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Countercurrents: The bias of choice

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Of the several kinds of bias that might corrupt an epidemiology study, selection bias is the most insidious. Readers and researchers should be aware of an unusual type of selection bias that can arise when study subjects pass through various disease stages before death from cancer.

The canonical transition is from no cancer to cancer, but other meaningful life events can occur: for example, a woman learning that she carries a mutation in a cancer susceptibility gene or being told that distant metastases have been found. Each of those transitions can affect the woman's quality of life and might influence her life choices. It is important to recognize the possible effects of those state transitions in designing research studies; often, the exposure under study might be subject to patient preference, and if so, the decision to have or not have the intervention might vary systematically according to the individual's health status and state of mind.

Here are some examples of exposures that are subject to choice:

- To have an operation, such a preventive oophorectomy
- To take a medication such as aspirin or tamoxifen
- To initiate a pregnancy
- To respond to an invitation to screening—for example, mammography

In those cases, the exposure and the outcome might not be independent, and the resulting bias might generate a spurious association where there is none. I refer to this as the "bias of choice." There are several examples where such bias might have led to erroneous conclusions with important public health impacts; the three that follow are lessons from personal experience.

In 2005, we reported the results of a case–control study of oophorectomy and breast cancer among women with *BRCA1* or *BRCA2* mutations[1]. We compared women having breast cancer (cases) with women not having breast cancer (controls), matching on age and year of birth. Only 3.5% of cases and 6.2% of controls had reported an oophorectomy in the past. The hazard ratio for oophorectomy and breast cancer was 0.44 in *BRCA1* carriers [95% confidence interval (CI): 0.29 to 0.66]. The error was that we did not consider the timing of disclosure of the genetic test result.

For the cases, the diagnosis of breast cancer usually precipitated the genetic test, and the typical patient with breast cancer was unaware of her mutation status until after her diagnosis. In contrast, the control patient was aware of her genetic mutation status when she was in a non-cancer state (by definition). The knowledge of a mutation in the family led her to seek genetic testing and, for some women, having the mutation might have caused a choice to seek preventive oophorectomy. In summary, most case patients did not undergo genetic testing until after the cancer diagnosis, but all of the control patients knew of their positive genetic status when they were cancer-free. Only 3.5% of the case patients underwent oophorectomy before their breast cancer.

To avoid the bias of choice, it is ideal to match the cases and controls on the date of genetic test disclosure; however, in our particular study, the date of genetic testing was not available. The preferred option is to conduct a prospective study restricted to women who know they are carriers at study entry. In 2016 and 2018, two prospective cancer studies, one from our group[2] and one from the Netherlands[3], took that approach and failed to replicate a preventive relationship between oophorectomy and breast cancer risk in *BRCA1* carriers. In our prospective study, 42% of the women in the cohort had an oophorectomy; in *BRCA1* carriers, the age-adjusted hazard ratio for breast cancer associated with oophorectomy was 0.96 (95% CI: 0.73 to 1.26; $p = 0.76$). This example of bias of choice occurs because the state of the woman (known carrier status vs. unknown carrier status) differs between the controls and cases and is strongly associated with the exposure under study (oophorectomy).

Prospective studies are not immune to the bias of choice. In the second example, we reported the result of a prospective record-linkage study of pregnancy and death from breast cancer in Ontario[4]. We found that women who had a baby after a diagnosis of breast cancer were much less likely to succumb to their cancer (odds ratio: 0.22; 95% CI: 0.10 to 0.49). We were aware that the cancer stage and other aspects of a woman's health might influence her decision to have a baby and her survival, and so we adjusted for all prognostic factors, including age, stage, estrogen receptor status, and treatment. The association was robust to those adjustments, and so we concluded that pregnancy might be therapeutic and was deserving of further study—however, we overlooked the bias of choice.

After publication, we realized that few women will choose to have a baby once they have been diagnosed with metastatic disease. On average, 2.0 years pass between distant recurrence and death[5]. In the study, we lacked access to the date of distant recurrence, but I suspect that there would have been a deficit of pregnancies in the 2-year interval between distant recurrence and death. In retrospect, it would have been safer to consider distant recurrence rather than death as the primary endpoint, but that date was not available to us. Women with no evidence of disease might be on even ground when choosing to have or not

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to have a baby. Of course, there are possible confounders as well (patient age, comorbidity, stage, grade, tamoxifen use, chemotherapy, and ovarian suppression), but they are pretty obvious and are rarely overlooked. Bias of choice is much more subtle.

Perhaps the most egregious error comes from ignoring bias of choice in observational studies of cancer screening. An observational approach to evaluating mammography screening in Canada was reported in 2014[6]. The authors compared mortality rates in women who did and who did not attend a screening mammography clinic as a result of an invitation by the province. They reported a 40% reduction across the board in association with participation in Canadian mammography screening programs. We conducted a cohort-based analysis of women enrolled in the Canadian National Breast Screening study (a randomized trial) and found that screening initiated before the age of 50 years was not associated with a decline in cancer mortality (hazard ratio: 1.10; 95% CI: 0.86 to 1.40)[7]. Both studies were conducted at roughly the same time period, in the same Canadian centres, using similar screening technology. Why the difference? In the randomized trial, we excluded women diagnosed with breast cancer before a first mammogram; Coldman *et al.*[6] did not. The pan-Canadian trial calculated expected mortality for participants using data from nonparticipants, thereby introducing many methodologic challenges[8]. A woman diagnosed with breast cancer before receiving an invitation to screening would not attend screening. Despite the challenges faced by the readers, the Coldman paper is cited today by advocates to extol the benefit of breast cancer screening in Canada; the randomized trial is ignored[9].

Bias of choice is rarely detected and is often overlooked by co-authors, reviewers, and editors. It is important to prove to the reader that bias of choice was avoided: authors merely have to provide the dates of diagnosis and of death for the women who died of cancer in the unscreened arm. If prevalent cases have been excluded from the controls, then no cases would be seen to be diagnosed in the controls before the study entry date, a steady increase in the incidence rate would be observed from study inception, and a climbing mortality rate would be evident in the control group. (Only rarely does a woman die from breast cancer in the year she is diagnosed.)

In summary, bias of choice is a type of selection bias that arises when the exposure under consideration is made as a conscious choice by the study subject—a choice that might be associated with the subject's health status at the time the decision is made. The relevant date is not the date of entry into the study, but the date of the intervention. For example, 2 women might be judged to be at equal at risk of breast cancer on the date of study entry (through matching or propensity analysis), but the health status of one or the other might change during the follow-up period—that is, she could find out that she has a *BRCA1* mutation or a distant recurrence. In the former case, she might opt for preventive surgery; in the latter case, she might forego having a baby.

Bias of choice should be suspected when the results of an observational study (case–control or prospective) are much more profound than those of a randomized trial. If the result seems too good to be true, then it probably is. Conscientious investigators should ask themselves if the exposure under study could be a choice made by the study subject, and if so, whether exposed and unexposed women might differ with respect to genetic status, cancer diagnosis, or evidence of recurrent disease. Ensuring that study subjects are matched for risk at baseline does not guarantee a lack of bias in observational studies. That is another reason that randomization is ideal even though it is not always an obtainable goal.

CONFLICT OF INTEREST DISCLOSURES

I have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and I declare that I have none.

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