosterone is a transcription factor regulating protein synthesis, and plays a key part in increasing intracellular protein levels. This results in tissue proliferation and heightened basal metabolism and energy consumption. As such, testosterone is among the most important anabolic hormones in the human organism. The pathophysiological effects have not been fully determined but it appears that testosterone stimulates growth of lung and colon cancer cells *in vitro*, a mechanism that can be halted with anti-androgens [2, 3]. Therefore, it is possible that levels of plasma testosterone may be associated with both cancer risk and survival after a cancer diagnosis.

There are only very few studies examining the association between plasma testosterone and overall cancer risk and/or

cancer types. The only exception is prostate cancer where several studies have reported divergent results [4–10]. Three population-based studies including 600–3600 men showed a positive association [4, 5, 9], while four studies with 300–3300 men did not find an association. Finally, a pooled analysis of 18 prospective studies including 10 324 men did not find an association between testosterone levels and prostate cancer risk [6]. For other common cancer types, results from a study of 4165 men aged 70–88 years suggested that increased testosterone levels may be associated with increased risk of lung cancer but not with colon cancer risk [9]. Thus, the association between testosterone levels and cancer risk has only been examined for a few specific cancer types and, to our knowledge, never in women.

Although male cancer patients have lower levels of plasma testosterone [11], just one study examining the association between testosterone levels and survival in 136 male cancer patients has been carried out showing a null association [12]. Furthermore, the only observational study of plasma testosterone values and gender differences in cancer aggressiveness has suggested that the higher risk of cancer death in men may be explained by the higher testosterone levels [13]. Hence, it

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remains unclear whether and to what extent, testosterone is associated with early death after cancer.

Importantly, there are no prospective studies of the general population including both men and women, examining the association between testosterone levels and risk of cancer, and the risk of early death after cancer. We therefore tested the hypothesis that plasma testosterone associates with increased risk of cancer and with increased risk of early death after cancer, in a prospective study of 8771 men and women from the general population with up to 30 years of follow-up.

materials and methods

setting and participants

Study participants were men and women examined in 1981 through 1983 in the Copenhagen City Heart Study [14, 15]. Participants were 20–94 years old and were randomly selected from the Danish Civil Registration System to represent the general population; the participation rate was 63% (supplementary Figure S1, available at *Annals of Oncology* online). All participants were white and of Danish descent. There were no losses to follow-up. The study was approved by Herlev Hospital and a Danish ethical committee (KF-100.2039/91). All participants gave written informed consent. For details see supplementary Material, available at *Annals of Oncology* online.

testosterone measurements and covariates

On the day of attendance, participants filled in a questionnaire which was reviewed together with an investigator. Furthermore, all participants had a physical examination carried out, and had blood samples drawn for biochemical analysis. For details on testosterone measurements and covariates, see supplementary Material, available at *Annals of Oncology* online.

statistical analysis

Statistical analyses were carried out using Stata 12.1 SE software. We used Cox proportional hazard regression models to analyse time to event and estimate hazard ratios with 95% confidence intervals (CIs). For details on statistical analysis, see supplementary Methods, available at *Annals of Oncology* online.

results

Baseline characteristics of participants in the testosterone quintiles are summarized in Table 1. We studied 4453 men and 4318 women from the Copenhagen City Heart Study. There were no losses to follow-up. Levels of testosterone associated with smoking status, number of pack-years, BMI, and alcohol consumption in men. In women, levels of testosterone associated with smoking status, cumulative smoking, BMI, alcohol consumption, level of education, menopausal status, and use of oral contraceptives. The number of cancers for men and women in

Table 1. Baseline characteristics of participants from the general population by quintiles of plasma testosterone

Characteristics	Plasma testosterone levels					P-trend
	1st quintile	2nd quintile	3rd quintile	4th quintile	5th quintile	
Men						
Testosterone levels, nmol/l	7.2 (6.2–8.2)	10.4 (9.7–11.2)	13.6 (12.8–14.4)	17.7 (16.5–18.8)	23.8 (21.6–26.7)	
No. of participants	906	895	875	898	879	–
Age, years	59 (49–66)	59 (49–66)	57 (48–65)	57 (48–66)	58 (49–65)	0.23
Current smokers, No. (%)	509 (56)	535 (60)	569 (65)	582 (65)	648 (74)	6×10^{-15}
Cumulative smoking, pack-years	30 (14–42)	29 (13–42)	30 (16–41)	30 (14–43)	30 (18–45)	1×10^{-3}
Body mass index, kg/m^2	27 (25–29)	26 (24–29)	26 (24–28)	25 (23–27)	24 (22–26)	3×10^{-76}
Alcohol consumption >252 g/week, No. (%)	161 (18)	164 (18)	172 (20)	163 (18)	213 (24)	3×10^{-3}
Less than 13 years of education, No. (%)	606 (67)	623 (70)	567 (65)	595 (66)	625 (71)	0.39
Low income, No. (%)	217 (24)	216 (24)	188 (22)	228 (25)	250 (28)	0.07
Women						
Testosterone levels, nmol/l	1.2 (1.1–1.4)	1.6 (1.5–1.7)	1.9 (1.8–2.0)	2.2 (2.1–2.3)	2.8 (2.6–3.2)	
No. of participants	930	911	937	845	695	–
Age, years	58 (48–65)	57 (47–64)	57 (47–64)	56 (47–64)	57 (47–65)	0.15
Current smokers, No. (%)	423 (45)	474 (52)	490 (52)	488 (58)	435 (63)	5×10^{-11}
Cumulative smoking, pack-years	10 (0–23)	11 (0–24)	13 (0–25)	15 (3–27)	15 (0–25)	6×10^{-9}
Body mass index, kg/m^2	24 (22–26)	24 (22–27)	24 (22–27)	24 (22–27)	24 (22–27)	0.02
Alcohol consumption >168 g/week, No. (%)	48 (5)	65 (7)	62 (7)	66 (8)	70 (10)	4×10^{-4}
Less than 13 years of education, No. (%)	615 (66)	599 (66)	628 (67)	596 (71)	488 (70)	0.01
Low income, No. (%)	320 (34)	299 (33)	317 (33)	293 (35)	252 (36)	0.28
Nulliparous, No. (%)	240 (26)	200 (22)	207 (22)	203 (24)	171 (25)	0.83
Postmenopausal, No. (%)	480 (52)	470 (52)	484 (52)	459 (54)	353 (51)	6×10^{-3}
Oral contraceptive use, No. (%)	58 (6)	48 (5)	29 (3)	35 (4)	14 (2)	4×10^{-3}
Hormonal replacement therapy, No. (%)	142 (15)	112 (12)	127 (14)	93 (11)	118 (17)	0.32

Continuous variables are shown as medians (interquartile range) and categorical variables are shown as numbers (%). Cut-off values of 168 g/week for women and 252 g/week for men are from the recommendation concerning alcohol consumption from the Danish National Board of Health.

each testosterone quintile are shown in supplementary Table S1, available at *Annals of Oncology* online.

testosterone levels and age

When we plotted testosterone levels as a function of 10-year age groups for men and women, testosterone levels seemed to decrease slightly with increasing age (supplementary Figure S2, available at *Annals of Oncology* online); however, testosterone levels were not significantly associated with age in men (*P*-trend: 0.23) or women (*P*-trend: 0.15) (Table 1).

survival after a cancer diagnosis

Risk of early death 5 years after cancer increased in both men and women with increasing testosterone levels (*P*-trend: 6×10^{-5} and 8×10^{-3}, respectively) (Figure 1 A and B).

For men, after adjustment for age at diagnosis, tumour stage at diagnosis, and time since blood sampling, the hazard ratio was 1.30 (95% CI 1.03–1.65) for the 2nd quintile, 1.31 (1.02–1.67) for the 3rd quintile, 1.52 (1.19–1.93) for the 4th quintile, and 1.52 (1.20–1.91) for the 5th quintile, versus the 1st quintile (Figure 1A). For women, corresponding hazard ratios were 1.09 (0.81–1.46), 1.17 (0.86–1.59), 1.03 (0.76–1.39), and 1.80 (1.32–2.46) (Figure 1 B). When we adjusted multifactorially, hazard ratios were slightly attenuated for both men and women, but trend tests remained significant (Figure 1A and B). Hazard

ratios for risk of early death after a cancer diagnosis during the entire follow-up period were similar (data not shown).

When testosterone was on a continuous scale, after adjustment for age at diagnosis, tumour stage at diagnosis, and time since blood sampling, a doubling of testosterone levels was associated with a hazard ratio for risk of early death after cancer of 1.21 (95% CI 1.09–1.33) for men (supplementary Table S2, available at *Annals of Oncology* online). The corresponding hazard ratio for women was 1.16 (1.00–1.34). After stratification on age at diagnosis, tumour stage, and time since blood sampling, a doubling of testosterone levels was generally associated with increased risk of early death after cancer. All tests of interaction between testosterone levels and other covariates were non-significant.

risk of cancer

Multifactorially adjusted hazard ratios for risk of any first cancer were 1.07 (95% CI 0.98–1.18) and 1.06 (0.93–1.22) for men and women, respectively, when testosterone levels doubled (Figure 2). For both men and women, we had 90% statistical power to exclude corresponding hazard ratios at 0.95 or below and/or 1.05 or above. When we used a competing risk regression model (i.e. with death as competing event) for risk of any first cancer and cancer types, results were similar (data not shown).

For men, a doubling of testosterone was not associated with risk of the majority of cancer types (Figure 2 A). The only exception
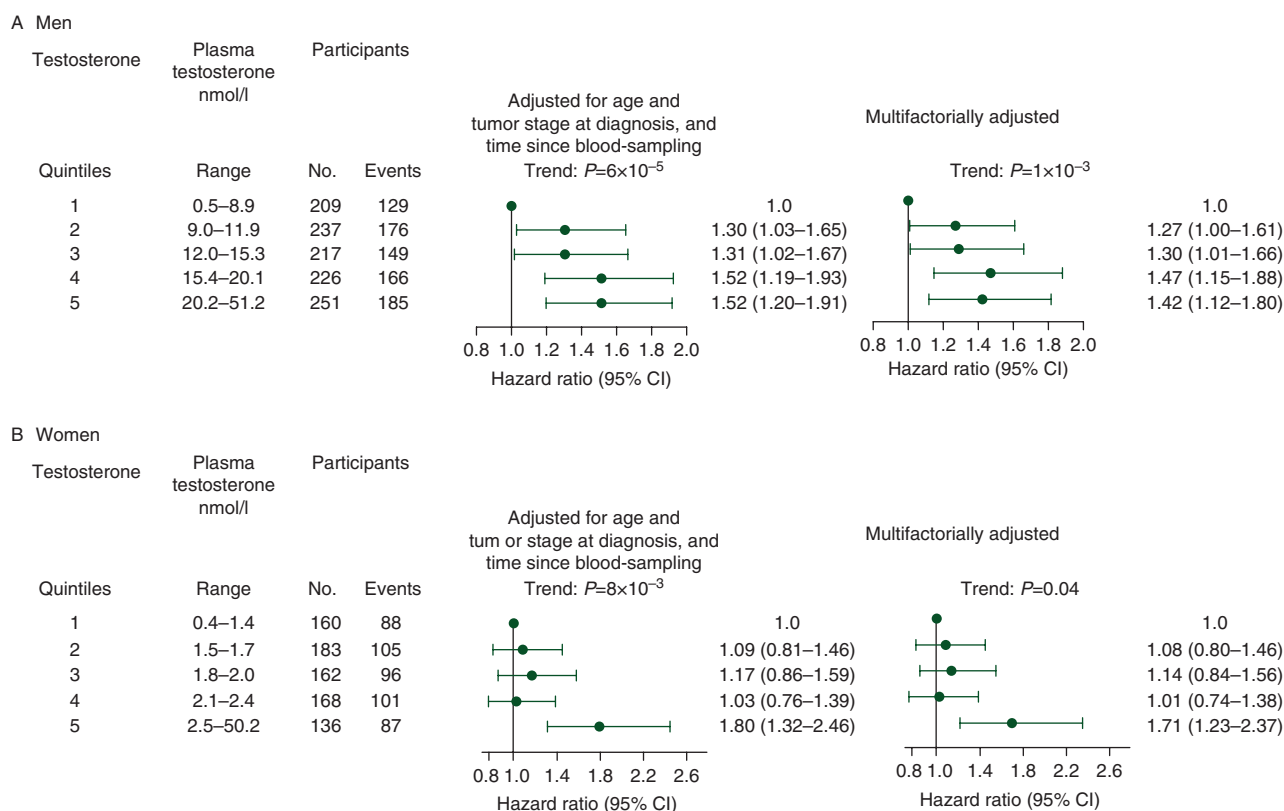
A Men

Testosterone	Plasma testosterone nmol/l	Participants		Adjusted for age and tumor stage at diagnosis, and time since blood-sampling Trend: $P=6\times10^{-5}$	Multifactorially adjusted Trend: $P=1\times10^{-3}$
Quintiles	Range	No.	Events	Hazard ratio (95% CI)	Hazard ratio (95% CI)
1	0.5–8.9	209	129	1.0	1.0
2	9.0–11.9	237	176	1.30 (1.03–1.65)	1.27 (1.00–1.61)
3	12.0–15.3	217	149	1.31 (1.02–1.67)	1.30 (1.01–1.66)
4	15.4–20.1	226	166	1.52 (1.19–1.93)	1.47 (1.15–1.88)
5	20.2–51.2	251	185	1.52 (1.20–1.91)	1.42 (1.12–1.80)

B Women

Testosterone	Plasma testosterone nmol/l	Participants		Adjusted for age and tumor stage at diagnosis, and time since blood-sampling Trend: $P=8\times10^{-3}$	Multifactorially adjusted Trend: $P=0.04$
Quintiles	Range	No.	Events	Hazard ratio (95% CI)	Hazard ratio (95% CI)
1	0.4–1.4	160	88	1.0	1.0
2	1.5–1.7	183	105	1.09 (0.81–1.46)	1.08 (0.80–1.46)
3	1.8–2.0	162	96	1.17 (0.86–1.59)	1.14 (0.84–1.56)
4	2.1–2.4	168	101	1.03 (0.76–1.39)	1.01 (0.74–1.38)
5	2.5–50.2	136	87	1.80 (1.32–2.46)	1.71 (1.23–2.37)

Figure 1. Risk of early death after a cancer diagnosis by testosterone quintiles in men (A) and women (B). Based on 1140 men and 809 women diagnosed with cancer during 30 years of follow-up after the Copenhagen City Heart Study 1981–1983 examination. Multifactorially adjusted was for age and tumour stage at diagnosis, time since blood sampling, smoking status, cumulative smoking, body mass index, alcohol consumption, level of education, and level of income for both men and women. For women parity, menopausal status, oral contraceptive use, and hormone replacement therapy were also adjusted for. CI, confidence interval.
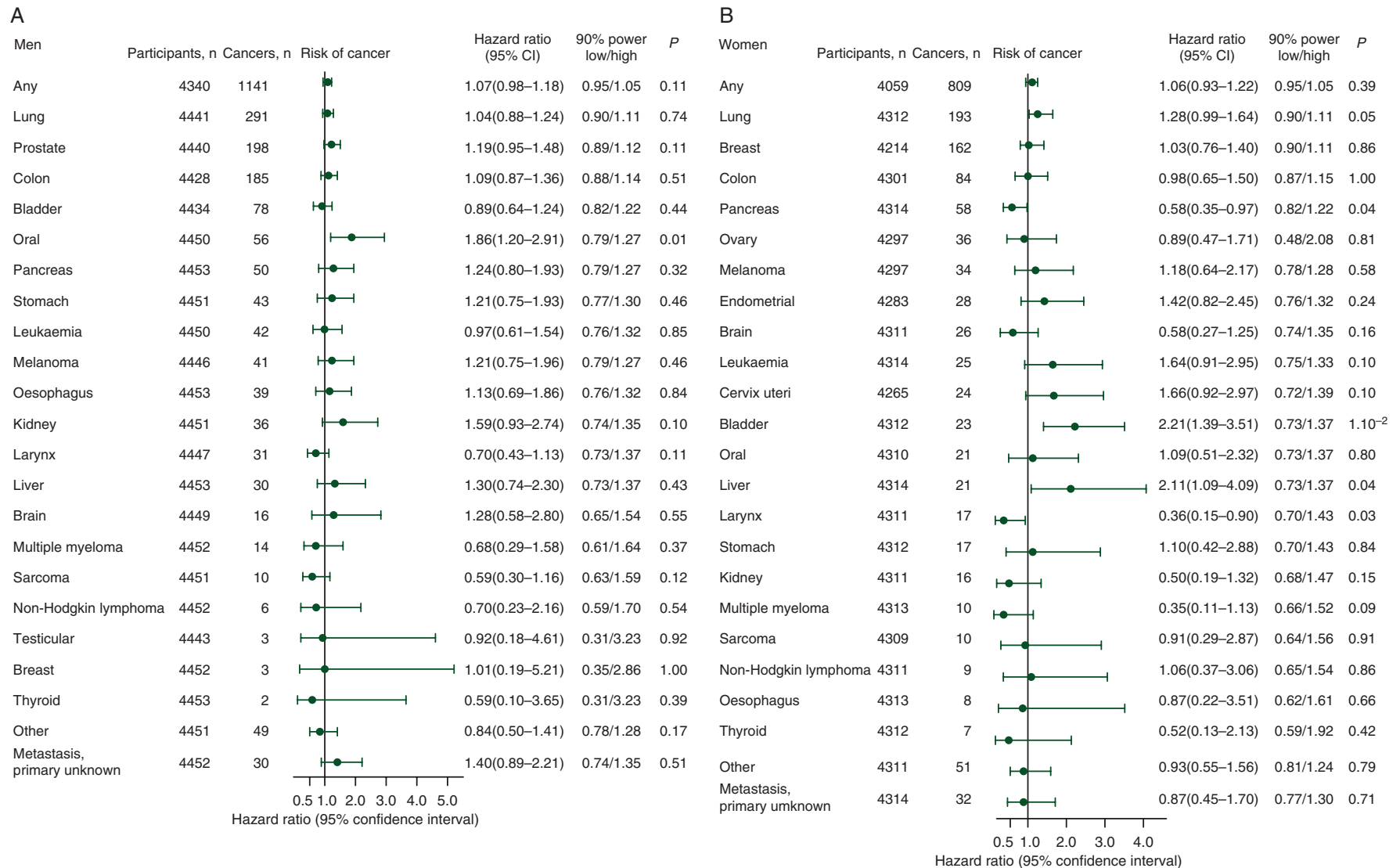
A

Men	Participants, n	Cancers, n	Risk of cancer	Hazard ratio (95% CI)	90% power low/high	P
Any	4340	1141		1.07(0.98–1.18)	0.95/1.05	0.11
Lung	4441	291		1.04(0.88–1.24)	0.90/1.11	0.74
Prostate	4440	198		1.19(0.95–1.48)	0.89/1.12	0.11
Colon	4428	185		1.09(0.87–1.36)	0.88/1.14	0.51
Bladder	4434	78		0.89(0.64–1.24)	0.82/1.22	0.44
Oral	4450	56		1.86(1.20–2.91)	0.79/1.27	0.01
Pancreas	4453	50		1.24(0.80–1.93)	0.79/1.27	0.32
Stomach	4451	43		1.21(0.75–1.93)	0.77/1.30	0.46
Leukaemia	4450	42		0.97(0.61–1.54)	0.76/1.32	0.85
Melanoma	4446	41		1.21(0.75–1.96)	0.79/1.27	0.46
Oesophagus	4453	39		1.13(0.69–1.86)	0.76/1.32	0.84
Kidney	4451	36		1.59(0.93–2.74)	0.74/1.35	0.10
Larynx	4447	31		0.70(0.43–1.13)	0.73/1.37	0.11
Liver	4453	30		1.30(0.74–2.30)	0.73/1.37	0.43
Brain	4449	16		1.28(0.58–2.80)	0.65/1.54	0.55
Multiple myeloma	4452	14		0.68(0.29–1.58)	0.61/1.64	0.37
Sarcoma	4451	10		0.59(0.30–1.16)	0.63/1.59	0.12
Non-Hodgkin lymphoma	4452	6		0.70(0.23–2.16)	0.59/1.70	0.54
Testicular	4443	3		0.92(0.18–4.61)	0.31/3.23	0.92
Breast	4452	3		1.01(0.19–5.21)	0.35/2.86	1.00
Thyroid	4453	2		0.59(0.10–3.65)	0.31/3.23	0.39
Other	4451	49		0.84(0.50–1.41)	0.78/1.28	0.17
Metastasis, primary unknown	4452	30		1.40(0.89–2.21)	0.74/1.35	0.51

0.5 1.0 2.0 3.0 4.0 5.0
Hazard ratio (95% confidence interval)

B

Women	Participants, n	Cancers, n	Risk of cancer	Hazard ratio (95% CI)	90% power low/high	P
Any	4059	809		1.06(0.93–1.22)	0.95/1.05	0.39
Lung	4312	193		1.28(0.99–1.64)	0.90/1.11	0.05
Breast	4214	162		1.03(0.76–1.40)	0.90/1.11	0.86
Colon	4301	84		0.98(0.65–1.50)	0.87/1.15	1.00
Pancreas	4314	58		0.58(0.35–0.97)	0.82/1.22	0.04
Ovary	4297	36		0.89(0.47–1.71)	0.48/2.08	0.81
Melanoma	4297	34		1.18(0.64–2.17)	0.78/1.28	0.58
Endometrial	4283	28		1.42(0.82–2.45)	0.76/1.32	0.24
Brain	4311	26		0.58(0.27–1.25)	0.74/1.35	0.16
Leukaemia	4314	25		1.64(0.91–2.95)	0.75/1.33	0.10
Cervix uteri	4265	24		1.66(0.92–2.97)	0.72/1.39	0.10
Bladder	4312	23		2.21(1.39–3.51)	0.73/1.37	1.10^{-2}
Oral	4310	21		1.09(0.51–2.32)	0.73/1.37	0.80
Liver	4314	21		2.11(1.09–4.09)	0.73/1.37	0.04
Larynx	4311	17		0.36(0.15–0.90)	0.70/1.43	0.03
Stomach	4312	17		1.10(0.42–2.88)	0.70/1.43	0.84
Kidney	4311	16		0.50(0.19–1.32)	0.68/1.47	0.15
Multiple myeloma	4313	10		0.35(0.11–1.13)	0.66/1.52	0.09
Sarcoma	4309	10		0.91(0.29–2.87)	0.64/1.56	0.91
Non-Hodgkin lymphoma	4311	9		1.06(0.37–3.06)	0.65/1.54	0.86
Oesophagus	4313	8		0.87(0.22–3.51)	0.62/1.61	0.66
Thyroid	4312	7		0.52(0.13–2.13)	0.59/1.92	0.42
Other	4311	51		0.93(0.55–1.56)	0.81/1.24	0.79
Metastasis, primary umknown	4314	32		0.87(0.45–1.70)	0.77/1.30	0.71

0.5 1.0 2.0 3.0 4.0
Hazard ratio (95% confidence interval)

Figure 2. Risk of any cancer and cancer types in men (A) and women (B) when testosterone levels double. Based on 4453 men and 4318 women from the general population who participated in the Copenhagen City Heart Study 1981–1983 examination. Numbers at risk vary due to varying number of participants with the cancer type in question before blood sampling. Hazard ratios were multifactorially adjusted for smoking status, cumulative smoking, body mass index, alcohol consumption, level of education, and level of income for both men and women. For women parity, menopausal status, oral contraceptive use, and hormone replacement therapy were also adjusted for. Cancer types were listed according to number of cases, except other cancers and metastases/primary unknown listed last.

was the multifactorially adjusted hazard ratio for risk of oral cancer which was 1.86 (1.20–2.91; $P = 0.01$). Similarly, for women, there was generally no evidence of an association between testosterone and risk of any cancer type (Figure 2B). However, a doubling in testosterone was associated with multifactorially adjusted hazard ratios for bladder and liver cancer of 2.21 (1.39–3.51; $P = 0.001$) and 2.11 (1.09–2.32; $P = 0.04$), respectively. Corresponding hazard ratios for pancreas and larynx cancer were 0.58 (0.35–0.97; $P = 0.04$)) and 0.36 (0.15–0.90; $P = 0.03$), respectively. After adjustment for the 22 multiple comparisons, these associations were no longer significant [i.e. ($22 \times P$-value) >0.05] (data not shown), suggesting that they could represent chance findings.

For both men and women, after multifactorial adjustment, increasing testosterone quintile was not associated with increasing risk of any cancer or any cancer type (Table 2).

discussion

The key finding of this study is that increased levels of plasma testosterone are associated with a 30%–80% increased risk of early death after cancer in both men and women from the general population. This is a novel finding. However, results do not support an association between testosterone levels and cancer risk.

A possible mechanism behind our findings for risk of early death after cancer could be that increased levels of testosterone stimulate intracellular protein synthesis, which is needed for rapid proliferation both in healthy and cancerous cells. Also, it is possible that cancer cells may benefit from the higher basal metabolism due to increased testosterone. However, the effect of testosterone on cancer cells and the possible inhibitory potential of anti-androgens remain unclear.

Table 2. Risk of any cancer and cancer types in men and women by testosterone quintile

Cancer type	Testosterone quintile										Total
	1st		2nd		3rd		4th		5th		
	N	HR	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	
Men											
Any	209	1	237	1.13 (0.94–1.36)	217	1.03 (0.85–1.25)	226	1.08 (0.89–1.31)	251	1.20 (0.99–1.46)	1140
Lung	46	1	64	1.31 (0.89–1.91)	58	1.17 (0.79–1.73)	65	1.25 (0.85–1.84)	58	1.06 (0.71–1.58)	291
Prostate	39	1	31	0.84 (0.52–1.34)	46	1.29 (0.84–1.98)	35	1.04 (0.65–1.65)	47	1.47 (0.95–2.30)	198
Colon	40	1	35	0.92 (0.58–1.44)	28	0.74 (0.45–1.20)	44	1.20 (0.77–1.85)	38	1.05 (0.66–1.67)	185
Bladder	17	1	22	1.30 (0.69–2.45)	10	0.57 (0.26–1.26)	15	0.87 (0.43–1.77)	14	0.77 (0.37–1.61)	78
Oral	5	1	11	2.28 (0.79–6.58)	9	1.97 (0.66–5.92)	13	2.85 (1.01–8.09)	18	4.00 (1.44–11.08)	56
Pancreas	10	1	11	1.10 (0.47–2.61)	5	0.49 (0.17–1.45)	14	1.41 (0.62–3.23)	10	1.00 (0.40–2.49)	50
Stomach	7	1	10	1.44 (0.55–3.79)	5	0.68 (0.22–2.17)	8	1.08 (0.39–3.02)	13	1.70 (0.66–4.40)	43
Leukaemia	7	1	12	1.84 (0.72–4.69)	8	1.18 (0.42–3.30)	8	1.24 (0.44–3.48)	7	1.19 (0.40–3.50)	42
Melanoma	5	1	12	2.63 (0.92–7.48)	6	1.26 (0.38–4.18)	10	2.27 (0.77–6.72)	8	2.04 (0.65–6.40)	41
Oesophagus	6	1	10	1.59 (0.58–4.41)	8	1.36 (0.47–3.97)	5	0.77 (0.23–2.56)	10	1.37 (0.47–3.96)	39
Kidney	7	1	4	0.60 (0.17–2.04)	6	0.89 (0.30–2.67)	7	1.04 (0.36–3.02)	12	1.76 (0.66–4.70)	36
Larynx	8	1	5	0.61 (0.20–1.86)	9	1.06 (0.40–2.81)	4	0.45 (0.13–1.53)	5	0.53 (0.17–1.71)	31
Liver	6	1	6	1.04 (0.33–3.25)	5	0.93 (0.28–3.10)	4	0.72 (0.20–2.60)	9	1.44 (0.48–4.31)	30
Other	9	1	6	0.69 (0.24–1.93)	10	1.24 (0.50–3.08)	11	1.32 (0.54–3.23)	13	1.62 (0.66–3.94)	49
Metastasis, primary unknown	8	1	7	0.89 (0.32–2.46)	5	0.64 (0.21–2.00)	4	0.47 (0.14–1.59)	6	0.59 (0.19–1.90)	30
Women											
Any	160	1	183	1.14 (0.92–1.41)	162	0.99 (0.80–1.23)	168	1.03 (0.83–1.28)	136	1.11 (0.88–1.40)	809
Lung	34	1	30	0.90 (0.55–1.46)	44	1.28 (0.82–2.02)	46	1.27 (0.81–1.98)	39	1.37 (0.86–2.19)	193
Breast	31	1	35	1.04 (0.64–1.68)	35	1.05 (0.65–1.71)	34	1.08 (0.66–1.77)	27	1.16 (0.69–1.96)	162
Colon	21	1	16	0.78 (0.41–1.51)	18	0.89 (0.47–1.67)	18	0.90 (0.47–1.70)	11	0.78 (0.37–1.62)	84
Pancreas	17	1	14	0.83 (0.41–1.69)	11	0.64 (0.30–1.38)	8	0.47 (0.20–1.09)	8	0.62 (0.26–1.45)	58
Ovary	12	1	5	0.42 (0.15–1.19)	4	0.34 (0.11–1.05)	8	0.68 (0.28–1.70)	7	0.82 (0.32–2.14)	36
Melanoma	5	1	9	1.85 (0.61–5.56)	7	1.46 (0.46–4.61)	8	1.85 (0.60–5.71)	5	1.50 (0.43–5.25)	34
Endometrial	3	1	7	2.39 (0.61–9.29)	8	2.74 (0.73–10.38)	6	2.24 (0.55–9.04)	4	1.61 (0.34–7.72)	28
Leukaemia	3	1	6	2.10 (0.52–8.43)	8	2.76 (0.73–10.45)	2	0.71 (0.12–4.29)	6	3.09 (0.76–12.53)	25
Cervix uteri	3	1	10	3.53 (0.97–12.89)	4	1.32 (0.29–5.94)	3	1.12 (0.22–5.61)	4	1.84 (0.40–8.39)	24
Bladder	2	1	4	2.33 (0.42–12.75)	6	3.59 (0.72–17.87)	4	2.48 (0.45–13.61)	7	5.97 (1.22–29.12)	23
Oral	3	1	4	0.99 (0.21–4.61)	5	1.36 (0.32–5.75)	3	0.82 (0.16–4.16)	6	1.99 (0.48–8.19)	21
Other	10	1	16	1.75 (0.79–3.88)	10	1.06 (0.44–2.56)	8	0.95 (0.37–2.41)	7	1.07 (0.40–2.87)	51
Metastasis, primary unknown	7	1	11	1.56 (0.60–4.06)	2	0.28 (0.06–1.36)	6	0.86 (0.28–2.59)	6	0.91 (0.29–2.91)	32

Only cancer types with a total >20 cases and >0 cases per quintile were included. Multifactorially adjusted for smoking status, cumulative smoking, body mass index, alcohol consumption, level of education, and level of income for men and women. For women, parity, menopausal status, oral contraceptive use, and hormone replacement therapy were also adjusted for.
HR, hazard ratio; CI, confidence interval.

For risk of early death after cancer, increasing testosterone was associated with increased risk of death in both men and women. To our knowledge, this has not been examined previously in population-based studies, but only in one small study of 136 male cancer patients, which did not find an association between plasma testosterone and risk of early death [12]. However, that study cohort consisted of a selected group of cancer patients and maximum follow-up was ~4 years. Furthermore, testosterone was measured after cancer diagnosis and, thus, may have decreased during the time leading up to diagnosis, making comparison to our findings difficult.

Previous studies on the association between testosterone and overall mortality have produced diverging results [16]. Two studies including 1568 and 2314 participants showed that low levels of testosterone were associated with increased risk of overall mortality [17, 18]. In contrast, two studies with 254 and 4255 participants did not find such an association [19, 20]. Finally, a study using genetic data on 1882 participants (i.e. with a lower risk of confounding and reverse causation) indicated that testosterone was not a causal factor in overall mortality [21]. Taken together, while the present study indicates that testosterone is associated with early death after a cancer diagnosis further research is needed to elucidate the role of testosterone in overall mortality.

For risk of cancer types, we observed an elevated risk of oral cancer in men. Due to the large number of cancer types ($n = 22$), we would expect to find at least one positive association by chance alone, and thus, cannot determine whether this association is true or a play of chance. Similarly, the results for decreased risk of pancreas and larynx cancer and increased risk of bladder and liver cancer in women are likely to be chance findings based on the small number of cases and the large number of parallel tests. Also, risk estimates for these four cancer types are symmetrically distributed around 1.00, also suggesting that these could be spurious results. Finally, when we corrected for multiple comparisons, these results were no longer statistically significant.

Supporting the validity of our findings, testosterone levels in our cohort were similar to those previously described, both overall and in age-specific categories [22]. We also found associations between testosterone and smoking and BMI, as seen in other studies [18, 23].

Our findings on cancer type risk are supported by results from other studies. First, our results on prostate cancer risk were similar to those of both a recent large prospective study of 3255 men from the Reduction by Dutasteride of Prostate Cancer (REDUCE) trial and a pooled analysis of 18 studies on testosterone and prostate cancer risk that reported a null association [6, 10]. In contrast to these findings, other studies have shown that risk of prostate cancer increases with increasing testosterone levels [4, 5, 9]. However, these studies used a case–control design, had fewer participants and prostate cancer cases, and/or older participants, which may explain the difference in results. Second, also in support of the results from our study, a population-based study of 3635 men did not find an association between testosterone levels and risk of colorectal cancer [9]. Conversely, Hyde et al. reported increased risk of lung cancer with increasing testosterone levels, even after exclusion of current smokers, i.e. who both have increased testosterone levels and increased risk of lung cancer. In the present study, we did not observe an increased risk of lung cancer in men despite having 291 lung cancer cases and >30 years of follow-up compared with 84 lung cancer cases and 7 years of follow-up in the study by Hyde et al. Additionally, we did not find an increased risk of lung cancer in women, and we were also able to adjust for both smoking status and cumulative smoking, limiting the possibility of influence from residual confounding. Taken together, our results suggest that increased testosterone levels are not associated with risk of incident cancer in men or women.

Our study has several strengths. The study population is representative of the general population, follow-up was up to 30 years without losses to follow-up, and the study population is well characterized. Furthermore, we had 8771 participants with 1950 cancer cases which overall gave us considerable statistical power. Yet another strength is that we were able to examine the association between testosterone levels and risk of death after a cancer diagnosis and risk of cancer separately in men and women.

The limited number of events for each individual cancer type reduced our statistical power. Nonetheless, we had 90% power to exclude clinically relevant changes of risk for most cancer types. Another potential limitation of our study is that our study population only included white participants of Danish descent, and thus our results may not necessarily apply to other ethnic groups. On the other hand, we are not aware of any data to suggest that results like the present should not be valid for men and women of all races. Finally, a potential limitation may be that we examined overall mortality after a cancer diagnosis and not cancer-specific mortality. However, 86% of all deaths after a cancer diagnosis were cancer related when we looked at the first three causes of death listed for each participant. This was even higher if we included all nine causes of death listed.

In conclusion, in this prospective study of 8771 men and women from the general population followed for up to 30 years, increased levels of testosterone were associated with a 30%–80% increased risk of early death after cancer, but with unchanged risk of incident cancer.

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