Premature Ovarian Failure in Cancer Survivors: New Insights, Looming Concerns

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As cure rates for childhood cancers continue to improve, management of long-term consequences of treatment move to the forefront for survivors. Women who undergo cancer treatment before age 21 are at risk for both acute ovarian failure (loss of ovarian function at the time of treatment) and premature ovarian failure (menopause before age 40 in someone with a return of regular menstrual cycles after treatment). Previously, Sklar et al. (1) presented their findings on the incidence and risk factors for acute ovarian failure in the Childhood Cancer Survivor Study Cohort. Here (2), they present their findings on premature ovarian failure. This study improves upon prior ones because it includes detailed information on type and dose of chemotherapy, radiation, and surgery, as well as differentiation between surgical and nonsurgical menopause. Increasing exposure to abdominopelvic radiation and alkylating agents was associated with a higher incidence of nonsurgical premature menopause. Although data were not presented on type of gynecologic surgery (hysterectomy alone versus hysterectomy and bilateral oophorectomy) and age at menopause to better understand the true onset of biologic menopause in these women, this study provides important data on the frequency of premature ovarian failure among childhood cancer survivors. Although all the children were treated between 1970 and 1986, this study may still underestimate the true incidence of premature menopause because the median age at time of analysis was 29 years and only 10% of the cohort had reached 40 years.

This study highlights the important issue of premature menopause, which has a public health impact beyond that attributable to survivors of childhood cancer. Of the estimated 213,000 cases of breast cancer diagnosed annually in the United States, approximately 8%, or 17,000, are in women under the age of 40 (3), some of whom receive chemotherapy and/or hormonal therapy that could induce premature menopause. Treatment for other forms of cancer among women in their twenties or thirties also contributes to this burden. Also, many women undergo hysterectomies and bilateral oophorectomies for non–cancer-related reasons. According to the Centers for Disease Control and Prevention, approximately 598,000 hysterectomies were performed from 1994 to 1999 in women under age 40; one-third of them also had a concurrent bilateral oophorectomy (4). Autoimmune disorders and treatment for conditions, such as endometriosis, may also be associated with an increased risk of premature menopause. Finally, although idiopathic ovarian failure occurs in only approximately 1% of women in the United States (5), that figure still translates into an estimated 120,000 menopausal women younger than age 40 (6).

The health consequences of premature menopause are still poorly understood. Although premature menopause has been widely associated with lower bone mineral density and increased osteoporosis risk, its impact on fracture risk is not well quantified (7–9). Fracture risk is related not only to bone mineral density but also to bone architecture and other factors including age, body mass index, frailty, family history, and likelihood of falls (10).

Although several small studies have reported relative risks (RRs) of approximately 1.5 for fracture among women who undergo menopause before age 50 compared with after age 50, the issue of when to begin screening and treatment for osteoporosis remains because most of these fractures occur later in life (11,12).

The effect of premature menopause on cardiovascular disease (CVD) risk is also controversial. Several observational prospective cohort studies have noted an increased risk of CVD among women who undergo bilateral oophorectomy before age 50 with relative risks ranging from 1.6 to 2.2 (13–16). Women who undergo early menopause have also been found to have more subclinical atherosclerosis, as evaluated by carotid artery intima-media thickness (17). However, women who undergo hysterectomies differ from those who do not. For example, in the Women’s Health Initiative (WHI) Observational Study, compared with women who did not have a hysterectomy, women who had a hysterectomy (regardless of oophorectomy status) were more likely to have a more adverse CVD risk profile, with a higher proportion having hypertension, diabetes, hypercholesterolemia, obesity, and inactivity, as well as higher unadjusted incidence rates of total and CVD mortality. However, after adjustment for traditional CVD risk factors, there were no statistically significant differences in overall mortality or CVD mortality among the groups. The authors concluded that the higher CVD incidence among hysterectomized women was due to their higher CVD risk profile—not the operation itself (18).

Balanced against the potential effects of hysterectomy on CVD risk is the issue of whether the age at initiation of postmenopausal hormone therapy (PHT) affects its risk–benefit ratio. Although the randomized WHI showed an increased risk of CVD events in the PHT arm compared with placebo, the average age at initiation of PHT was 63 years (19). Therefore, the question still remains whether the effect of starting PHT closer to the time of natural menopause would differ from starting PHT many years after menopause. In the estrogen-alone arm of the WHI, there was a suggestion of a decreased risk of coronary events in women aged 50–59 at study entry (RR = 0.66, 95% confidence...
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Potential benefits of premature menopause include a 30–50%
lower risk of breast cancer among women who undergo meno
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women who undergo bilateral oophorectomy (24–26).
So, where does this leave women who have experienced premature menopause and those weighing the risks and benefits of treatment options that may lead to premature menopause? The current study helps clinicians to identify women at increased risk of this outcome, so that prevention, screening, and treatment strategies can be implemented at an earlier stage. We do know that premature menopause may lead to decreased bone density. Therefore, prevention measures to optimize bone health, such as weight-bearing exercise, adequate dietary calcium and vitamin D, and avoidance of smoking, should be emphasized early in life. Screening for osteoporosis should be started sooner in these women, perhaps before age 50. Decisions about pharmacologic treatment, however, will be complex and will require consideration of overall fracture risk. As for CVD, aggressive attempts at modulating risk factors, such as blood pressure, body mass index, and cholesterol levels, and encouraging cardioprotective lifestyle behaviors, should be implemented early in life. More research needs to focus on understanding the cardiac effects of estrogen deprivation. To provide the best care to the individual, we need to understand both the effects and the efficacy of our interventions.

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