adult cardiovascular diseases than prematurity.[4] We reanalyzed our study population by dividing the births within each gestational age category into smaller and larger birth weights by their *z* score of birth weight by gestational age. Adjusting for gestational week within each category as well as year of birth, larger infants did have the best survival for any given gestational age. For 22 to 27, 28 to 32, 33 to 36, and 37 to 42 weeks, the relative risks of mortality were 0.39 (95% confidence interval [CI], 0.30-0.49), 0.45 (95% CI, 0.40-0.50), 0.40 (95% CI, 0.36-0.46), and 0.53 (95% CI, 0.50-0.55), respectively.

We agree that predisposing genetic factors contribute to prematurity[5] as well as subsequent reproductive potential; this is an important area for future investigation. A twin-pair study would be ideal for examining genetic contributions while controlling for potential environmental confounders. Furthermore, comparisons between twin sibships would be useful for examining contributors to birth weight, given that twin siblings have identical gestational age at birth. We limited our study population to singleton births given the strong association and potential confounding effect between multiple gestation and preterm birth. Furthermore, compelling twin-pair studies require known zygosity (identical vs fraternal twinning) based on ultrasound confirmation, genetic confirmation, or self-reported zygosity based on resemblance.[6] Further analyses to disentangle the relative contributions of birth weight and length of gestation to long-term health outcomes, including twin-pair studies, are essential to improving the understanding of the fetal origins of adult disease.

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1. Higgins RD, Delivoria-Papadopoulos M, Raju TN. Executive summary of the workshop on the border of viability. *Pediatrics*. 2005;115(5):1392-1396.
2. Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Menacker F, Munson ML. Births: final data for 2003. *Natl Vital Stat Rep*. 2005;54(2):1-116.
3. *Intrauterine Growth Restriction*. Washington, DC: American College of Obstetricians and Gynecologists; January 2000 (reaffirmed 2008). ACOG Practice Bulletin 12.
4. Nuyt AM. Mechanisms underlying developmental programming of elevated blood pressure and vascular dysfunction: evidence from human studies and experimental animal models. *Clin Sci (Lond)*. 2008;114(1):1-17.
5. Wilcox AJ, Skaerven R, Lie RT. Familial patterns of preterm delivery: maternal and fetal contributions. *Am J Epidemiol*. 2008;167(4):474-479.
6. Lichtenstein P, De Faire U, Floderus B, Svartengren M, Svedberg P, Pedersen NL. The Swedish Twin Registry: a unique resource for clinical, epidemiological and genetic studies. *J Intern Med*. 2002;252(3):184-205.

Homocysteine Levels, Paraoxonase 1 (PON1) Activity, and Cardiovascular Risk

To the Editor: Dr Bhattacharyya and colleagues[1] described a strong link between genetic determinants and activity of paraoxonase 1 (PON1), oxidative stress, all-cause mortality, and major adverse coronary events. The authors suggested that their findings support the hypothesis that fewer oxidized lipids in the low-density lipoprotein cholesterol particle would be of clinical benefit, an idea for which I am not aware of any trial support.

The suggested mechanistic link is not as clear-cut as the authors imply, and other mechanisms can contribute to the protective role of PON1. Although the notion that PON1 has an antioxidant function is assumed, I know of no biochemical basis for that function. It seems unlikely that the paraoxonase or arylesterase activities measured are related to the suggested antioxidative function of PON1; paraoxon and phenylacetate are artificial substrates,[1,2] convenient for monitoring hydrolytic activity of PON1, which is not a putative redox activity.

However, there is a natural substrate for PON1 in humans, homocysteine-thiolactone (HcyTL); it has been suggested that PON1 should be more aptly named homocysteine-thiolactonase.[2] HcyTL is generated in an error editing process during protein synthesis to remove the nonprotein amino acid homocysteine,[2] a risk factor for many degenerative diseases. HcyTL is similarly detrimental because it also modifies protein lysine residues, impairing or altering protein function, including the redox function and the unique lysine-based cross links, pyridinoline in collagen and isodesmosine in elastin.[2] Thus, it is possible that PON1 could protect against cardiovascular risk by hydrolyzing HcyTL, thereby minimizing protein damage.[2] A finding that the natural homocysteine-thiolactonase activity of PON1 is a predictor of coronary heart disease is consistent with such function.[3]

Homocysteine and associated HcyTL levels can be reduced by over-the-counter B vitamins, folate, or betaine. Homocysteine-lowering vitamin therapy resulted in a significant 25% reduction in stroke[4] and an 80% reduction in hip fractures in persons with stroke.[5] Such therapy did not lower the frequency of myocardial infarction events,[4] but PON1 status was not assessed in those studies.

Given this, it would be helpful for the authors to report the homocysteine levels of the study participants and its relation to PON1 activity, preferably for HcyTL.

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1. Bhattacharyya T, Nicholls SJ, Topol EJ, et al. Relationship of paraoxonase 1 (PON1) gene polymorphisms and functional activity with systemic oxidative stress and cardiovascular risk. *JAMA*. 2008;299(11):1265-1276.
2. Jakubowski H. Calcium-dependent human serum homocysteine thiolactone hydrolase: a protective mechanism against protein *N*-homocysteinylation. *Biol Chem*. 2000;275(6):3957-3962.
3. Domagała TB, Łacinski M, Trzeciak WH, Mackness B, Mackness MI, Jakubowski H. The correlation of homocysteine-thiolactonase activity of the paraoxonase (PON1) protein with coronary heart disease status. *Cell Mol Biol (Noisy-le-grand)*. 2006; 52(5):4-10.
4. Lonn E, Yusuf S, Arnold MJ, et al. Homocysteine lowering with folic acid and B vitamins in vascular disease. *N Engl J Med*. 2006;354(15):1567-1577.
5. Sato Y, Honda Y, Iwamoto J, Kanoko T, Satoh K. Effect of folate and mecobalamin on hip fractures in patients with stroke: a randomized controlled trial. *JAMA*. 2005;293(9):1082-1088.

In Reply: Mr Vos contends that there is no evidence that PON1 possesses antioxidant activity. Rather, he proposes that the homocysteine-thiolactonase activity of PON1 confers the established cardioprotective properties. As stated in our study, we agree that the true physiological function of PON1 remains to be fully elucidated. However, our report of a relationship between a functional PON1 Q192R polymorphism and decreased systemic levels of oxidative stress provides compelling evidence that a genetic determinant of PON1 (either the polymorphism Q192R or another in linkage disequilibrium with it) is associated with systemic indices of oxidant stress. The linkage disequilibrium bin in which the Q192R polymorphism resides lies entirely within the *PON1* gene. Thus, the strong association between this polymorphism and systemic measures of oxidative stress argue strongly that *PON1* is somehow linked to oxidant stress in vivo.

The suggestion that HcyTL represents the "true" endogenous substrate for paraoxonase linking it to cardiovascular pathophysiologic processes, although intriguing, remains to be established. Quantitative studies have not convincingly shown site-specific modification of proteins with HcyTL coupled with demonstration of proatherosclerotic functional consequences at pathophysiologically relevant levels of protein adduct generation. Unfortunately, we do not have data on homocysteine and HcyTL available for our study participants.

With regard to the suggestion of renaming PON1 because of its ability to use HcyTL as substrate, we disagree. PON1 is quite promiscuous and functions as an esterase/lactonase on a broad array of substrates, including a variety of oxidized lipids, homoserine lactone, and even the acetyl ester of salicylic acid.[1-3] We certainly agree that paraoxon pesticide is not the endogenous substrate but see no reason to change the enzyme's name.

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1. Draganov DI, Teiber JF, Speelman A, Osawa Y, Sunahara R, La Du BN. Human paraoxonases (PON1, PON2, and PON3) are lactonases with overlapping and distinct substrate specificities. *J Lipid Res*. 2005;46(6):1239-1247.
2. Khersonsky O, Tawfik DS. Structure-reactivity studies of serum paraoxonase PON1 suggest that its native activity is lactonase. *Biochemistry*. 2005;44(16): 6371-6382.
3. Teiber JF, Horke S, Haines DC, et al. Dominant role of paraoxonases in the inactivation of the Pseudomonas aeruginosa quorum sensing signal N-(3-oxododecanoyl)-L-homoserine lactone. *Infect Immun*. 2008;76(6):2512-2519.

Germline Genomic Homozygosity and Cancer Risk

To the Editor: Dr Assié and colleagues[1] reported a significant association between germline homozygosity in the human genome and increased cancer risk. They also reported an increased loss of heterozygosity (LOH) in cancer cells at the same sites as those of increased genome homozygosis. These findings are important for consanguineous populations, and the authors cited studies that showed an increased risk of cancer in inbreeding populations. However, they have considered only studies from Pakistan and Croatia, which are supportive of their findings.

Human inbreeding is widespread in developing countries of the tropical and subtropical regions of the Eastern hemisphere and involves ethnically different populations.[2] These populations overall have a lower incidence of cancers than Western populations, with the exception of Pakistan, which has a higher incidence of breast and other cancers.[3] In their article, Assié et al[1] cite a study from Pakistan showing that inbreeding increases the risk of breast cancer. Among citizens of the United Arab Emirates, however, inbreeding seems to decrease the risk of several cancers, including breast cancer.[4] Because this opposite result is from a distinct ethnic group, the risk differences may arise from different frequencies in different populations of the low-penetrance, tumor-susceptibility alleles that Assié et al propose as the main mechanism of increased cancer risk.

If LOH at a particular locus is carcinogenic (eg, involving a tumor suppressor allele), human inbreeding will decrease the odds of cancer because it decreases heterozygosity. In the offspring, inbreeding increases the probability of homozygosity of the wild-type allele. Homozygosity of a mutated cancer allele (and a cancerous phenotype) is unlikely because most homozygotes will die prematurely, as suggested by animal experiments for *Brca1*[5] and by the lack of reports of cancerous human *BRCA1* and *BRCA2* homozygotes in spite of statistical odds to the contrary. Thus, at least 2 mechanisms that rely on increased homozygosis may be