Risk for familial breast cancer increases with age

Peto and Mack published a provocative paper suggesting that the age of onset for breast cancer is genetically determined[1]. If correct, such a model would have broad implications[2]. Their data seemed to show that for a woman with a first-degree relative who has had breast cancer, the risk that she will herself develop breast cancer increases with age up to the age at which the relative's cancer was diagnosed, and remains constant thereafter. Easton discussed the possible mechanisms underlying such unusual findings and concluded that "[e]pidemiological observations alone will probably be too weak to determine whether an age-related constant risk model of the type suggested by Peto and Mack, a more conventional susceptibility model, or some mixture of the two is correct"[2]. We resort to the largest resource on familial cancer, the Swedish Family-Cancer Database, and show epidemiologically that the constant risk model is wrong, probably owing to data truncation. The Database, containing information from registered families on medically verified cancers, has been used in over 100 family studies on all main types of cancer, including breast cancer[3–6] (more information about the Database is provided in Web Note A).

We plotted the incidence of breast cancer in 2,148 daughters diagnosed between 1961 and 1998 according to the age at which their mothers were diagnosed with breast cancer (Fig. 1). (In contrast, the study by Peto and Mack was based on only 419 cases[1].) For mothers diagnosed at 30–39 years, daughters' risks were high, about 200 in 100,000 between ages 30–39. These rates differed markedly from others, as indicated by the 95% confidence interval bars. For mothers diagnosed at more advanced ages, we found no large differences in the incidences of breast cancer in daughters, and, except in two cases, incidence rates in daughters continued to increase with age, contrary to the prediction of the Peto and Mack model. The incidence of breast cancer in daughters decreased with age in two cases: for daughters age 55–59 years whose mothers were diagnosed at age 30–39 years, and for daughters age 60–66 years whose mothers were diagnosed at age 50–59 years. These are artifacts of truncation. The study ended in 1998, and the oldest daughters at that time would have been 51 years old if they were born to 25-year-old mothers who were diagnosed at age 39 years in the first year of the study (1961). This is why only one individual was diagnosed with breast cancer in the final period (Fig. 1).

Our data on breast cancer incidence in daughters and mothers do not support the hypothesis of constant incidence. For the youngest mothers diagnosed, at age 30–39 years, daughters' incidences were very high at an early age, but the incidences still increased with age. This population could include carriers of mutations in *BRCA1* and *BRCA2*. For mothers diagnosed at all other ages, the increase in breast cancer incidence in daughters was close to linear and superimposable at all ages. Our data also show that population or data truncation may lead to the seeming constancy or even decrease in breast cancer incidence with age, which may explain the results of Peto and Mack.

Note: Supplementary information is available on the Nature Genetics website.

Competing interests statement

The authors declare that they have no competing financial interests.

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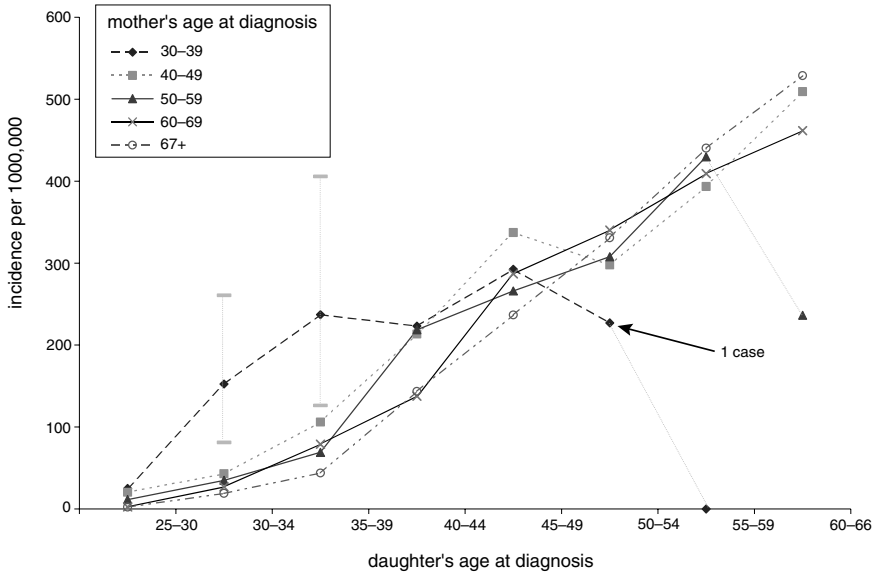

Fig. 1 Breast cancer incidence in 2,148 daughters of different ages plotted according to their mothers' ages at diagnosis. For daughters age 30–34 and 35–39 years whose mothers were diagnosed at age 30–39 years (13 cases each), the daughters' risk of breast cancer is related to mothers' age at diagnosis. Vertical bars, 95% confidence intervals. The apparent decrease in incidence at higher ages are shown with lighter lines because they are truncation artifacts. Incidence was calculated by dividing the number of diagnosed breast cancers in each five-year age band by person-years at risk.