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Breast Imaging and Breast Cancer Prevention

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Abstract Earlier detection of breast cancer through periodic screening is the only currently available intervention likely to reduce breast cancer-related mortality in the near term; prevention would be preferable. The alteration of proliferative changes and the assessment of intermediate endpoints may establish some interventions as more likely than others to interrupt the progression to lethal cancer. However, since not all breast cancers are fatal, the endpoint that will ultimately be accepted as proof of prevention success will be a reduction in breast cancer mortality.

Methods of detection and monitoring must be carefully tailored so that the influences of the detection techniques do not alter the prevention results. © 1993 Wiley-Liss, Inc.

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The earlier detection of breast cancer by periodic screening using mammography has been shown to reduce mortality for women ages 40–75 by 25–30% [1,2]. Although this could result in the saving of 10,000–15,000 lives each year, it is certainly not the solution to the more than 46,000 lives that are lost each year from breast cancer. The problem of breast cancer will only be solved by the discovery of a universal cure, or by devising methods of prevention. Since the development of breast cancer is likely multifactoral, and since the majority of cases are sporadic and based on statistical probabilities, it is unlikely that there will be a single method of prevention. The time over which the prevention technique must be applied is also unclear. As a woman ages, the probability increases that a cell will acquire the requisite DNA damage without repair and without cell death, permitting its unrestrained growth. Given that there are multiple ways for DNA to be altered, including the process of cell division itself, it will be difficult to develop a perfect prevention. It will be especially difficult to develop a prevention that does not itself cause harm. Although far from the solution, for the foreseeable future, mammographic screening is the method that most likely will result in a reduction in breast cancer mortality.

BREAST IMAGING AND PREVENTION TRIAL ENDPOINTS

Breast imaging technologies will be valuable in the development of prevention strategies in several ways. Mammography should be used to monitor any changes that may occur in the breast as treatments are tested. The accurate measure of a prevention's success will depend on how the diagnosis of cancer is determined and what is the accepted endpoint. As with the screening trials, many problems can be avoided if mortality is the measured endpoint. If the endpoint is mortality, then a uniform exposure to screening is critical since women undergoing aggressive screening will likely have fewer deaths than those who are not screened, or not screened as aggressively [3]. Women in a rigor-

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ous screening program will likely have reduced mortality. If screening is not evenly applied the results may be skewed.

If detection is the endpoint, significant problems can arise. Since mammography can, on average, detect cancers two years before they become clinically evident in women ages 40–49, and as many as four years earlier for women ages 50 and over [4,5], detection, as an endpoint, can be influenced by lead time and detection bias. All participants in trials should be monitored in the same fashion at least annually. Both screens and controls should be evaluated using a carefully designed schedule of mammography and clinical breast examination with the same instructions in breast self-examination given to both groups prior to randomization. Specific rules for intervention should be determined so that the results are not biased by an overly aggressive or less aggressive approach to detection and diagnosis.

The diagnosis of "cancer" should be carefully defined. An aggressive screening program is likely to result in detecting more cancers earlier and could skew results when compared to women who are evaluated less aggressively. Since the natural history of breast cancer detectable by mammography may be as long as 15 or more years [if ductal carcinoma *in situ* (DCIS) is counted as cancer], specific endpoints for the "proof" of prevention must be determined. Participation in screening outside of the trials must be carefully monitored since this can significantly bias the outcome.

MAMMOGRAPHIC MONITORING OF PREVENTION TRIAL PARTICIPANTS

Specific rules for evaluation should be adopted so that groups are comparable. The significance of DCIS must be agreed upon since its detection is enhanced by screening. Thresholds for intervention should also be defined. A program that decides that the positive predictive value for biopsy must be maintained at a high percentage will, of necessity, have to miss cancers [6,7]. In particular, the handling of solitary circumscribed lesions should be determined so that the approach is uniform. Similarly, the thresholds for intervening when calcifications are detected should be defined. An aggressive approach to these may lead to a diagnosis of cancer years before a less aggressive approach.

INTERMEDIATE ENDPOINTS

There is considerable interest in establishing intermediate measures of abnormal proliferation that could be used to test potential interventions that down-regulate the abnormal process. There are no strong markers for proliferation that can be detected by mammography. The only correlation with such changes are the calcifications that can be associated with large-cell, comedo type DCIS. These tumors are prone to central necrosis, and the calcifications that develop are often quite typical, forming fine, linear, branching structures. Using needle biopsy techniques and mammographic guidance, it might be possible to obtain cytologic or histologic material to confirm the diagnosis and provide pretreatment material prior to excision and definitive treatment. Test agents could be employed in an effort to reverse the proliferative process, followed by repeat needle biopsy and definitive excision several days to weeks later. Although there is likely little therapeutic disadvantage from a delay of as much as several weeks for the definitive treatment of DCIS, the participation of patients in a trial in which definitive therapy is purposely delayed may be problematic. In addition, the relationship of DCIS to invasive cancer remains controversial, and the significance of an alteration in the process as demonstrated using intermediate endpoints will also be controversial. Ultimately a reduction in mortality will have to be shown.

CORRELATES TO PREVENTION

Trials should be designed to carefully monitor the basic information concerning the individual's breast tissue. Some previous studies have suggested that women who have greater proportions of fibrous connective tissue in their breasts are at higher risk. Other studies have suggested that "nodularity" of the breast tissue seen mammographically correlates with risk [8]. These parameters should be monitored, if for no other reason than the fact that "dense" tissues can mask the earlier detection of cancers.

The effects of the prevention should be recorded. The breast tissues are fairly stable over

time as seen by mammography. Changes associated with the prevention may be important in assessing overall effect.

DETERMINING HIGH-RISK LESIONS

There are as yet no imaging methods that accurately determine who is at risk for developing breast cancer. The appearance of the breast tissues should be reevaluated using modern mammography and magnetic resonance imaging (MRI) to determine whether there are significant determinants that may predict for future cancer development so prevention can be targeted at high-risk populations. The evaluation of teenage women and women in their early twenties by MRI may provide some future insights as to who develops cancer.

Lobular carcinoma *in situ* (LCIS) is almost exclusively found in women who have radiographically dense breasts. This may merely be an age phenomenon since LCIS is virtually only found in younger women. The reason for this should be explored to determine whether there are sub-groups in whom this high-risk lesion is common.

TECHNIQUE AND MAMMOGRAPHIC QUALITY

The detection of preclinical disease is strongly dependent on the quality of the mammography. Trials should include quality control procedures and technologist and radiologist training to ensure that all participants obtain high quality mammograms [9,10] with skilled interpretation. Double reading increases the yield of cancers, and should be encouraged. Poor quality studies or poor interpretation can result in delayed diagnoses [11].

EFFECTS OF CHEMOPREVENTION ON THE BREAST

Although relatively uncommon, hormone replacement therapy can have a dramatic effect on the mammographic appearance of the breast [12,13]. The overall radiographic density of the breast can be affected, and multiple cysts can appear. Women who are being studied should be monitored for changes. Measures that increase the radiographic density of the breast may reduce the sensitivity of cancer detection and compromise the net benefit.

CONCLUSION

Prevention trials should involve breast imaging in a carefully designed and monitored fashion so that potential biases will not be introduced, and possibly important correlates will not be overlooked. Since detection is the early endpoint, carefully agreed upon rules for intervention must be defined so that women involved in the trials are subject to uniform and high quality diagnosis. Mortality reduction is the ultimate endpoint.

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