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We thank B. Descomp and I. McPherson for stimulating discussion.

Response
We thank Drs. Gerber and Saintot for their interest in our work. We agree that information on BMI and fat deposition patterns would help to clarify the possible relationship between serum cholesterol levels and ovarian cancer. Had we collected this information, we certainly would have presented it in our article (1).

The issue of how to handle the data on cholesterol and vitamin E, given the high degree of collinearity between the two, is an interesting one. α-Tocopherol and cholesterol were assessed singly, and both were observed to be associated with increased risk of ovarian cancer. To further describe the relationship between cholesterol, α-tocopherol, and ovarian cancer, the data were analyzed two ways. The approach most pertinent to the question raised by Drs. Gerber and Saintot was a stratified analysis in which women were classified according to both factors jointly. The results of this analysis showed that, compared with a serum profile of low cholesterol and low α-tocopherol levels, high cholesterol levels were associated with increased risk of ovarian cancer when α-tocopherol levels were low, and this association was stronger and statistically significant when α-tocopherol levels were high. High α-tocopherol levels were associated with reduced risk of ovarian cancer only in the presence of low cholesterol levels. If these substances are truly related to the risk of ovarian cancer, then the absolute circulating concentrations are the exposures of primary interest. The disadvantage of the vitamin E/cholesterol ratio suggested by Gerber and Saintot vis-à-vis stratified analysis is that the ratio adjusts away the absolute concentrations and is thus only a measure of the relative balance between α-tocopherol and cholesterol concentrations. For example, the low/low and high/high strata from our stratified analysis may have been very similar if transformed to the ratio estimate, thus obscuring the important—and significantly different—associations between these two groups with disparate absolute concentrations.

The data that Gerber and Saintot present in their table showed that case subjects had significantly lower cholesterol levels than control subjects, which is in the opposite direction to the association we observed. It is therefore worth noting the difference in how the two studies were designed. Ours was a prospective study nested within a population-based cohort (1), whereas Gerber and Saintot present data from a hospital-based case-control study in which blood drawing occurred after the case subject was diagnosed with ovarian cancer (2). Prevalent ovarian cancer may directly or indirectly affect circulating micronutrient and cholesterol levels, so that whether a serum profile is a consequence or a predictor of ovarian cancer is indeterminable from the latter design.

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References


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Fatal Hepatic Coma Attributed to Paclitaxel
Paclitaxel (Taxol) is increasingly being used to treat ovarian and breast cancers (1). Well-known adverse effects from this drug are myelosuppression and neurotoxicity.

We report here on a patient who died as a result of a hepatic coma that developed within 48 hours after receiving the first dose of paclitaxel; this patient did not have a history of alcohol abuse or acute or chronic hepatitis. This 47-year-old female had disseminated breast cancer unresponsive to several previous chemotherapeutic regimes. She was treated with intravenously administrated paclitaxel at a dose of 175 mg/m². On admission, before treatment, she was subjected to various laboratory tests. These tests revealed elevated levels of serum aspartate aminotransferase (AST) at 339 U/L (normal level, <27 U/L), alanine aminotransferase (ALT) at 56 U/L (normal level, <25 U/L), lactate dehydrogenase (LDH) at 1349 U/L (normal
range, 140-280 U/L), alkaline phosphatase at 319 U/L (normal range, 25-90 U/L), γ-glutamyltransferase (γ-GT) at 417 U/L (normal range, 10-30 U/L), and bilirubin at 54 μmol/L (normal level, <17 μmol/L) as a result of multiple hepatic metastases. After receiving paclitaxel, the patient was discharged from the hospital and was in good clinical condition.

Within 24 hours, however, the patient was readmitted because of progressive mental disturbance and lethargy. On readmission, she was in a stupor. Medications at the time of readmission were filgrastim (granulocyte colony-stimulating factor) given subcutaneously once daily at a dose of 300 μg, clodronic acid (bisphosphonate) given four times daily by mouth at a dose of 400 mg, and metoclopramide given by suppository three times daily at a dose of 20 mg. General examination did not reveal abnormalities. Neurologic examination did not reveal any focal neurologic signs, and cerebral computed tomography (CT) showed no signs of cerebral metastases or other pathologic findings. An electroencephalogram (EEG) demonstrated a symmetric, high-voltage, slow-wave encephalogram which was consistent with a nonfocal encephalopathy. Laboratory tests revealed a serum ammonia level of 417 μg/dL (normal range, 10-70 μg/dL) and an aspartate transaminase (AST) level of 86 U/L (normal range, 10-30 U/L), and bilirubin at 54 μmol/L (normal level, <17 μmol/L), which were consistent with hepatic encephalopathy. Laboratory tests also revealed that the serum ammonia level was not as- 

frequent complication of paclitaxel therapy. The safety of paclitaxel in patients with mild hepatic function abnormalities was established by safety analyses at the time paclitaxel was first approved by the Food and Drug Administration for treatment of ovarian and breast carcinomas. Rare episodes of hepatic necrosis and hepatic encephalopathy leading to death, however, have been previously reported as part of the ongoing surveillance of paclitaxel safety. Addenda to the paclitaxel clinical brochure were disseminated by Bristol-Myers Squibb to investigators and reported to health authorities in February 1993, reporting a case of suspected hepatic encephalopathy resulting in death, and in March 1993, reporting an episode of hepatic necrosis resulting in death. In a recent search of the adverse-events database for paclitaxel, which includes clinical trial results as well as worldwide postmarketing surveillance, one additional case of hepatic encephalopathy and three episodes of hepatic failure, all in patients with extensive liver metastases, were found that resulted in death.

Two ongoing prospective studies, sponsored by Bristol-Myers Squibb and initiated in 1992, are designed to address the relationship between baseline hepatic impairment and the safety and pharmacokinetics of paclitaxel and to provide data to guide dose adjustments in patients with liver impairment. Veenk and colleagues from Cancer and Acute Leukemia Group B (CALGB) (Bristol-Myers Squibb [BMS] study CA139-078) are conducting a phase I and pharmacokinetics study of paclitaxel as a 24-hour infusion in patients with liver dysfunction. BMS CA139-155 is a trial conducted by Ver- 

Drs. Feenstra, Vermeer, and Stricker have reported a case of fatal coma suspected to be hepatic in origin in a patient following treatment with paclitaxel. To our knowledge, this is the first report in the literature of such a complication related to paclitaxel (Taxol).

As they note, hepatic injury is an infrequent complication of paclitaxel treatment. The safety of paclitaxel in patients with mild hepatic function abnormalities was established by safety analyses at the time paclitaxel was first approved by the Food and Drug Administration for treatment of ovarian and breast carcinomas. Rare episodes of hepatic necrosis and hepatic encephalopathy leading to death, however, have been previously reported as part of the ongoing surveillance of paclitaxel safety. Addenda to the paclitaxel clinical brochure were disseminated by Bristol-Myers Squibb to investigators and reported to health authorities in February 1993, reporting a case of suspected hepatic encephalopathy resulting in death, and in March 1993, reporting an episode of hepatic necrosis resulting in death. In a recent search of the adverse-events database for paclitaxel, which includes clinical trial results as well as worldwide postmarketing surveillance, one additional case of hepatic encephalopathy and three episodes of hepatic failure, all in patients with extensive liver metastases, were found that resulted in death.

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