A cluster of cancers diagnosed in families raises concern about family risk and the need for counseling. Because family members share similar genes or may have experienced common environmental challenges, it would not be surprising to find clusters of cancers in families. The investigation by Bermejo and Hemminki (1) raises some provocative questions regarding a family member being diagnosed with cancer and other family members later being diagnosed with the same cancer. Bermejo and Hemminki used the Swedish Family Cancer Database to explore the pattern of familial risk after diagnosis of the first cancer in a family. The main theme in the analysis was to determine if the risk of familial risk after diagnosis of the first cancer in a family would motivate other family members to seek examinations for cancer. If true, this would most likely lead to increased diagnoses of other family members in the period shortly after the diagnosis of the first cancer and would artificially inflate the cancer risk. The authors refer to this bias as “surveillance bias.” The cancers that are investigated are breast, prostate, colorectal, cervix, lung, and invasive melanoma. The authors present data in which a parent is a proband and similar data in which a sibling is a proband.

The methodology of the study was that the first person diagnosed with cancer in a family was designated as the proband. If the proband is a parent, the offspring of the proband were followed from the proband’s year of diagnosis until a diagnosis of cancer (invasive or in situ), death, or until some other noncancer endpoint was reached in the offspring. If the proband is a sibling, other siblings were followed for cancer diagnosis. Relative risks were calculated to compare the incidence among relatives of probands with the incidence of cancer in the general population. One would expect that if surveillance bias is present, a cancer diagnosis in a family would be highest in the year in which the proband’s cancer was diagnosed and would taper off with more follow-up time. If the mean preclinical sojourn time for asymptomatic cancers is short, however, this method of analysis would be unlikely to result in increased relative risk, whereas if the mean preclinical sojourn time is relatively long, the method could show the existence of surveillance bias.

The methodology requires further discussion. It is necessary to distinguish between parent and sibling probands, as the authors have done. If a comparison of parent–offspring pairs is made in which the parent is the proband, detecting cancer in an offspring depends on the number of offspring in the family. The more offspring, the higher the likelihood that there will be a family member who will have another similar cancer. Therefore, the cancer risk depends on family size. Thus, the observed risk of the offspring will not be appropriate as an estimate of individual cancer risk unless there is an adjustment for family size. However, because the numerator and denominator in the relative risk ratio were calculated from the same database, it would be expected that the distribution of family size would similarly affect both the numerator and denominator. The mixture of different family sizes leads to increased variability in the numerator of the relative risk.

In the case in which the proband is a sibling, the proband’s family size tends to be larger than that of the general population (2); i.e., the larger the family size, the higher the probability of a cancer diagnosis in the family. This phenomenon is often referred to as length-biased sampling. As a result, there will be (on average) more siblings in the proband’s family. Thus, the relative risk will be inflated. The implication is that the individual’s risk of cancer calculated in this way is incorrect. This bias will equally affect each year of follow-up.

The authors present confidence intervals for relative risk for each follow-up period (six in all) at six cancer sites. However, they present no statistical tests that are directly relevant to the existence of surveillance bias. If surveillance bias is present, it would result in a larger relative risk during the year of the proband’s diagnosis compared with that in any subsequent year.

Consider the data in Table 1 (1), in which the proband is a parent. Restricting attention to invasive cancers only, there are six periods in which the relative risk is calculated. If surveillance bias is present, one would expect the highest relative risk in year 0 (the same year of the proband’s diagnosis). However, if surveillance bias was not present, the probability of the relative risk being highest in year 0 for a cancer site would be one in six if the magnitude of the relative risk is random. For four of the six cancer sites, the relative risk was the highest in year 0. Thus, to calculate a test of statistical significance under the hypothesis of the nonexistence of surveillance bias, one must calculate the probability of at least four of the sites having the highest relative risk in year 0. According to my calculations, this probability is .0087. The formula for this calculation is that the probability of $k$ of $N$ cancer sites having the largest relative risk among $n$ follow-up periods is as follows: $P(k) = \frac{N!}{k!(N-k)!}(n-1)^{N-k}/n^N$ (this expression is the binomial distribution for the probability of $k$ successes in $N$ independent trials where the probability of success is $1/n$).

Therefore, the probability of at least $k = 4$ out of $n = 6$ relative risks being the highest among $N = 6$ cancer sites is $P(4) + P(5) + P(6) = .0087$. Among the in situ outcomes, three of four sites had the highest relative risk in year 0 among the parent probands. The probability, due to chance, of having three or more outcomes in which the relative risk is highest in year 0 is .015. Thus, it appears that evidence for surveillance bias exists for the parent–offspring pairs for both invasive and in situ cancers. The sibling–sibling pairs are not suitable for investigating the existence of surveillance bias because the family sizes of the probands tend to be larger than those of the general population.

Correspondence to: Marvin Zelen, PhD, Harvard School of Public Health, 655 Huntington Ave., Boston, MA 02115 (e-mail: zelen@hsph.harvard.edu).

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It is apparent that in counseling, care must be taken with respect to using cancer risks derived from observations on families. Such data have inherent biases, not only because of possible surveillance bias but also because of the biases present due to fluctuations in family size. Controlling for family size may lead to more precise analyses. Comparing the risks using sibling probands may not be appropriate due to the length-biased sampling, which induces larger-than-average family sizes.

REFERENCES
