tamoxifen plus ovarian suppression will translate into an overall survival benefit. With few deaths, the confidence intervals within cohorts are wide and all contain the overall hazard ratio of 1.14. The role of a high body-mass index is under investigation in the ongoing TEXT and SOFT trials, and suboptimal ovarian suppression in patients receiving an aromatase inhibitor with ovarian suppression has been investigated in the SOFT Substudy (SOFT-EST).²

In the TEXT and SOFT combined analysis, 567 women (12%) had HER2-positive tumors, according to local pathologic findings. These women did not appear to derive an advantage from exemestane plus ovarian suppression as compared with tamoxifen plus ovarian suppression. Of these women, 483 received chemotherapy (85%) and 310 received HER2-targeted therapy (55%), according to drug availability at enrollment. In TEXT and SOFT, the timing of chemotherapy and HER2-targeted therapy differ relative to the initiation of endocrine therapy; this shows the complexity and need for further investigation before HER2 status is used for selection of endocrine therapy, which is planned once central assessment of HER2 status is available.

The designs of TEXT and SOFT assumed that the magnitude of treatment effect would be similar to that observed in postmenopausal women — a numerically larger population in which aromatase inhibitors are a standard endocrine therapy. Aromatase inhibitors are now all off-patent drugs. The cost of treatment for breast cancer is nevertheless a substantial economic burden especially, but not only, in low-income and middle-income countries.³,⁴ Cost should be included in the various cost–benefit considerations that patients and health care providers discuss when planning treatment strategies. The American Society of Clinical Oncology launched a new initiative to identify clinically meaningful outcomes that warrant the financial cost of treatments that have modest increments of benefit. Within this framework, the combined findings of TEXT and SOFT were assessed, and adjuvant treatment with ovarian suppression plus exemestane was considered to be a high-value option with a modest increase in cost.⁵

Olivia Pagani, M.D.
Institute of Oncology of Southern Switzerland
Lugano, Viggianello, Switzerland
Meredith M. Regan, Sc.D.
International Breast Cancer Study Group Statistical Center
Boston, MA
Prudence A. Francis, M.D.
Peter MacCallum Cancer Centre
Melbourne, VIC, Australia
for the TEXT and SOFT Investigators
and the International Breast Cancer Study Group

Since publication of their article, the authors report no further potential conflict of interest.

DOI: 10.1056/NEJMc1409366

Evidence for Camel-to-Human Transmission of MERS Coronavirus

TO THE EDITOR: Azhar et al. (June 26 issue)¹ report on the transmission of the Middle East respiratory syndrome coronavirus (MERS-CoV) from camels to a human patient. Our independent investigation of the same case led to a similar but less definite conclusion.² Azhar et al. prove transmission by means of the cultivation of viruses from the patient and a camel in his possession, determining 100% sequence identity between the virus isolates. However, both isolates...
deviated from the original, uncultured virus in at least two sequence positions (C10154T and G25800T). The original genotype (C10154 and G25800) is confirmed by our data. Mutations in both isolates must therefore have occurred independently during virus cultivation.

For silent mutations such as C10154T we can simplistically assume a relative likelihood of $10^{-4}$ (genome size, 30 kb; approximately 104 third codon positions). The combined likelihood of both mutations would be approximately $10^{-8}$. The nonsilent mutation at position 25800 has not been observed during MERS-CoV cultivation, making its dual occurrence even less likely. A low RNA concentration in samples from camels raises doubts regarding the possibility of cultivating the virus and points to other explanations, such as cross-contamination between cell cultures.

**The Authors Reply:** Unique nonsynonymous and synonymous mutations throughout the viral genome have been found by others by means of direct sequencing or cultivation. Amino acid changes seem to cluster between positions 77 and 98 in the ORF3 protein, with at least three unique mutations having been reported only once. As we discuss in our article, cross-contamination was unlikely because the two samples were collected and processed at different times and locations. The isolate from the camel was cultivated and isolated 3 days before the isolate from the patient was cultivated, as shown by the deposition dates of the sequences in GenBank. Although it is more likely to recover virus with a high RNA titer than with a low RNA titer, that does not mean it cannot otherwise be done. In addition, different samples with presumably different virus concentrations were collected and used for polymerase-chain-reaction assay and culture. The detection of MERS-CoV RNA in an air sample from the camel barn, with sequences identical to those in samples obtained from the patient and the source camel, provided additional evidence that the camels were infected with the same virus.

Tariq A. Madani, M.D.
Esam I. Azhar, Ph.D.
Anwar M. Hashem, Ph.D.

King Abdulaziz University
Jeddah, Saudi Arabia

tmadani@kau.edu.sa

---

Since publication of their article, the authors report no further potential conflict of interest.