Sir,

Errors arising from skewness in the data and right censoring in respect of cancers discovered after the time period observed in previous studies are compounded in the paper by Cibula et al. (2010) which reviews this literature.

Because hormonal contraceptives are taken at a much younger age than hormone replacement therapy (HRT), there is much longer to wait before post-menopausal cancers are reported among the women. Published studies exhibit skewness of the data towards younger women and the associated right censoring whereby the researchers neglect to consider the post-menopausal cancers that are more reflective of the hormonal- and pregnancy-related risk factors.

It is understandable if these researchers, who consider only time intervals and do not follow cohorts, are missing the cancer-inducing effects of hormonal contraceptives while recognizing the higher risks of breast cancer from HRT. The women taking HRT do so when they are entering the post-menopausal age band (50+) within which their breast cancers are likely to be discovered. So, the risks of breast cancer from the use of HRT are more easily discovered within a few years by following women after they take the treatment. But the women taking hormonal contraceptives are much younger and the cancers corresponding to these drugs they are taking are not likely to be discovered until 30+ years later (if the average age of women taking the pill is mid-20s and the average age of women on diagnosis with breast cancer is 62 or 63). Premenopausal breast cancers are more often attributable to genetic factors and are less influenced by reproductive and hormonal risk factors than post-menopausal. The studies on which this paper (Cibula et al., 2010) is based do not follow up the women for a sufficiently long time after the usage of hormonal contraceptives and suffer from this kind of right censoring.

Such errors can explain the paradox that HRT is now considered more conducive to breast cancer than hormonal contraceptives when hormonal contraceptives are chemically similar to HRT and often taken in higher doses and for a more extended period of time than HRT.

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This letter from Dr. Carroll was forwarded to the authors of the Cibula et al. review, who declined to respond. Therefore, the editor-in-chief has provided the following note.

Editor’s reply: Hormonal contraception and risk of cancer

The review by Cibula et al. noted that none of the large prospective oral contraceptive (OC) cohort studies with prolonged follow-up involved an increased overall risk of cancer incidence or mortality among ever-users of OC (Cibula et al., 2010). The authors analyzed studies involving breast, ovarian, endometrial and cervical cancers, as well as non-reproductive cancers. Patrick Carroll’s letter refers to the fact that hormone replacement therapy (HRT) has a stronger association with breast cancer than OCs, even though the hormone dosage in contraceptives is higher than in HRT. Also, OCs are taken for an average of 4–5 years, which is longer than the average exposure to HRT (Collaborative Group on Hormonal Factors in Breast Cancer, 1996). Carroll correctly suggests that right censoring might explain this paradox. If a follow-up study terminates when the subject women are aged 50, then any cancer events that occur after the age of 50 are not included in the study; i.e. they are censored. If one visualizes a follow-up chart, the events at the right-hand side are missing or right-censored.

Right censoring may have a bearing on the OC risk, but the effect of right censoring on OC follow-up studies may not be large. Let’s take breast cancer as an example, as did Carroll.

First, the effects of hormones on breast cancer are temporary because hormones promote existing pre-clinical tumours and do not appear to initiate new cancers. Thus, the increased breast cancer risk associated with OC use disappears within 10 years of discontinuing OC use (Collaborative Group on Hormonal Factors in Breast Cancer, 1996). Also, the increased risk of breast cancer associated with HRT use disappears within 2–5 years of discontinuation (Collaborative Group on Hormonal Factors in Breast Cancer, 1997; Chlebowskii et al., 2009).

Second, although many OC studies do not involve prolonged follow-up and would be susceptible to right censoring, those that do follow patients into the menopause find no increase in OC risk of breast cancer. In a case–control study among women aged 35–64 years involving 4575 breast cancer cases and 4682 controls, the relative risk of breast cancer was 1.0 (95% confidence interval (CI) 0.8, 1.3) for current users and 0.9 (95 CI 0.8, 1.0) for previous users (Marchbanks et al., 2002).

It appears then that OC hormone effects on breast epithelium are short term and therefore are unlikely to extend into the menopausal years. If the promotion theory is not correct, however, the Marchbanks et al. study was reassuring because the effects were not so large as to be measurable.
Patrick Carroll’s note about right censoring is a cautionary reminder about the potential weaknesses of the relevant epidemiological studies. It is always prudent to re-consider the concepts that guide our understanding of health and science and, when necessary, to revise them.

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