Outcomes of Angioplasty vs Thrombolysis by Hospital Angioplasty Volume

To the Editor: Dr Magid and colleagues[1] concluded that patients treated at hospitals that performed more than 16 primary angioplasty procedures per year (93.5% of the procedures in the study) had lower in-hospital mortality rates with primary angioplasty than with thrombolytic therapy. Several other National Registry of Myocardial Infarction publications have also focused on primary angioplasty.[2-5] The inverse relationship between procedure volume and in-hospital mortality in this registry has been previously noted,[4,5] but the finding regarding superiority of primary angioplasty over thrombolytic therapy stands in contrast to previous publications where equivalence was demonstrated.[2,3]

Magid et al suggest that the inclusion of low-volume primary angioplasty centers in previous reports explains this inconsistency, but Rogers et al[3] found equivalent in-hospital mortality rates for myocardial infarction among hospitals with noninvasive catheterization or percutaneous transluminal coronary angioplasty (PTCA) capabilities, and higher mortality rates at hospitals that offer coronary artery bypass graft surgery. The authors also suggest that their findings support the improved outcomes for primary angioplasty at higher-volume centers shown in early randomized studies where streptokinase or 3-hour alteplase infusions were used as the thrombolytic agents. However, they misquote the findings of the Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes (GUSTO-IIb) study, which compared PTCA with thrombolysis using the superior front-loaded 90-minute infusion regimen of alteplase, when they cite an early mortality benefit with primary PTCA. In fact, there were identical in-hospital mortality rates in GUSTO-IIb and there was no difference in 30-day mortality ($P=.37$).

The study by Magid et al may be misinterpreted by readers as showing that angioplasty is superior to thrombolytic therapy. This has only been proved for patients with cardiogenic shock, a subgroup not included in this study. Similarly, recent observational reports have undermined the evidence-based treatment recommendations regarding thrombolytic therapy in the elderly.[6] Registries are a useful way to audit whether treatments are given appropriately, but because of physician bias in selecting treatments and investigator bias in choosing inclusion and exclusion criteria in retrospective studies, only randomized trials can establish the superiority of one treatment over another. Treating as many eligible patients as possible with the best reperfusion strategy available in the shortest time possible remains the most important message on this subject. This will usually be thrombolytic therapy unless a cardiac catheterization laboratory is immediately available.

Eric R. Bates, MD
Division of Cardiology
University of Michigan Medical Center
Ann Arbor

1. Magid DJ, Calonge BN, Rumsfield JS, et al. Relation between hospital primary angioplasty volume and mortality for patients with acute MI treated with primary angioplasty vs thrombolytic therapy. *JAMA*. 2000;284:3131-3138.
2. Tiefenbrunn AJ, Chandra NC, French WJ, Gore JM, Rogers WJ. Clinical experience with primary percutaneous transluminal coronary angioplasty compared with alteplase (recombinant tissue-type plasminogen activator) in patients with acute myocardial infarction. *J Am Coll Cardiol*. 1998;31:1240-1245.
3. Rogers WJ, Canto JG, Barron HV, Boscarino JA, Shoultz DA, Every NR. Treatment and outcome of myocardial infarction in hospitals with and without invasive capability. *J Am Coll Cardiol*. 2000;35:371-379.
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To the Editor: Dr Magid and colleagues[1] found lower mortality rates in patients with acute myocardial infarction treated with primary angioplasty than those treated with thrombolysis at hospitals with high or intermediate volumes of primary angioplasty.

However, 2 points require closer examination. The first is the lack of data on hospital length of stay. Since the end point was in-hospital mortality, the procedure with earlier discharge (usually primary angioplasty) clearly has the advantage of reducing the time for detecting in-hospital events. The second point is the timing of thrombolysis. It is well known that for each hour of delay, the absolute risk reduction for death decreases by 0.16%.[2] This source of possible confounding could be addressed by comparing the outcomes of patients who were admitted within 1 and 2 hours of symptom onset and received thrombolysis.

Aldo Mariotto, MD
Head, Service for Community Medicine
Health Authority No. 6 "Friuli Occidentale"
Pordenone, Italy

1. Magid DJ, Calonge BN, Rumsfeld JS, et al. Relation between hospital primary angioplasty volume and mortality for patients with acute MI treated with primary angioplasty vs thrombolytic therapy. *JAMA*. 2000;284:3131-3138.
2. Collins R, Peto R, Baigent C, Sleight P. Aspirin, heparin, and fibrinolytic therapy in suspected acute myocardial infarction. *N Engl J Med*. 1997;336:847-860.

In Reply: We agree with Dr Bates that treating as many eligible patients as possible with timely reperfusion therapy is important. We found that only 71% of eligible patients with acute myocar-

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Letters Section Editors: Stephen J. Lurie, MD, PhD, Senior Editor; Jody W. Zylke, MD, Contributing Editor.

dial infarction received reperfusion therapy and recommended that efforts "be made to increase reperfusion rates for eligible patients."[1] However, we would like to address 3 other points.

First, although Bates suggests that the study by Rogers et al[2] demonstrates equivalence of primary angioplasty and thrombolytic therapy, this study did not directly compare these therapies.

Second, we believe the reason for the difference in results between our study and the previous National Registry of Myocardial Infarction study conducted by Tiefenbrunn et al[3] is that the studies were conducted during different periods. The period of the study by Tiefenbrunn et al was June 1994 to October 1995, whereas our study was conducted from June 1994 to July 1999. When we limited our analysis to the same period used by Tiefenbrunn et al, we found similar mortality outcomes with primary angioplasty and thrombolysis. However, when we analyzed data for the subsequent period (November 1995 to July 1999), we found significantly lower mortality rates with primary angioplasty compared with thrombolysis. In subgroup analyses we found a clear temporal trend of reduction in mortality over time with primary angioplasty. This is likely due to the more widespread use of coronary stents and glycoprotein IIb/IIIa inhibitors and is consistent with other studies reporting improved outcomes over time with elective angioplasty.[4]

Finally, Bates suggests that only randomized trials can establish the superiority of one treatment over another. While we agree that there are limitations to using observational data, our study was able to assess outcomes for a large number of patients at a large number of hospitals in settings more reflective of current clinical care than typically occurs in randomized trials. Furthermore, a meta-analysis of 10 randomized trials comparing primary angioplasty with thrombolytic therapy[5] found that mortality was 34% lower with primary angioplasty than with thrombolytic therapy. This result compares favorably with our findings at high-volume and intermediate-volume primary angioplasty hospitals, where the adjusted mortality was 35% and 39% lower, respectively, with primary angioplasty compared with thrombolysis.[1]

We agree with Dr Mariotto that patients admitted within 2 hours of symptom onset are likely to derive the most benefit from reperfusion therapy, but this advantage is applicable to both primary angioplasty and thrombolytic therapy.[6] In our study, the proportion of patients who arrived within 2 hours of symptom onset was similar for the primary angioplasty and thrombolytic therapy groups. In addition, we controlled for the time from symptom onset to hospital arrival in our analyses. With regard to Mariotto's second point, differential lengths of stay have been noted with primary angioplasty vs thrombolysis. In our analyses controlling for length of stay, the results were similar to those found in the primary analysis.

David J. Magid, MD, MPH
Bruce N. Calonge, MD, PhD
Colorado Permanente Clinical Research Unit
Denver
John S. Rumsfield, MD, PhD
University of Colorado Health Services Center
Denver

1. Magid DJ, Calonge BN, Rumsfield JS, et al. Relation between hospital primary angioplasty volume and mortality for patients with acute MI treated with primary angioplasty vs thrombolytic therapy. *JAMA*. 2000;284:3131-3138.
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3. Tiefenbrunn AJ, Chandra NC, French WJ, Gore JM, Rogers WJ. Clinical experience with primary percutaneous transluminal coronary angioplasty compared with alteplase (recombinant tissue-type plasminogen activator) in patients with acute myocardial infarction. *J Am Coll Cardiol*. 1998;31:1240-1245.
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Timing of Antiretroviral Treatment Initiation

To the Editor: In their Research Letter, Dr Chaisson and colleagues,[1] using data from an ongoing study,[2] address the uncertainty of the timing of antiretroviral treatment initiation,[3,4] and conclude that both CD4 cell counts and viral load should be considered in deciding when to initiate antiretroviral therapy.

Even though the interpretation of their results in Table 2 appears to be correct, we believe that certain issues related to principles of logistic regression are inadequately addressed. The authors suggest that achieving "reduction of HIV RNA to less than 400 copies/mL on at least 1 occasion within 6 months of starting treatment (initial response)" and "response with no subsequent elevation of HIV RNA level to more than 1000 copies/mL (durable response)" were evaluated using multivariable logistic regression.

Logistic regression using risk factors measured in their original units leads to a less arbitrary and more powerful analysis. The distribution of continuous data into sometimes arbitrary categories may compromise the statistical efficiency and may require more complicated modeling.[5] Therefore, an apt initial analysis would include a logistic regression model with viral load and CD4 cell counts used as continuous variables.

In addition, it is assumed that each explanatory variable used in multivariable logistic regression has an independent effect on the outcome. Since immunological and virological markers are likely to be correlated, the effect of each variable on the outcome could depend on the other variable. A high correlation between the independent variables means that they have indistinguishable influences on the outcome and, thus, estimates of their regression coefficients are not reliable.[5]

Assessment of any possible interaction between the 2 "risk" variables (viral load and CD4 cell count) would strengthen the analysis. In the absence of interaction, the additive multivariable logistic regression could be used to examine the main effects of these variables (assuming they each have an independent effect on outcome).

Finally, an examination of Table 2 might lead to some misinterpretation; for example, the odds ratio for achieving initial response for the category "CD4 cell count >350/mm^3" is 1.8 (95% confidence interval [CI], 1.10-2.96). This increased risk is rela-

tive to the reference category of "CD4 cell count <200." For the category "RNA 25 000-100 000 copies/mL" the odds ratio for achieving initial response is also 1.8 (95% CI, 1.10-2.90). The reference category for this is "RNA >100 000 copies/mL." The authors should have made it clearer that the odds ratios given for viral load and CD4 cell count are not comparable since they have different reference categories. Furthermore, a table with the odds ratios for all possible combinations of CD4 cell count and viral load categories would perhaps allow for an easier interpretation of the results.

Tassos C. Kyriakides, PhD
Peter Guarino, MPH
Veterans Affairs Cooperative Studies Program Coordinating Center
West Haven, Conn

1. Chaisson RE, Keruly JC, Moore RD. Association of initial CD4 cell count and viral load with response to highly active antiretroviral therapy. *JAMA.* 2000;284:3128-3129.
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In Reply: Dr Kyriakides and Mr Guarino raise several important issues regarding the analysis of data derived from observational cohorts. Analysis of linear data, such as CD4 cell counts or viral loads, is more statistically powerful when the data are kept continuous, rather than categorized. In general, categorization of data (such as CD4 cell count <200/mm^3) reduces statistical power and can underestimate effects that might be found with linear data. This is only a problem if a negative result is obtained when analysis of continuous data would yield a positive result. Our analysis found important differences by the CD4 cell strata we used, so no underestimation of effect resulted. In addition, categorization of laboratory data is important in clinical practice, for physicians need thresholds on which to base therapeutic interventions. Rather than being arbitrary, our cut points were based on widely used and accepted thresholds of CD4 cell counts and viral loads that have been validated both prognostically and therapeutically. While an analysis that reports that the relative hazard of treatment failure is 1.001 for each 1-cell decline in the CD4 cell count below 500/mm^3 might be statistically powerful, it would have little utility for clinicians. We believe our analysis was sufficiently powered and clinically framed to provide both valid and useful results.

Kyriakides and Guarino suggest that a strong correlation between CD4 cell counts and viral loads would result in unreliable estimates of their regression coefficients. In our data, viral load and CD4 cell count were not highly correlated, with an r of –0.23. We are confident, therefore, that CD4 cell count and viral load are indeed independent variables. Kyriakides and Guarino also suggest that we assess whether there is an interaction between CD4 cell counts and viral loads with respect to outcomes. We found no interaction between CD4 cell counts and viral loads with respect to durable responses to highly active antiretroviral therapy. When analyzing initial response to therapy, we found that there was an interaction between these variables in those patients with both low CD4 cell counts and high viral loads; otherwise, no interaction was seen.

We agree that is important for readers to realize that the odds ratios in Table 2 have different referent groups depending on the category. Space did not permit, but we can provide a more detailed table to interested researchers.

Richard E. Chaisson, MD
Richard D. Moore, MD, MHSc
Johns Hopkins University School of Medicine
Baltimore, Md

Chlamydia trachomatis and Cervical Squamous Cell Carcinoma

To the Editor: Dr Anttila and colleagues[1] presented data linking *Chlamydia trachomatis* with cervical squamous cell carcinoma (SCC). However, because the serologic methods they used to measure human papillomavirus (HPV) infection are of limited sensitivity and narrow spectrum,[2] the apparent increased risk of SCC associated with *C trachomatis* infections may be due to residual confounding caused by misclassification of the primary confounding variable, HPV. To assess *C trachomatis* as an independent cofactor in this study population, we suggest the analysis be restricted only to those women who are seropositive for HPV.

To date, only cigarette smoking and multiparity have emerged as risk factors for SCC after adequate adjustment for HPV status.[3] Other genital infections have not been associated with a consistently increased risk for SCC after adjustment for HPV status. However, we agree that *C trachomatis* infection may act as a cofactor in HPV-induced tumorigenesis via an inflammatory pathway. It is likely that the etiologic fraction of HPV-induced SCC cases attributable to any given cofactor is small, and individual assessment of only a few components will continue to lead to weak and inconsistent associations.

We propose that smoking, multiparity, and cervical inflammation increase the risk of HPV-induced SCC via a common tumor-promoting pathway of cellular oxidative and nitrative stresses that can cause DNA damage. Specifically, tobacco metabolites, such as polycyclic aromatic hydrocarbons (PAHs) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone [NNK], are known to be present in the cervical mucus[4] and to promote genotoxicity via well-described pathways. Similarly, highly reactive nitric oxide is produced in high concentrations for protracted periods during both inflammatory responses (from infiltrating macrophages to aid in cytotoxicity) and during parturition (from cervical keratinocytes to enhance the breakdown of the extracellular matrix required for cervical ripening).[5] Resultant DNA damage from these nitrative and oxidative stresses would normally trigger apoptotic cell death, prevent-

ing the propagation of genetic damage in a homeostatic process that allows the physiologic function of nitric oxide signaling to proceed without adverse cellular consequences. However, in cells that express the HPV oncogenic proteins E6 and E7, normal apoptotic signaling cascades and cell cycle control mechanisms induced by DNA damage are dysregulated, leading to unchecked propagation of genetically unstable cell populations. Thus, measurement of the common downstream genotoxic effects of several such disparate environmental exposures may be necessary to adequately assess the underlying associated risk of proposed cofactors, such as *C trachomatis,* in HPV-induced SCC.

Patti E. Gravitt, MS
Philip E. Castle, PhD
Division of Cancer Epidemiology and Genetics
National Cancer Institute
Rockville, Md

1. Anttila T, Saikku P, Koskela P, et al. Serotypes of *Chlamydia trachomatis* and risk for development of cervical squamous cell carcinoma. *JAMA.* 2001;285:47-51.
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To the Editor: Dr Anttila and colleagues[1] reported that *C trachomatis* antibodies are associated with a 2.5-fold increased risk of invasive cervical SCC after adjustment for serum antibodies to HPV types 16, 18, and 33.

While advantages of this study include its nested case-control design and the use of the microimmunofluorescence (MIF) assay for ascertainment of past *C trachomatis* infection, we are concerned that the study does not adequately control for the strong effect of HPV infection. Oncogenic HPV types are the central, and probably necessary, cause of invasive cervical cancer.[2] Cofactors may act by increasing susceptibility to HPV infection or by inducing progression from HPV infection to invasive cancer. The current approach to assessing the role of cofactors for progression is restriction of analyses to HPV-positive women. By simply adjusting for HPV seropositivity, residual HPV confounding is expected because HPV serology is less sensitive than the detection of HPV DNA using current criterion standard assays based on the polymerase chain reaction.[3] Given the high prevalence of HPV DNA in invasive carcinoma worldwide (>99%),[2] misclassification of HPV among cases must have occurred, as only 37% of SCC cases were seropositive for HPV type 16,18, or 33. Further evidence for residual confounding is that the associations between *C trachomatis* seropositivity and cervical SCC in Table 1 are little modified following adjustment for HPV seropositivity.

The stronger associations due to chlamydial serovars G, I, and D are intriguing. However, the odds ratios (ORs) in Table 1 for the different serotypes are generally similar. It is also unclear that an increased risk of cervical SCC may be attributable to a single serotype since complex antigenic relationships exist between different *C trachomatis* serotypes using the MIF assay.

Furthermore, MIF reactivity to increasing number of serotypes may not be an appropriate surrogate for increasing number of exposures to different *C trachomatis* serotypes. As *C trachomatis* serotypes fall into 2 major antigenic groups, *C trachomatis* antibody reactivity to multiple serotypes may be due to an infection with 1 serotype and subsequent exposure to a serotype from a heterologous antigenic group.[4] Although the authors claim that SCC risk increases with a greater number of *C trachomatis* serotypes in Table 2, the trend does not seem to be linear (OR=6.0 for 2 serotypes and OR=4.2 for $\geq$ 3 serotypes).

While we agree with Anttila et al that *C trachomatis* infection may be an important cofactor of HPV in cervical carcinogenesis, more strict control for HPV infection is required (ie, restriction to HPV-DNA–positive cases and controls) to provide stronger evidence.[5]

Jennifer S. Smith, PhD, MPH
Nubia Muñoz, MD
Silvia Franceschi, MD
International Agency for Research on Cancer
Lyon, France
José Eluf-Neto, MD, MSc, PhD
Universidade de São Paulo
São Paulo, Brazil
Rolando Herrero, MD, PhD
Costa Rica Cancer Institute
San José, Costa Rica
Rosanna W. Peeling, PhD
Laboratory Centre for Disease Control
Winnipeg, Manitoba

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To the Editor: Dr Anttila and colleagues[1] described a serological correlation between past *C trachomatis* infection and the development of cervical SCC. They also described a potential clinical relevance for *C trachomatis* serovar typing since certain serovars, in particular serovar G, were associated with SCC. We previously described *C trachomatis* serovar number 19, serovar Ga.[2,3] Serovar G (prototype strain UW-57) and Ga (prototype strain IOL-238) can be distinguished by using specific monoclonal antibodies (8.2C4 and 8.3H8) and by genotyping due to an additional BstU1 site in VS4 of the *omp1* gene. A statistical difference in the clinical course of infection between the serovars G and Ga has been described: serovar Ga was associated with symptoms in both men and women and specifically with dysuria in men.[4] As discussed by Anttila et al, some *C tra-*

chomatis serovars may be more virulent than others, are perhaps less sensitive to certain antibiotics and could play a role in carcinogenesis. In the light of differences in virulence among serovars, it would be interesting to investigate whether the serological responses to the serovar G identified by Anttila et al are really responses to serovar G or, in fact, to serovar Ga.

Confirmation of the results of Anttila et al is important since a positive association between *C trachomatis* and SCC would have a profound effect on the justification and initiation of suggested screening programs for *C trachomatis* infections. Not only would this reduce late complications such as pelvic inflammatory disease, ectopic pregnancy, and infertility, but also the incidence of cervical cancer. During the 18th International Papillomavirus Conference,[5] 4 studies were presented describing the association between *C trachomatis* and SCC and another study is in progress. In 2 studies, this association was observed, but not in 2 others. Two of these studies used follow-up cohorts with long lag times and collected both serum samples and cervical swabs in which *C trachomatis* (and HPV) can be detected by the polymerase chain reaction and included questionnaires to investigate possible demographic, behavioral, and biological confounders. Also, the relationship between *C trachomatis* and precursor lesions needs to be studied further to elucidate the possible role of *C trachomatis* as a cofactor in the development of SCC.

Servaas A. Morré, PhD
Department of Pathology
University Hospital Vrije Universiteit
Amsterdam, the Netherlands

Jacobus M. Ossewaarde, MD, PhD
Research Laboratory for Infectious Diseases
National Institute of Public Health and the Environment
Bilthoven, the Netherlands

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5. In: Program and abstracts of the 18th International Papillomavirus Conference; July 23-28, 2000; Barcelona, Spain. van den Brule AJC et al. Development of HPV induced cervical intraepithelial neoplasias: infection with *Chlamydia trachomatis* as a possible cofactor? Abstract 63:130; Castle PE et al. Inflammation and co-infection with STDs other than HPV as risk factors for progression of HPV infections to high-grade squamous intraepithelial lesions and cervical cancer. Abstract 70:134; Smith JS et al. Evidence for *Chlamydia trachomatis* as an HPV cofactor in the etiology of invasive cervical cancer in Brazil and the Philippines. Abstract 71:135; Wallin KL et al. *Chlamydia trachomatis* infection, a risk factor in cervical cancer development: a population based prospective study. Abstract 113: 157; Molano M et al. Prevalence of human papillomavirus and *Chlamydia trachomatis* in the general population from Colombia. Abstract 160:181 .

To the Editor: Dr Anttila and colleagues[1] reported that *C trachomatis* serotype G was most strongly associated with subsequent development of cervical SCC, and that increasing numbers of exposures to different serotypes of *C trachomatis* also increased the risk. However, the direct etiological role of *C trachomatis* serotype G and superinfection of different serotypes in the pathogenesis and development of SCC is still unknown.

In urogenital chlamydial infections, the serovar D, D variants, E, and F are predominant, while G, H, I, I variants, J, and K are less common. We obtained endocervical swabs from 1917 Japanese pregnant women in several maternity hospitals in Sapporo, Japan, between February and July 1997. All women were asymptomatic and had no clinical signs of infection. Restriction fragment length polymorphism analysis was used to distinguish all 18 classic serovars of *C trachomatis* originally determined by the MIF test.[2,3] With the application of the polymerase chain reaction, sufficient quantities of specific segments of chlamydial DNA can be amplified for restriction digests without culturing of clinical isolates.

We distinguished 218 strains in 1917 clinical specimens.[3] Among the 218 specimens, 207 (95.0%) were serotyped (43 as serovar D, 53 as serovar E, 24 as serovar F, 39 as serovar G, 15 as serovar H, 15 as serovar I, 5 as serovar J, 9 as serovar K, and 4 as mixed); the rest were not classified by this method. Of the mixed infections, 2 were D/F, the others were D/J and G/I. We have followed up 39 women with serotype G and 4 women with different serotypes of *C trachomatis* for 3 years (1998-2000), and none of them have developed SCC or pelvic inflammatory diseases. We speculated that there was no difference in prototype serovar distribution of *C trachomatis* between symptomatic and asymptomatic populations.

Further studies are necessary to establish the precise role of *C trachomatis* serotypes in the pathogenesis and development of SCC. On the other hand, it also seems necessary to reevaluate the stereotyping, organ specificity, and transmission patterns of some *C trachomatis* strains associated with infections, which were originally based on the results of the MIF test.

Kei Numazaki, MD, PhD
Masami Ikehata, MD, PhD
Shunzo Chiba, MD, PhD
Department of Pediatrics
Sapporo Medical University
School of Medicine
Sapporo, Japan

1. Anttila T, Saikku P, Koskela P, et al. Serotypes of *Chlamydia trachomatis* and risk for development of cervical squamous cell carcinoma. *JAMA.* 2001;285:47-51.
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In Reply: The letters from Ms Gravitt and Dr Castle, and from Dr Smith and colleagues, question our finding of an association between *C trachomatis* infection and cervical SCC. They claim that the relatively low sensitivity of HPV serology leads to significant nondifferential misclassification bias that makes it difficult to control for residual confounding by HPV by simply adjusting for HPV seropositivity. However, it is inappropriate to compare the results of cross-sectional studies (which generally show a 99% positivity rate for HPV DNA among SCC cases) and

longitudinal studies (which have found a 37% positivity rate for serum antibodies to HPV 16, 18, or 33 among women who will subsequently develop SCC). In most cases, HPV infection is usually transient. Therefore, HPV DNA positivity simply reflects the point prevalence of HPV infection, whereas HPV seropositivity is a more stable marker of past exposure to HPV. Also, recent sexual activity could increase the HPV DNA positivity among control subjects but not among those already exposed to HPV, and this could lead to significant systematic bias and hence underestimate the role of sexually transmitted cofactors. Furthermore, the association between *C trachomatis* and cervical carcinoma was specific for SCC but not for cervical adenocarcinoma or other noncervical anogenital carcinomas.[1] Only a longitudinal approach can assess temporal association, which is critical and probably different for different microorganisms or carcinogens in general.

We previously discussed the problem of residual confounding by HPV in an article that originated from the same serum bank material.[2] The estimate of the association changed relatively little after adjustment for HPV, suggesting that the effect associated with *C trachomatis* cannot be entirely explained by residual confounding. We did not discuss residual confounding in our recent article because of the small numbers of cases in different serotype strata, and because *C trachomatis* serotype–specific confounding is likely to remain weak. We believe it may not be appropriate to perform analyses within the strata of HPV-seropositive individuals only. For instance, Trichopoulos et al[3] were able to discover the association between smoking and hepatocellular carcinoma only among hepatitis B surface antigen–negative individuals but not among hepatitis B surface antigen–positive individuals. In another recent article, we more thoroughly studied the effect of nondifferential misclassification bias on the interaction between *C trachomatis* and HPV by using different test sensitivity and specificity values for HPV-16 serology.[4] We concluded that nondifferential misclassification bias could not explain the strong interaction observed between *C trachomatis* and HPV-16. Another manuscript describing the association between smoking and cervical SCC is now undergoing peer review.

Regarding serum antibodies to more than 1 serotype and increasing risk for development of SCC, we suggested that serological cross-reactivity might be an alternative explanation. However, we disagree with Smith et al that the trend should necessarily be linear. In fact, a plateau effect might better explain current data about original antigenic load and antibody response to *C trachomatis*.[5]

Drs Morré and Ossewaarde and Dr Numazaki and colleagues discuss the role of specific *C trachomatis* serotypes in asymptomatic vs symptomatic infections. Interestingly, serotype G seems to be common not only in Europe but also in Japan. Unfortunately, we are unable to comment on the possible role of the recently discovered serovar Ga.

We think that a follow-up period of 3 years is simply too short to draw any definitive conclusions regarding the role of *C trachomatis* infection in cervical carcinogenesis, particularly among young pregnant women.[6] We found that the risk associated with *C trachomatis* was linked to long lag time, ie, the long time period between exposure and cancer diagnosis. [2] This is in line with other longitudinal studies recently reported at the 18th International Papillomavirus Conference.[6]

When studying the role of *C trachomatis* in cervical precursor lesions, one should be able to distinguish between progressing lesions and regressing lesions. Obviously, the true end point, ie, cervical cancer, cannot be used for ethical reasons. Perhaps new SCC-specific tumor markers such as p16 can be used in future prospective studies using high-grade squamous intraepithelial lesions as a surrogate end point.

Continuing research on the potential cofactors that determine the risk for cervical cancer is important. Unfortunately, confounding can never be totally excluded in epidemiological studies. However, prospective studies will ultimately provide the strongest evidence of the interaction between HPV and cofactors.

Tarja Anttila, MD
Pentti Koskela, PhD
National Public Health Institute
Oulu, Finland

Matti Lehtimen, MD
National Public Health Institute
Helsinki, Finland

Joakim Dillner, MD
Department of Virology
Malmö University Hospital
University of Lund
Lund, Sweden

Jorma Paavonen, MD
Department of Obstetrics and Gynecology
University of Helsinki
Helsinki

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RESEARCH LETTER

Y2K Revisited: A Human Component?

To the Editor: Few events in recent times have been as anticlimactic as the Y2K transition. Whether it was because of thorough preparedness or overstated worries about a largely nonexistent problem, January 1, 2000, came and went uneventfully in the electronic world. Yet, in all the attention about internal electronic dates, the possible effect of Y2K on the timing of human mortality may have been overlooked.

Methods. I determined the total number of deaths for the past 4 years that occurred each month at Yale-New Haven Hospital, exclusive of fetal deaths. Cause of death was determined from the death certificate and grouped into 1 of 10 categories. Statistical analysis of outlier months was performed using the Fisher protected least significant difference test.

Results. The number of deaths per month at Yale-New Haven Hospital has remained relatively constant near a mean of 75. However, in January 2000, there were 123 deaths (FIGURE), which is more than 5 SDs above the mean monthly deaths for past 4 years ($P<.001$). Only 3 of the deaths occurred on January 1, and they were not related to equipment failure. The deaths were relatively evenly distributed over the month with 61 deaths on or before January 16th and 62 of the deaths afterward. There were no changes in hospital policies or staffing during this month. The age distribution of the deaths was essentially the same as other months, with a slightly higher representation in those aged 61 through 70 years. The causes of death (TABLE) were similar to those in January 1999 and January 2000 with an overrepresentation of deaths from chronic pulmonary disease and a slight underrepresentation from deaths due to acute vascular events (ie, myocardial infarctions, ruptured aneurysms, and strokes). Only 1 death certificate indicated influenza as a cause of death.

A less significant peak in the death count occurred in May 1997. That month had an unusually high number of medical examiner deaths (12%). Elimination of all medical examiner cases from the analysis decreased the variance in the number of deaths for May 1997 below statistical significance but increased the difference for January 2000.

Comment. A variation of 5 SDs in the number of deaths for January 2000 is unlikely to be random. The data also reveal a seasonal trend in the number of deaths, which parallels national statistics that show relative peaks in January and February and relative troughs in July and August.[1] During the peaks, death rates are typically 20% above the mean for the year. This trend is at least partly due to seasonal trends in influenza death rates and the January 2000 epidemic was particularly severe nationally.[1] The US mortality rate from influenza peaked at 11% in January 2000 compared with a mean mortality rate of 7% over the year.[1] However, a 4% increase in mortality due to influenza and a 20% increase in mortality from seasonal variation do not account completely for the 63% increase seen at Yale-New Haven Hospital during January 2000.

Although it is not possible precisely to explain the high mortality rate in January 2000, a likely contributing factor was the desire of patients to live into the next century. Most physicians have seen, at least anecdotally, the powerful effect of the patient's will to live, and a number of studies have supported a role for nonmedical factors in affecting patient outcomes.[2-6] The overrepresentation of deaths due to chronic pulmonary disease and underrepresentation of deaths due to acute vascular events seen in January 2000 are consistent with this hypothesis. Being difficult to define, evaluate, or alter, "will to live" has been often disregarded as nonscientific. Yet, these data suggest a role for the patient's state of mind in postponing his or her own outcome.

Figure. Number of Deaths Each Month at Yale-New Haven Hospital

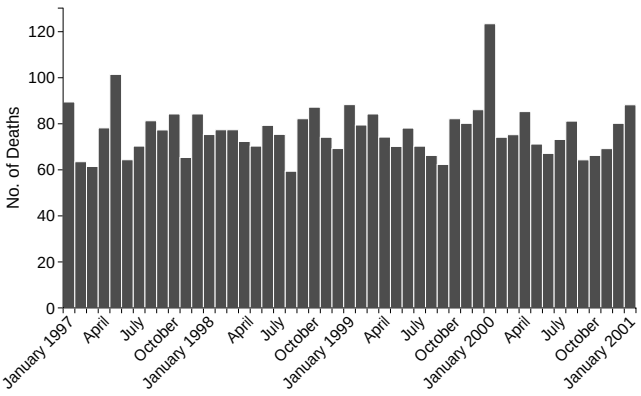

Table. Causes of Death (January Only)*

Cause of Death, %	1999, 2001	2000
Sepsis, pneumonia, overwhelming infection, AIDS	21	19
Arteriosclerotic cardiovascular disease (coronary artery disease, myocardial infarction, arrhythmia, ruptured aneurysm, dissection)	20	15
Prematurity, congenital defects, SIDS	13	10
Malignancies, neoplasms	13	14
Congestive heart disease (heart failure)	9	9
Other major organ failure (liver, kidney, multisystem)	8	7
Cerebrovascular event, stroke, cerebral hemorrhage	7	4
Homicide, suicide, trauma, overdose	4	6
Chronic pulmonary disease (COPD, pulmonary fibrosis, cystic fibrosis)	4	13
Other chronic disease (diabetes, Parkinson disease, Alzheimer disease, seizures)	2	4

*To minimize the effect of seasonal variations in causes of death, January 2000 causes were compared with causes of death from the January previous and following. AIDS indicates acquired immunodeficiency syndrome; SIDS, sudden infant death syndrome; and COPD, chronic obstructive pulmonary disease.

John H. Sinard, MD, PhD
Yale-New Haven Hospital
New Haven, Conn

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