In 1987, Jacobson et al. (1) suggested that mothers of twins might be protected against subsequent breast cancer. This prediction was based on laboratory studies of the effects of alpha-fetoprotein (AFP) on the growth of human breast cancer implanted in animals, combined with the well-known approximate doubling of the levels of maternal serum AFP during twin versus singleton pregnancies.

This theory was put to the test quite promptly in the setting of the Cancer and Steroid Hormone Study. The results provided support for the hypothesis that a twin pregnancy is associated with a reduced risk of breast cancer (1); nonetheless, a specific role for AFP could not be inferred with confidence, because twinning is only a surrogate for AFP and twin pregnancies differ from singleton pregnancies in a number of ways other than in AFP levels.

In the correspondence (2, 3) that followed publication of the Jacobson et al. (1) paper in 1989, we argued that speculation about alternative explanations for the finding was no substitute for studies in which actual levels of AFP during pregnancy are compared for cases and controls. The paper by Richardson et al. (4) in this issue of the Journal seems to be the first to address directly a possible protective effect for AFP; it is a welcome addition to the epidemiologic literature on pregnancy and breast cancer.

The results of the Richardson et al. study (4) support the notion that AFP may underlie the inverse association between twin pregnancies and breast cancer. However, as do many pioneering studies, this study raises a number of new questions. The remainder of this commentary concentrates on two, namely, 1) whether AFP is the causally relevant variable and 2) what we ought to make of the finding regarding an interaction between AFP and age at first full-term pregnancy.

We can be fairly confident that the pattern of results is not an artifact of the confounding effects of race, prior abortions, prior miscarriages, alcohol consumption, prepregnancy weight, height, and years of education; all of these variables were considered in the analysis. However, only one of the myriad of biologic changes that occur during pregnancy was measured directly in the study. Consequently, future investigations need to be concerned with the possible confounding effects of such additional biologic variables.

Some data pertinent to this issue of confounding are provided by studies of multiple markers used in prenatal screening for congenital anomalies. Although these studies do not provide a link to breast cancer, they do enable evaluation of one necessary element of possible confounding of the relation between AFP and breast cancer, that is, correlation between the potential confounder and AFP during pregnancy. For example, studies of prenatal screening indicate that AFP during pregnancy is essentially independent of human chorionic gonadotropin ($r = 0.03$) and that its correlation with unconjugated estriol is of only modest magnitude ($r = 0.23$) (5, 6). Results such as these help to bolster a causal interpretation of the findings of Richardson et al. (4) regarding AFP and breast cancer. Examination of other biologic variables that may account for the observed association would clearly be helpful.

What is particularly striking about the results of the Richardson et al. (4) study is the magnitude of the association with AFP. Among women who had their first child before age 21 years, the risk of breast cancer was reduced by at least 35 percent, with a point estimate of 57 percent. This magnitude is striking since it is based on a single specimen obtained within what is just one of the two or more pregnancies experienced by the great majority of the study subjects. A single measurement of a dynamic process is unlikely to reflect well the total exposure across even a single pregnancy. Additionally, since correlation between levels of AFP during different pregnancies is not high (e.g., $r = 0.31$ in one study (7)), a single measure is unlikely to capture adequately a woman's total exposure to AFP during her reproductive life or even dur-
cancers were diagnosed. Previous work (9, 10) has direct information on the ages of the cases when their diagnosis. They provide no evidence for the increased risk associated with an elevated AFP level in pregnancies occurring at older ages. Richardson et al. (79 percent of cases and 81 percent of controls), examined a possible interaction between AFP and age at first full-term pregnancy. Specifically, the case-control differences in AFP were —61.6 ng/ml for the youngest category versus 25.8 ng/ml for the oldest category of age at first full-term pregnancy. Therefore, it is difficult to postulate why the association between risk and AFP level during a particular pregnancy would vary according to the age at which an earlier pregnancy occurred. The authors do present data separately for the limited number of first pregnancies that were studied, but the comparison of the associations with AFP in first pregnancies versus subsequent pregnancies is not statistically reliable. Thus, I am less convinced than the authors are that their results specifically support AFP as an explanation for the inverse association between breast cancer and an early full-term pregnancy.

Although Richardson et al. (4) indicate that they examined possible interactions between AFP and all of the other variables, the unadjusted results seem to suggest that AFP interacts at least as strongly with age at index pregnancy as it does with age at first full-term pregnancy. Specifically, the case-control differences in AFP were —61.6 ng/ml for the youngest category versus 25.8 ng/ml for the oldest category of age at index pregnancy. The corresponding differences for the youngest and oldest categories of age at first full-term pregnancy were —29.6 and 30.5, respectively. It would be important in future studies to evaluate these two interactions simultaneously and to explore further the possible increased risk associated with an elevated AFP level in pregnancies occurring at older ages.

Finally, it is not clear whether Richardson et al. (4) examined a possible interaction between AFP and age at development of breast cancer. They provide no direct information on the ages of the cases when their cancers were diagnosed. Previous work (9, 10) has suggested that some factors have different associations with breast cancer diagnosed at different ages. Large data sets will be needed to disentangle the three possible interactions involving AFP and age at first birth, age at the birth for which AFP level is measured, and age at diagnosis.

Despite these limitations and interpretational complexities, the study by Richardson et al. (4) deserves close attention. Efforts to replicate and elaborate on the findings seem warranted. On a more general level, attempts to relate biologic measures, notably estrogens and other hormones measured in women who are not pregnant, to the risk of breast cancer have not provided particularly impressive results (11). The approach here, namely, studying biologic measures during pregnancy, may prove to be more productive.

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