Breast Cancer Mortality and Age at Diagnosis

To the Editor: The study by Dr van de Water and colleagues[1] found that increasing age was associated with higher breast cancer mortality in postmenopausal women with hormone receptor–positive tumors. There are methodological issues in measuring the effect of age on disease-specific mortality.

Classifying patients on the basis of whether there was evidence of breast cancer at the time of their death may be misleading. For instance, if an 80-year-old woman with a known pulmonary metastasis dies, her death will be attributed to breast cancer. However, without a postmortem examination, it is not possible to determine the exact cause of death, which may be due to a non–disease-specific condition such as unstable coronary artery disease. If a 36-year-old woman with breast cancer dies in a motor vehicle crash, it will be impossible without a postmortem examination to definitively determine whether the death is due to the motor vehicle crash or to a complication of her malignancy, such as a pulmonary tumor embolism.[2]

The authors also do not consider the irremediable confounding effect of age on mortality. For example, if a 75-year-old woman undergoing a mastectomy develops a sudden drop in her blood pressure, goes into cardiac arrest, and dies during the procedure, breast cancer will be listed as her cause of death. However, when a 40-year-old patient undergoing a mastectomy experiences a drop in her blood pressure, she probably will be successfully resuscitated. Do the different outcomes reflect the effect of age on disease-specific mortality or the effect of age on mortality in general?

The point is that age will always be a confounder for mortality, be it all-cause mortality or disease-specific mortality. The difference in disease-specific mortality between age categories is a measure of both the effect of the disease and the effect of age on mortality. Focusing on disease-specific outcomes, such as local and distant relapses,[3] or modeling excess mortality[4] would have helped in answering the question of whether older women with breast cancer are undertreated.[5]

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Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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In Reply: Drs Biau and Porcher comment on the accurateness of the end point of disease-specific mortality in our study of 9766 postmenopausal patients diagnosed with breast cancer included in the TEAM (Tamoxifen Exemestane Adjuvant Multinational) randomized controlled trial. Disease-specific mortality was defined as death due to breast cancer as indicated on the case report form. Patients with distant metastases at the time of death were considered to have died due to breast cancer. Biau and Porcher argue that attributing death to breast cancer when evidence of disease is present may be misleading. We agree that ascertainment of cause of death is not always easy, regardless of age. Unfortunately, postmortem examinations are usually not available and physicians must rely on history and clinical course to assign a cause of death.

Biau and Porcher also comment on the confounding effect of age on mortality; it may be that elderly patients have a higher probability of dying from any situation or disease. They suggest we perform additional analyses focusing on other outcomes or modeling excess mortality. We performed additional analyses in which we used disease recurrence, which may be determined more accurately as an end point (Table 5 in article). Relative survival is calculated by the ratio of observed survival among patients and survival expected based on the general population of corresponding age, sex, and year of diagnosis. We did not analyze relative survival in our study. However, a recent population-based study conducted in the Netherlands among breast

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cancer patients confirmed a decreased relative survival with increasing age.[1] Additionally, in our article, we presented alternative survival analyses to further enhance the strength of our findings. In a competing risk analysis,[2] we analyzed disease-specific mortality, taking into account the age-associated risk of dying from other competing causes that may have affected the risk of disease-specific mortality. The use of various end points and different analyses all confirmed a worse breast cancer outcome with increasing age among postmenopausal women with hormone receptor–positive breast cancer.

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Time Spent Sedentary and Active and Cardiometabolic Risk Factors in Children

To the Editor: Dr Ekelund and colleagues[1] reported that time spent sedentary is unrelated to established cardiometabolic risk factors after adjusting for time spent in moderate- to vigorous-intensity physical activity (MVPA). Although the authors studied 20 871 children and adolescents and measured sedentary time in an objective way, we believe it is premature to conclude that sedentary time is not associated with adverse cardiometabolic health outcomes in children.

First, different types of sedentary behavior may have different metabolic effects and future studies should therefore investigate specific sedentary behaviors and not only the total accumulated time spent sedentary. For instance, sleeping 6 hours or less or more than 8 hours per night,[2] TV viewing,[3] and video game playing[4] have been negatively associated with cardiometabolic health.

Second, though the cut point used to define sedentary behavior (<100 counts/min on an accelerometer) provides a useful estimate of sitting time, standing still time may also be included as sedentary time. This issue is an important one because breaks (interruptions) in sitting time can significantly improve cardiometabolic health.

Third, it is surprising that children with lower levels of sedentary time combined with lower levels of MVPA had the worst cardiometabolic outcomes. This group of children moves around a lot but at a low intensity.

Finally, food intake was not measured in this study and should be included in future research because of the strong link between poor dietary habits and cardiometabolic health and also because screen-time sedentary behavior has been shown to increase caloric intake in the absence of hunger.[5]

It will be important to better characterize the patterns and types of sedentary behavior in future studies with proper measurement of energy intake before drawing conclusions about sedentary time. In the meantime, the take-home message should be to increase children's participation in MVPA and reduce their screen-related sedentary time.

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In Reply: Dr Chaput and colleagues argue that it is premature to conclude that sedentary time is not associated with cardiometabolic health outcomes in children. Our study concluded that "higher levels of time in MVPA appear to be associated with better cardiometabolic risk factors regardless of the amount of time spent sedentary in youth." Our conclusion was strongly supported by the data, but we do not dismiss a potential role of specific sedentary behaviors in relation to cardiometabolic risk. The association between time in MVPA and cardiometabolic risk factors was strong, consistent in both continuous and stratified analyses, and the magnitude of the association did not materially change following adjustment for sedentary time. However, sedentary time was not associated with cardiometabolic risk markers following mutual adjustment for time in MVPA.

We only examined the associations with total sedentary time. Specific sedentary behaviors, such as TV viewing, may have different associations with cardiometabolic health outcomes. We stated that: "decreasing TV time in youth may still be an important public health goal as TV viewing may be associated with other unhealthy behaviors such as snacking and soft drink consumption. Further TV viewing is also associated with exposure to advertisements that often promote unhealthy dietary habits."