Choices for young women at intermediate risk of breast cancer

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Women with an inherited mutation in BRCA1 or BRCA2 have a lifetime risk of breast cancer that approaches 80%1-3. At that level of risk, many women will entertain prevention options that are drastic (for example, preventive mastectomy) or expensive (for example, a lifetime of annual screening by magnetic resonance imaging). But what of women at intermediate levels of risk ... 10%-25%, say?

The latter group of women includes those with a strong family history of breast cancer but no BRCA mutation4, those with a mutation in CHEK25,6, those in the highest category of mammographic density7, and those with a past history of lobular carcinoma in situ or atypical hyperplasia8,9. At this level of risk, surgical prevention is chosen by few. Dietary modification and exercise have not been shown to be very helpful in premenopausal women. In 2012 (as in 2001), options come down to tamoxifen and mammography. Currently, tamoxifen is the sole drug approved for chemoprevention in premenopausal women (raloxifene and aromatase inhibitors are to be avoided in ovulating women), and mammography remains the cornerstone of screening.

In the United Kingdom, the Family History Study was undertaken to estimate how much life expectancy might reasonably be gained by an offer of annual mammography to women at moderate risk10. Annual mammography was offered for 4 years to 67,10 women with a family history of breast cancer who were younger than 50 years of age, but who were negative for both BRCA mutations. Their mortality experience was compared with that of two historical cohorts11,12. During the study, 96 invasive cancers were found, and the sensitivity of mammographic screening was 72% for invasive cancers. Compared with women in the control cohorts who developed invasive breast cancer, women who received an annual mammogram had smaller tumors (<2 cm: 70% vs. 55%, p = 0.0094) that were more likely to be node-negative (68% vs. 53%, p = 0.0083) and grade I or II (54% vs. 51%, p = 0.0072). Nevertheless, 32% of the cancers in the mammography cohort were node-positive or larger than 2 cm in size. Duffy and colleagues estimated that, at 10 years, the breast-cancer-specific mortality was lower by 20% in the experimental cohort than in the control subjects (relative risk: 0.80; 95% confidence interval: 0.66 to 0.96; p = 0.02). Even if the difference in the mortality rate was in fact attributable to screening (and not to treatment differences), a 20% lowering of mortality is modest, and other options must be entertained.

In favour of the program, almost all women offered mammography were compliant with the recommendation. How does their compliance compare with compliance to tamoxifen? Two large trials—National Surgical Adjuvant Breast and Bowel Project P-1 and IBIS-I (International Breast Cancer Intervention Study)—demonstrated a reduction of up to 43% in the incidence of breast cancer in high-risk women (most being women who did not carry a BRCA mutation)13,14. The protective effect of tamoxifen appeared to extend beyond the 5-year period of active treatment.

Despite the established benefit of tamoxifen in the prevention of breast cancer, only a small proportion of eligible women take that option15. In our cohort of established BRCA carriers, fewer than 5% under the age of 50 opted for tamoxifen chemoprevention16. Fear of side effects seems to be the major deterrent17,18. However, data from tamoxifen prevention trials suggest that serious adverse events (endometrial cancer and venous thromboembolism) are rare in women younger than 5019. The risks fall off rapidly after the active phase of treatment. Side effects in women younger than 50 are generally benign—notably, hot flashes, vaginal discharge, and irregular vaginal bleeding20—and don’t significantly affect quality of life21,22.

Perhaps a combination of mammography and tamoxifen is best. Tamoxifen causes a significant reduction in breast tissue density in young women, thereby increasing the sensitivity of mammography23,24. In a subset of patients in the Breast Cancer Prevention Trial, chemoprevention with tamoxifen...
(compared with placebo) resulted in a 44.4% reduction in mammographic density (15.2%, \( p = 0.01 \)) \(^\text{25}\). Also, a reduction in breast density appears to be a good surrogate marker for a reduction in cancer risk: the nsabp-1 study \(^\text{26}\) observed a reduction of 63% in the risk of breast cancer incidence in women who experienced a 10% or greater decline in mammographic density with tamoxifen.

Given the foregoing observations, the combination of tamoxifen with mammographic surveillance seems to us to be a much better option than relying on mammography alone. If a 40% reduction in cancer incidence with tamoxifen is coupled with a 20% reduction in mortality from screening, perhaps a halving of the mortality rate is within reach.

**CONFLICT OF INTEREST DISCLOSURES**

The authors have no financial conflicts of interest to declare.

**REFERENCES**


10. FH01 Collaborative Teams. Mammographic surveillance in women younger than 50 years who have a family history of breast cancer: tumour characteristics and projected effect on mortality in the prospective, single-arm, FH01 study. *Lancet Oncol* 2010;11:1127–34.


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