In Reply: Dr Fan points out that our definition of corticosteroid insufficiency does not conform to that of the ACCM,[1] which states that a corticotropin test should not be used to identify patients with septic shock or acute respiratory distress syndrome who should receive glucocorticoids. In the HYPOLYTE study, patients with adapted corticosteroid function had a short median time of exposure to hydrocortisone (median, 34 hours; interquartile range, 20-49). We reported a decreased hospital-acquired pneumonia rate at day 28 in all patients, but the study was neither designed nor powered to evaluate the safety of treatment in patients with adapted corticosteroid function. Regarding the threshold of cortisolemia, the current definition of critical illness–related corticosteroid insufficiency was not available at the time the study was started. When using this definition,[1] the risk of hospital-acquired pneumonia at day 28 remained lower in the hydrocortisone group (hazard ratio, 0.41; 95% CI, 0.20-0.88; $P=.02$). We thus believe that a corticotropin test should be performed to identify trauma patients who may benefit from prolonged low-dose hydrocortisone. In a systematic review of corticosteroid use in patients with severe sepsis,[2] a long course of low-dose corticosteroids did not alter superinfection rate (relative risk, 1.01; 95% CI, 0.82-1.25; $P=.92$). Also, the rate of polyneuromyopathy, which is low in trauma patients, was not increased in septic patients treated with corticosteroids.[3]

Dr Johnson suggests that hydrocortisone may have biased the diagnosis of hospital-acquired pneumonia. In the setting of community-acquired pneumonia, patients treated with a high dose of glucocorticoid presented a slightly decreased body temperature (less than 0.5°C) as compared with patients treated with placebo.[4] To our knowledge, the effects of stress-dose hydrocortisone on body temperature in patients with corticosteroid insufficiency are unknown. In our study, body temperature exceeded 38.0°C in 23 of 28 episodes (82.1%) of hospital-acquired pneumonia in the corticosteroid group and in 35 of 47 episodes (74.5%) in the placebo group, with no difference between the 2 groups ($P=.60$). It is unlikely that the antipyretic properties of hydrocortisone explain the decreased hospital-acquired pneumonia rate in the hydrocortisone group.

Drs Salluh and Póvoa question the safety of corticosteroids. Pharmacological (ie, prednisolone) and physiological (ie, hydrocortisone) glucocorticoids display different properties. Stress doses of hydrocortisone reprogram rather than inhibit immune cells.[5] Corticosteroid effects depend on the inflammatory status of the host[6]; thus, the timing of corticosteroid initiation is critical, and no patients were treated late in our study. The suggestion by Salluh and Póvoa to consider combined lower respiratory tract infections is questionable. First, the morbidity of tracheobronchitis remains unknown in trauma patients whereas pneumonia clearly increases morbidity. Second, mechanical ventilation–free days, a surrogate marker of the efficacy of the treatment of pneumonia, increased with hydrocortisone in our study.

We agree that evaluation of mortality is critical, and there is no randomized study using stress doses of hydrocortisone that have shown an increased mortality rate in sepsis, acute respiratory distress syndrome, or trauma. In a recent systematic review,[3] analyses of the trials investigating a prolonged course (>5 days) of stress-dose corticosteroid treatment in sepsis and septic shock demonstrated a significant reduction in 28-day all-cause mortality and hospital mortality with no increase in superinfections. In the setting of trauma, the most frequent causes of deaths are acute intracranial hypertension and hemorrhagic shock, which occur within the first few hours. We believe that mortality should remain a safety end point but not a primary end point for evaluation of stress-dose hydrocortisone in patients with multiple trauma. Our study was not powered to test the noninferiority of hydrocortisone vs placebo on mortality.

Antoine Roquilly, MD
Pierre Joachim Mahe, MD
Karim Asehnoune, MD, PhD

Author Affiliations: Department of Anesthesiology, University Hospital of Nantes, Nantes, France (karim.asehnoune@chu-nantes.fr).
Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

1. Marik PE, Pastores SM, Annane D, et al; American College of Critical Care Medicine. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. *Crit Care Med*. 2008;36(6):1937-1949.
2. Sprung CL, Annane D, Keh D, et al; CORTICUS Study Group. Hydrocortisone therapy for patients with septic shock. *N Engl J Med*. 2008;358(2):111-124.
3. Annane D, Bellissant E, Bollaert PE, et al. Corticosteroids in the treatment of severe sepsis and septic shock in adults: a systematic review. *JAMA*. 2009; 301(22):2362-2375.
4. Snijders D, Daniels JMA, de Graaff CS, van der Werf TS, Boersma WG. Efficacy of corticosteroids in community-acquired pneumonia: a randomized double-blinded clinical trial. *Am J Respir Crit Care Med*. 2010;181(9):975-982.
5. Keh D, Boehnke T, Weber-Cartens S, et al. Immunologic and hemodynamic effects of "low-dose" hydrocortisone in septic shock: a double-blind, randomized, placebo-controlled, crossover study. *Am J Respir Crit Care Med*. 2003; 167(4):512-520.
6. Glass CK, Ogawa S. Combinatorial roles of nuclear receptors in inflammation and immunity. *Nat Rev Immunol*. 2006;6(1):44-55.

RESEARCH LETTER

Fifteen-Year Follow-up of Association Between Telomere Length and Incident Cancer and Cancer Mortality

To the Editor: Telomeres are nucleoprotein structures that cap the ends of chromosomes and confer chromosomal stability. Telomere shortening to a critical length due to extensive DNA replication or oxidative stress facilitates genomic mutations and may induce malignant transformation.[1]

We have previously shown that low leukocyte telomere length (TL) is associated with an increased risk of cancer incidence and mortality.[2] Although the associations were of considerable strength, independent of standard risk factors, and consistent in subgroups, the number of incident cases of cancer was less than 100. We extended the follow-up from 10 to

15 years, increased the number of events to 137, and added data from a second TL measurement because a single measurement may underestimate the true association.

Methods. A prospective population-based cohort study was conducted on a random sample of 1000 persons aged 40 to 79 years in Bruneck, Italy, beginning in 1990 with clinical and laboratory evaluations every 5 years. The study was approved by the ethics committee of Bolzano province, and all participants provided written informed consent. This evaluation focused on the period between the first reexamination and fourth reexamination (1995-2010). Telomere length was available for 787 participants free of cancer in 1995 (96.9%) and 558 participants in 2005 (98.1%). Telomere length was assessed in leukocytes from fasting blood samples with quantitative polymerase chain reaction, and values were corrected for reaction efficiency.[2] Incident cancer and cancer-related death as of October 2010 were ascertained by review of medical records, including histopathological workup and death certificates containing detailed information on cause and circumstances of death (follow-up rate, 100%).[2]

To quantify within-person variability of TL and C-reactive protein level, regression dilution ratios (RDRs) were calculated based on 1995 (baseline) and 2005 values.[3] Long-term average ("usual") TL based on TL measured in 1995 and 2005 was estimated by multivariate regression calibration.[3] Separate Cox models using baseline and usual TL to predict cancer incidence and cancer mortality over the 15-year period were fitted for TL tertile groups and continuous $\log_e$ TL. The proportional hazard assumption was confirmed using Schoenfeld residuals. A 2-sided $P < .05$ was considered significant. Statistical analyses were performed with Stata version 10.1 (StataCorp, College Station, Texas).

Results. Distribution of baseline variables and their correlations with TL were outlined in the previous report.[2] The age- and sex-adjusted RDR of TL was 0.59 (95% confidence interval [CI], 0.52-0.65) comparable with that of C-reactive protein (RDR, 0.56; 95% CI, 0.48-0.64).

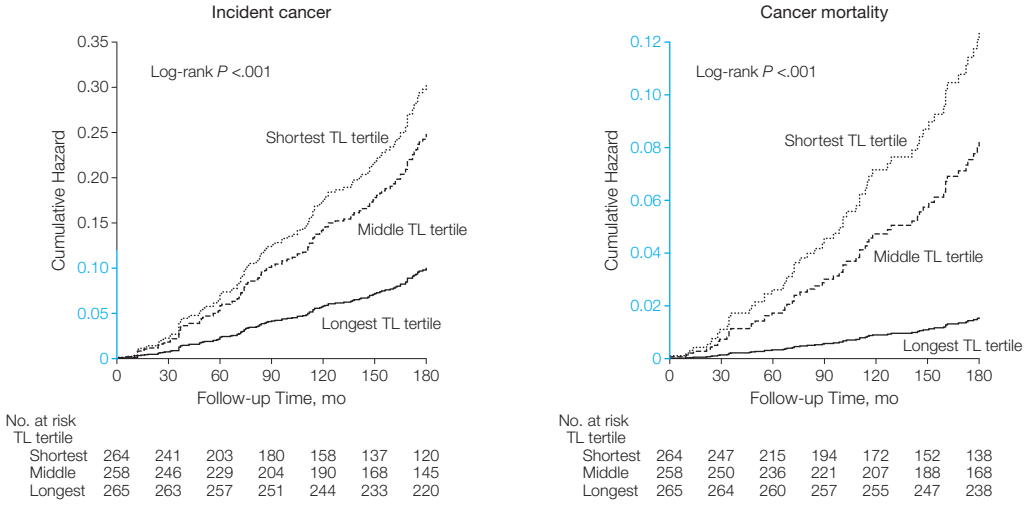
During follow-up, 137 of 787 participants were diagnosed with cancer (incidence rate, 14.3 per 1000 person-years; 95% CI, 12.1-16.9) and 62 of 787 participants died from cancer. Incidence rates of cancer in the longest, middle, and shortest TL tertiles were 5.9 (95% CI, 3.9-9.0), 16.9 (95% CI, 12.9-22.2), and 22.8 (95% CI, 17.8-29.2), respectively. The adjusted hazard ratio per 1-SD lower baseline TL (SD=0.52) was 1.56 (95% CI, 1.32-1.85) and 1.88 (95% CI, 1.48-2.40) for cancer incidence and cancer mortality, respectively (TABLE). Cox models

Table. Association of Telomere Length (T/S Ratio) With Cancer Incidence (n = 137) and Cancer Mortality (n = 62) During 15 Years of Follow-up[a]

	Tertile Groups of Baseline TL[b]			HR (95% CI) per 1-SD Lower $\log_e$ TL		
	Longest (n = 265)	Middle (n = 258)	Shortest (n = 264)	Baseline TL	Usual TL	Usual TL and Usual Levels of Covariates[c]
Incident Cancer						
Cases, No.	22	52	63			
Follow-up, No. of person-years	3724	3079	2761			
Incidence, cases per 1000 person-years (95% CI)	5.9 (3.9-9.0)	16.9 (12.9-22.2)	22.8 (17.8-29.2)			
Cox models HR (95% CI)						
Age- and sex-adjusted	1 [Reference]	2.61 (1.58-4.31)	3.38 (2.06-5.52)	1.61 (1.37-1.90)	2.26 (1.71-3.00)	2.26 (1.71-3.00)
Multivariable model 1[d]	1 [Reference]	2.41 (1.45-4.00)	3.03 (1.84-4.98)	1.56 (1.32-1.85)	2.16 (1.61-2.89)	2.16 (1.61-2.89)
Multivariable model 2[e]	1 [Reference]	2.43 (1.46-4.03)	3.02 (1.84-4.97)	1.56 (1.32-1.85)	2.15 (1.61-2.88)	2.16 (1.61-2.89)
Cancer Mortality						
Cases, No.	4	23	35			
Follow-up, No. of person-years	3834	3270	2933			
Incidence, cases per 1000 person-years (95% CI)	1.0 (0.4-2.8)	7.0 (4.7-10.6)	11.9 (8.6-16.6)			
Cox models HR (95% CI)						
Age- and sex-adjusted	1 [Reference]	5.73 (1.98-16.63)	9.20 (3.25-26.05)	1.96 (1.54-2.48)	3.15 (2.10-4.73)	3.15 (2.10-4.73)
Multivariable model 1[d]	1 [Reference]	5.09 (1.74-14.85)	8.14 (2.86-23.20)	1.88 (1.48-2.40)	2.97 (1.96-4.51)	3.11 (2.04-4.74)
Multivariable model 2[e]	1 [Reference]	5.18 (1.77-15.12)	8.17 (2.86-23.29)	1.88 (1.48-2.40)	2.98 (1.96-4.53)	3.11 (2.04-4.75)

Abbreviations: CI, confidence interval; HR, hazard ratio, TL, telomere length.
[a] HRs with 95% CIs were derived from Cox regression analysis. Separate models were fitted for tertile groups of baseline TL and continuous $\log_e$ TL (baseline and usual [1 SD=0.52]). Usual TL considered the variability of TL over time and was estimated by multivariate regression calibration. Cancer incidence included any cancer except nonmelanoma skin cancer. Only the first incidence of cancer was considered in the analysis.
[b] The median for the longest TL (T/S ratio) tertile was 2.22 (range, 1.60-5.93); for the middle tertile, 1.29 (range, 1.05-1.59); and for the shortest tertile, 0.81 (range, 0.19-1.04).
[c] By means of multivariate regression calibration, usual levels of alcohol consumption, body mass index, $\log_e$ high-sensitivity C-reactive protein, vitamin D, and low-density lipoprotein were calculated (based on 1995 and 2005 measurements) and included in the Cox model.
[d] HRs in this model were adjusted for age, sex, social class, pack-years of smoking, alcohol consumption, presence of diabetes, physical activity, body mass index, $\log_e$ high-sensitivity C-reactive protein level, vitamin D level, and low-density lipoprotein cholesterol level.
[e] HRs in this model were adjusted for everything in model 1 and for the presence of chronic infection and level of interleukin 6.

Figure. Cumulative Hazard Curves for Cancer Incidence and Cancer Mortality by Telomere Length Tertile, 1995-2010



The median telomere length (T/S ratio) for the shortest-length tertile was 0.81 (range, 0.19-1.04); for the middle-length tertile, 1.29 (range, 1.05-1.59); and for the longest-length tertile, 2.22 (range, 1.60-5.93). There were 137 cases of cancer incidence and 62 cases of cancer mortality. TL indicates telomere length. Y-axis shown in blue indicates range from 0 to 0.12.

including usual instead of baseline TL yielded hazard ratios of 2.15 (95% CI, 1.61-2.88) and 2.98 (95% CI, 1.96-4.53) for cancer incidence and cancer mortality, respectively. Cumulative hazard plots by tertiles of baseline TL are shown in the FIGURE.

Comment. This 15-year follow-up corroborates our previous findings[2] that short telomeres are associated with cancer incidence and cancer mortality. An RDR of 0.59 and the stronger associations for usual TL underscore the importance of telomere dynamics in carcinogenesis and the need for multiple measurements of TL in the characterization of individual cancer risk. The variability of TL over time is similar to previous evaluations on telomere dynamics[4,5] and may reflect the cumulative effect of environmental and behavioral exposures, varying telomerase activity, and stress-induced repopulation of peripheral blood by recently dividing hematopoietic bone marrow cells.[6] Additional variability may arise from shifts in the cellular composition of peripheral blood leukocytes. Limitations include that the population was entirely white, TL measurements were available in leukocytes only, and power to analyze individual cancer types was limited.

Peter Willeit, MD
Johann Willeit, MD
Anita Kloss-Brandstätter, PhD
Florian Kronenberg, MD
Stefan Kiechl, MD

Author Affiliations: Department of Public Health and Primary Care (Dr P. Willeit), University of Cambridge, Cambridge, United Kingdom; and Departments of Neurology (Drs J. Willeit and Kiechl) (stefan.kiechl@i-med.ac.at) and Medical Genetics, Molecular and Clinical Pharmacology (Drs Kloss-Brandstätter and Kronenberg), Innsbruck Medical University, Innsbruck, Austria.

Author Contributions: Dr Kiechl had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: P. Willeit, J. Willeit, Kiechl.
Acquisition of data: P. Willeit, J. Willeit, Kloss-Brandstätter, Kronenberg, Kiechl.
Analysis and interpretation of data: P. Willeit, Kiechl.
Drafting of the manuscript: P. Willeit, Kiechl.
Critical revision of the manuscript for important intellectual content: J. Willeit, Kloss-Brandstätter, Kronenberg.
Statistical analysis: P. Willeit, Kiechl.
Obtained funding: J. Willeit, Kronenberg.
Administrative, technical, or material support: J. Willeit, Kloss-Brandstätter, Kronenberg.
Study supervision: Kloss-Brandstätter, Kronenberg.
Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.
Funding/Support: Dr P. Willeit was supported by a scholarship from the Dr Johannes and Hertha Tuba Foundation. Dr Kronenberg was supported by a grant from the Competence Centers for Excellent Technologies Center, ONCOTYROL, and the Integriertes Forschungs und Therapiezentrum of Innsbruck Medical University. The study was supported by the Pustertaler Verein zur Prävention von Herz und Hirngefaesserkrankungen, Gesundheitsbezirk Bruneck, and the Assessorat fuer Gesundheit, Province of Bolzano, Italy.
Role of the Sponsors: The funding organizations had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

1. Calado RT, Young NS. Telomere diseases. *N Engl J Med*. 2009;361(24):2353-2365.
2. Willeit P, Willeit J, Mayr A, et al. Telomere length and risk of incident cancer and cancer mortality. *JAMA*. 2010;304(1):69-75.
3. Fibrinogen Studies Collaboration. Correcting for multivariate measurement error by regression calibration in meta-analyses of epidemiological studies. *Stat Med*. 2009;28(7):1067-1092.
4. Houben JM, Giltay EJ, Rius-Ottenheim N, Hageman GJ, Kromhout D. Telomere length and mortality in elderly men: the Zutphen Elderly Study. *J Gerontol A Biol Sci Med Sci*. 2011;66(1):38-44.
5. Farzaneh-Far R, Lin J, Epel E, Lapham K, Blackburn E, Whooley MA. Telomere length trajectory and its determinants in persons with coronary artery disease: longitudinal findings from the heart and soul study. *PLoS One*. 2010;5(1):e8612.
6. Lin J, Epel E, Cheon J, et al. Analyses and comparisons of telomerase activity and telomere length in human T and B cells: insights for epidemiology of telomere maintenance. *J Immunol Methods*. 2010;352(1-2):71-80.