Outcomes of Modern Screening Mammography

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The University of California, San Francisco, Mobile Mammography Screening Program is a low-cost, community-based breast cancer screening program that offers mammography to women of diverse ethnic backgrounds (36% nonwhite) in six counties in northern California. Analysis of data collected on approximately 34,000 screening examinations from this program shows that the positive predictive value and sensitivity of modern screening mammography to be lower for women aged 40 to 49 years compared to women aged 50 and older. This lower performance is due to the lower prevalence of invasive breast cancer in younger women and possibly to age differences in breast tumor biology. Because of this lower performance, women in their forties may be subjected to more of the negative consequences of screening, which include additional diagnostic evaluations and the associated morbidity and anxiety, the potential for detecting and surgically treating clinically insignificant breast lesions, and the false reassurance resulting from normal mammographic results. Since the evidence is not compelling that the benefits of mammography screening outweigh the known risks for women aged 40 to 49 years, women considering mammography screening should be informed of the risks, potential benefits, and limitations of screening mammography, so that they can make individualized decisions based on their personal risk status and utility for the associated risks and potential benefits of screening. [Monogr Natl Cancer Inst 1997:22:105–111]

Randomized controlled screening mammography trials have not conclusively demonstrated a reduction in breast cancer mortality for women aged 40 to 49 years, at least not for the first seven to nine years after the initiation of screening (1–3). If screening mammography is effective in reducing breast cancer deaths among women aged 40 to 49 years, the reduction in deaths does not occur for at least a decade following the initiation of screening, and it appears to be smaller than the reduction observed in women aged 50 and older, resulting in a small absolute benefit from screening younger women (4). Screening mammography may be less effective for women aged 40 to 49 years in part because mammography is less sensitive in younger women. Some have argued that with the improvement in the quality of modern mammography, specifically its sensitivity, the results reported from previous randomized controlled trials are not generalizable to women today. However, the question remains whether the performance of modern screening mammography has improved for younger women. We review evidence of the performance of modern screening mammography from the University of California, San Francisco (UCSF), Mobile Mammography Screening Program and discuss possible explanations as to why the performance may differ in younger compared to older women. We also present the potential negative consequences of performing widespread screening mammography among young women based on the performance of modern screening mammography. Lastly, we discuss the potential association between widespread screening mammography and the decrease in breast cancer mortality in the United States reported in 1992 and 1993 (5).

Definitions

There are several parameters used to evaluate the performance of screening mammography. The most widely used parameters are the percent of all screening examinations that have abnormal results (or simply, “percent abnormal”), the positive predictive value (PPV) of mammography, the yield of breast biopsy, and the sensitivity of mammography. For our purposes here, an “abnormal” screen is a screening examinations that requires any additional tests beyond the standard two-view examination, be it additional mammographic views, ultrasound, clinical breast exam, fine needle aspiration, or breast biopsy. The PPV of screening mammography is the percent of women with abnormal screening examinations who are subsequently diagnosed with breast cancer. The yield of breast biopsy is the percent of women who undergo breast biopsies that result in a diagnosis of breast cancer. The sensitivity of mammography is calculated as the number of true positive examinations divided by the number of true positive plus false negative examinations. A true positive examination is defined as an abnormal mammographic examination (of a specified breast) that is performed within 13 months prior to the date of a biopsy with a diagnosis of breast cancer and a false negative examination is defined as a normal mammographic examination (of a specified breast) that was performed within 13 months prior to the date of a biopsy with a diagnosis of breast cancer that was presented clinically.

Breast cancer is defined as any invasive cancer or ductal carcinoma in situ (DCIS). DCIS is a proliferation of cells with malignant features that is confined within the mammary ducts. DCIS is a “nonobligate” premalignant lesion—that is, it has the potential to progress to invasive cancer but does not always automatically do so. DCIS lesions are easier to detect because...
they usually present as microcalcifications (6,7) on mammography, whereas invasive cancer usually presents as noncalcified masses. Of those DCIS lesions that progress to invasive cancer, most do so slowly, taking five to 10 years to develop into invasive cancer (8–12). Since the identification and growth rates of DCIS are different than for invasive breast cancer and because the proportion of mammographically detected cancer that is DCIS varies with age (13), data on the parameters defined above are presented separately for invasive cancer and all breast outcomes (invasive cancer and DCIS).

Performance of Modern Screening Mammography

The percent abnormal of first screening examinations increases with age from 6.4% in women aged 40 to 49 years to 8.0% in women aged 60 to 69 years (Table 1). The PPV of mammography also increases with age, with women aged 50 to 59 years having about a twofold higher PPV of mammography than women aged 40 to 49 years (Table 1). This means for every 100 women in their forties with abnormal mammographic results, about 2.5 will have invasive cancer, compared with 6.3 and 12.2 per 100 women in their fifties and sixties, respectively. The PPV of mammography is somewhat higher for all ages of women when all breast cancer outcomes are considered but still remains low for women aged 40 to 49 years, with only 4.6 cancers for every 100 abnormal first screening examinations. The PPV of mammography we report for first screening mammography is consistent with that reported by the Canadian National Breast Cancer Screening Study for women aged 40 to 49 years (4.4%) (14) and somewhat higher than that reported for modern screening mammography by a recent British Columbia study (2.0%) (15,16).

The observed increase in PPV with increasing age is most likely due to the higher prevalence of breast cancer in older women. The incidence of breast cancer increases approximately 1.5-fold every 10 years from age 40 to age 70, with approximately 76% of all invasive breast cancers diagnosed after age 50 (17). Thus, even though women aged 50 and older only comprise 30% of all women in the United States (18), the majority of breast cancer is detected at or after age 50. Our results reflect this increasing incidence, as the number of breast cancers detected per 1,000 first screening examinations doubles with each 10-year increase in age (Table 1).

In addition to age, a family history of breast cancer affects the PPV of mammography. The relative risk of breast cancer is two to three times higher in women who have had a first-degree relative diagnosed with breast cancer (19,20). The higher risk of breast cancer among women with a family history of breast cancer increases the prevalence of breast cancer in these women, and consequently the PPV (Table 1). This is particularly true for women aged 40 to 49 years and women aged 50 to 59 years with a family history, since the relative increase in risk of breast cancer, compared to women without a family history, is higher for women under 60 than for those aged 60 and older (20).

The percent abnormal and the PPV of mammography is also affected by the percentage of the population being screened for the first time. The percent abnormal for subsequent screening examinations is lower for all ages of women, but it decreases with increasing age (Table 1). The lower percent abnormal on subsequent screening is primarily due to fewer examinations being interpreted as abnormal when first-screening films are available for comparison. This results in higher PPVs for mammography on subsequent screening examinations for women of all ages (Table 1). Of note, however, is that the PPV for subsequent screening mammography for women aged 40 to 49 years is still low (6%) and less than both the PPV of subsequent screening mammography for women age 50 to 59 years (16%) and the PPV of first screening mammography for women ages 50 to 59 (9%).

Another measure of the performance of modern screening mammography is the yield of cancer diagnosed per breast biopsy performed. The number of biopsies per 1,000 exams increases with age, as does the yield of cancer (Table 2). Therefore, even though more biopsies are performed in older women, more cancer is detected per biopsy performed. For women aged 40 to 49 years, one in five biopsies will have invasive cancer or DCIS and only one in 10 will have invasive cancer (Table 2). The yield of cancer is greater in older women, for whom about one in three biopsies will have invasive cancer or DCIS, and about one in four will have invasive cancer. The lower yield of invasive cancer in younger women is due to the lower incidence of breast cancer in these women and the higher proportion of mammographically detected cancer being DCIS (Table 2).

Many may feel that the low PPV of modern mammography, which results in many abnormal examinations that do not result in a diagnosis of breast cancer (false-positive), is acceptable as long as cancer does not go undetected. Therefore, the critical question is, How sensitive is mammography in detecting breast cancer among women who have the disease? Studies of modern

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Table 1. Performance of first and subsequent screening mammography

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>40 to 49</th>
<th>50 to 59</th>
<th>60 to 69</th>
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</thead>
<tbody>
<tr>
<td>First screening</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Abnormal exams (%)</td>
<td>6.4</td>
<td>6.8</td>
<td>8.0</td>
</tr>
<tr>
<td>Breast cancers/1,000 exams</td>
<td>3</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(2, 4)</td>
<td>(5, 8)</td>
<td>(9, 16)</td>
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<tr>
<td>PPV mammography</td>
<td></td>
<td></td>
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<tr>
<td>Average-risk†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive cancer only (%)</td>
<td>2.6</td>
<td>6.3</td>
<td>12.2</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(1.7, 4.0)</td>
<td>(4.4, 9.0)</td>
<td>(9.1, 16.1)</td>
</tr>
<tr>
<td>All breast cancer (%)</td>
<td>4.6</td>
<td>9.0</td>
<td>14.9</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(3.3, 6.3)</td>
<td>(6.6, 12.0)</td>
<td>(11.4, 19.1)</td>
</tr>
<tr>
<td>Family history of breast cancer‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All breast cancer (%)</td>
<td>9.2</td>
<td>16.4</td>
<td>12.1</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(4.3, 17.8)</td>
<td>(9.1, 27.3)</td>
<td>(4.0, 29.1)</td>
</tr>
<tr>
<td>Subsequent screening†‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal exams (%)</td>
<td>3.2</td>
<td>2.5</td>
<td>2.0</td>
</tr>
<tr>
<td>Breast cancers/1,000 exams</td>
<td>2</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(1.3)</td>
<td>(2.6)</td>
<td>(1.5)</td>
</tr>
<tr>
<td>PPV mammography</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Average-risk†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All breast cancer (%)</td>
<td>6.0</td>
<td>16.0</td>
<td>12.5</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(3.0, 11.5)</td>
<td>(8.9, 26.7)</td>
<td>(4.7, 27.6)</td>
</tr>
</tbody>
</table>

*Data from UCSF Mobile Mammography Screening Program, 1985–1996. Excludes women with a history of breast cancer or mastectomy, palpable mass by history or physical exam, or family history of breast cancer. All breast cancer includes invasive cancer and ductal carcinoma in situ.
†Defined as at least one first-degree relative (mother, sister, or daughter) with breast cancer.
‡Includes only second screening examinations.
screening mammography (16, 21–26) report overall sensitivities of screening mammography (71.1% to 91.5%) similar to those published for clinical trials (27, 28). Two studies report the sensitivity of mammography by age, and they show that sensitivity is still lower for women less than age 50 years (63% and 80%) compared to women aged 50 and older (89% and 94%) (16, 23).

A recent study (21) that evaluated the sensitivity of modern screening mammography by decade of age showed that the sensitivity of mammography to detect invasive breast cancer is still lower among women aged 40 to 49 years compared with women aged 50 and older (75% versus 92%). An updated analysis of these data (21) found similar results (Table 3). Conventional thinking has been that the lower sensitivity is due to the lower fat content of younger women’s breasts, making them less radiolucent on film screen mammography (and thus obscuring small tumors) than those of older women. However, two recent studies have shown that the sensitivity of mammography does not vary according to breast density among younger women (21, 28).

Rather, the lower sensitivity in younger women is more likely a result of rapid tumor growth rates (21).

Even though the absolute benefit of screening women aged 40 to 49 years is small (4, 18, 29) and the ability to detect invasive cancer is less in comparison to older women, why not do it anyway? The main reasons to not recommend mass screening are the following: 1) the burden of unnecessary workups of false-positive examinations with associated morbidity, anxiety, and cost; 2) the potential to detect lesions that may be clinically insignificant yet are treated anyway; and 3) the false reassurance resulting from a normal screening test result.

**False-Positive Examinations**

Nationwide, about 11% of all screening examinations are read as abnormal (range 3–57%), with the average PPV of mammography for women aged 40 to 49 years being about twice as low as that for women aged 50 and older (2.0 versus 4.7) (30). Even at institutions with well-trained, full-time mammographers, about 6% of first screening mammography examinations are read as abnormal and the PPV of mammography is low (13). One consequence of the low PPV of mammography is an increase in the number of diagnostic evaluations. Since the PPV of mammography is low in women aged 40 to 49 years, these women may be subjected to the greatest harm, since they will undergo the greatest number of diagnostic tests to find the fewest cancers. For example, among 100 average-risk women aged 40 to 49 years with an abnormal first screening examination, about 95 do not have cancer (Table 1) and must undergo further diagnostic evaluation, which may include tests such as clinical breast examination, additional mammography, ultrasound, needle aspiration, or excisional biopsy. On average, approximately 1.5 to two additional diagnostic tests are performed per abnormal screening examination (13, 31). Because many mammographic abnormalities are nonpalpable, needle localization biopsy is often required. Although risk is low, there are complications associated with biopsies, such as hematomas, infection, and scarring, and from wire localization itself, complications such as vasovagal reactions (7%) and, in rare cases, prolonged bleeding (1%) and extreme pain (1%) (32). In addition, a substantial proportion of women have increased anxiety about breast cancer, compared to women with normal mammographic results, even after learning they do not have cancer (33–36). Twenty-nine percent have persistent anxiety 18 months after an abnormal mammographic result compared to women with a normal mammographic result (13%), and women who undergo breast biopsies have especially high anxiety (33). However, such anxiety does not appear to interfere with subsequent adherence to screening. In contrast, women who do not have anxiety about breast cancer, or women who have decreased anxiety about breast cancer after undergoing screening mammography, are less likely to obtain subsequent annual mammography. Lastly, some women may be wrongly labeled as being at higher risk of breast cancer as a result of having a false-positive mammographic examination which may affect recommendations for subsequent screening and insurance status.

Assuming a high level of mammography performance (13), if 10,000 average-risk women aged 40 to 49 years undergo screening mammography for the first time, approximately 640 will have an abnormal finding requiring some additional test (including 150 biopsies); 30 will have cancer, 17 of which will be invasive cancer and 13 DCIS. In comparison, if 10,000 average-risk women aged 50 to 59 years undergo screening mammography for the first time, approximately 680 women will have an abnormal finding requiring some additional test (including 188 biopsies); 60 will have cancer, 42 of which will be invasive and 18 DCIS (Table 4). Thus, women aged 40 to 49 years will undergo a similar number of biopsies to diagnose half as many

### Table 2. Results of breast biopsies in women after first screening mammography*

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>40 to 49</th>
<th>50 to 59</th>
<th>60 to 69</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast biopsies/1,000 exams</td>
<td>15</td>
<td>19</td>
<td>28</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(13, 17)</td>
<td>(17, 23)</td>
<td>(24, 34)</td>
</tr>
<tr>
<td>Breast biopsy interpretation</td>
<td></td>
<td></td>
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<tr>
<td>Invasive cancer (%)</td>
<td>56</td>
<td>71</td>
<td>82</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(77.4, 97.0)</td>
<td>(77.0, 96.2)</td>
<td>(77.0, 96.2)</td>
</tr>
<tr>
<td>DCIS (%)</td>
<td>11</td>
<td>22</td>
<td>34</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(16, 30)</td>
<td>(26, 43)</td>
<td>(26, 43)</td>
</tr>
<tr>
<td>All breast cancers (%)</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(14, 26)</td>
<td>(24, 40)</td>
<td>(34, 51)</td>
</tr>
</tbody>
</table>

*Data from UCSF Mobile Mammography Screening Program, 1985–1996. Excludes women with a history of breast cancer or mastectomy, palpable mass by history or physical exam, or family history of breast cancer.

†Ductal carcinoma *in situ.*

‡All breast cancer includes invasive cancer and ductal carcinoma *in situ.*
Risk of breast cancer (Table 5). However, for younger women, the risk of a false-positive test is the highest because the incidence of breast cancer is lower in these women. It is important to emphasize that these numbers are based on abnormal mammographic examination after five screening exams and 11.8% after three exams (Personal communication from Anthony Miller, Ph.D.). In contrast, a study of women aged 40 to 69 years in a health maintenance organization has reported a 21% 10-year cumulative risk of a false-positive exam after only three screening examinations (37).

### Overdiagnosis of Clinically Insignificant Lesions

The point of screening is to discover potentially fatal cancers early enough to prevent death. However, screening tends to discover cancers that may never have produced symptoms. The best example of this is DCIS. The natural history of DCIS is unknown, in particular, the natural histories of many small mammographically detected DCIS lesions. Numerous studies have shown that only 15% to 25% of DCIS lesions progress to invasive cancer over 5 to 10 years (38–42) and maybe as few as 7% (12). Of breast cancers detected by screening mammography in average-risk women aged 40 to 49 years, approximately 44% are DCIS, compared to 20%–30% of those detected in women aged 50 and older (Table 2). Given that the natural history of DCIS is unknown, the current clinical dilemma lies in not being able to distinguish which lesions will progress to invasive cancer. Thus, screening mammography may be benefiting some women through early detection of potentially fatal breast cancers, while it is potentially harming other women through detection of clinically insignificant lesions that, for lack of good prognostic indicators, are almost always treated surgically (43).

### Potential for False Reassurance

Of 100 women aged 40 to 49 years with invasive breast cancer, about 22 will go undetected by screening mammography, compared with 9 of 100 women aged 50 to 59 years with invasive cancer (Table 3). This means potentially 22 women aged 40 to 49 years with invasive breast cancer will be told their screening examination is normal and may be falsely reassured that they do not have breast cancer and thus not seek medical attention for breast symptoms. For women who do not have breast cancer, they may also be reassured by having a normal screening examination that they do not have breast cancer. The annual risk of breast cancer for a 40-year-old woman is about 1 in 625 (17); having a normal screening examination decreases her risk to about 1 in 2500 (44). Although the very low risk of breast cancer after a normal screening examination may reassure women that they do not have breast cancer, the risk of breast cancer before mammography is already quite low. The need for reassurance from mammography may not be necessary if women in their forties understood that the risk of breast cancer prior to mammography is already very low (45). Thus, screening mammography is not justified solely to reassure women that breast cancer is not present; moreover, women should be informed that cancer may go undetected by mammography.

### Potential for False Reassurance

<table>
<thead>
<tr>
<th>Risk</th>
<th>Age (years)</th>
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<tbody>
<tr>
<td></td>
<td>40</td>
</tr>
<tr>
<td>Abnormal exam*</td>
<td>30%</td>
</tr>
<tr>
<td>False-positive exam*</td>
<td>28%</td>
</tr>
<tr>
<td>Biopsy*</td>
<td>7.5%</td>
</tr>
<tr>
<td>Breast cancer†</td>
<td>1.5%</td>
</tr>
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</table>

*Calculations based on results presented in Table 1 and 2.
†Risk of breast cancer in the next 10 years for a 40-, 50-, and 60-year-old woman (17).
Decreased Breast Cancer Mortality in the United States—Is It From Screening?

Recently published data from the National Cancer Institute (NCI) show that among white women from 1989 to 1993, breast cancer mortality has decreased 8% in women 40–49, 9% in women 50–59, and 5% in women 60–69 (5). Proponents of screening mammography for women aged 40 to 49 years have suggested that this decrease is due to the improvement in, and widespread use of, modern screening mammography (5). There are many reasons why breast cancer mortality may be decreasing in the United States, however, including more widespread use of adjuvant therapy, improved detection by mammography, a shift in the risk factors for breast cancer in the population, earlier reporting of breast symptoms, and cohort effect. No randomized controlled trial has been conducted to test whether modern mammography results in a reduction in breast cancer mortality among women aged 40 to 49 years.

An indirect way to examine whether the increase in modern mammography utilization has affected breast cancer mortality is to look at NCI’s population-based Surveillance, Epidemiology, and End Results (SEER) tumor registry data (17) to see if there has been a decrease in the incidence of late-stage disease. Specifically, if mammography accounts for the observed decrease in breast cancer mortality, then screening should advance the time of diagnosis and result in a lower rate of breast cancer cases having lymph node involvement. In other words, a lower rate of lymph node involvement would result in a decrease in breast cancer mortality, since lymph node involvement has the greatest impact on breast cancer survival.

In examining the population-based SEER tumor registry data for white women (17), we considered all DCIS lesions and invasive tumors that were less than 20 mm without associated positive lymph nodes to be consistent with screening or early-stage cancer; invasive tumors 20 mm or larger or those tumors associated with positive lymph nodes regardless of tumor size were considered to be inconsistent with screening or late-stage cancer (46). Among women in their fifties and sixties, with the increase in the rate of early-stage disease, there has been a persistent decrease in late-stage disease since 1986 (Figure 1a and 1b). Therefore, it appears as if there has been a shift from more advanced-stage disease to earlier-stage disease, such that the rate of tumors consistent with screening is higher than the rate of tumors not consistent with screening. The increase in early-stage disease has been tied to the dramatic increase in use of screening mammography (47,48). Therefore, the six-year decline in late-stage disease for women aged 50 to 59 and 60 to 69 years suggests that the decline in breast cancer mortality observed in 1992 and 1993 may be due, in part, to screening mammography. Other likely explanations for the decline in late-stage disease could be earlier reporting of breast symptoms or cohort effect.

For women aged 40 to 49 years, the rate of tumors not consistent with screening was similar in 1983 as in 1991 (Fig. 1c). Not until 1992 was there a decline in tumors not consistent with screening or late-stage disease for women aged 40 to 49 years. Therefore, although modern mammography has resulted in an increase in breast cancer cases consistent with screening among younger women, it has not resulted in a shift from more advanced-stage disease to early-stage disease. Thus, given that there has not been a persistent decline in late-stage disease, it is less likely that the decrease in breast cancer mortality observed in 1992 and 1993 among white women aged 40 to 49 years is due to screening mammography. As noted above, there are many reasons why breast cancer mortality may have declined in the United States, including improved breast cancer treatment. The United Kingdom has also reported a 9.8% decline in breast cancer mortality among women aged 40 to 49 years between 1989 and 1994, despite the fact that younger women do not undergo regular screening mammography, since mass screening is not recommended for women under age 50 (49). Taken together, these results suggest that the decline in breast cancer mortality among women aged 40 to 49 years is less
likely due to early detection from screening mammography and more likely due to other reasons, such as improved breast cancer treatment.

Conclusion

There are associated risks with undergoing screening mammography, including additional diagnostic evaluations and the associated morbidity and anxiety, the potential for detecting and surgically treating clinically insignificant breast lesions, and the false reassurance resulting from a normal mammographic result. Before mass screening is recommended to healthy persons, the benefits of the intervention should be proven to clearly outweigh the risks. Given that the small absolute benefit (4) does not clearly outweigh the known risks, health practitioners should instead inform women of the risks, potential benefits, and limitations of screening mammography, so that each woman can make an individualized decision based on her personal risk status and utility for the associated risks and potential benefits of screening. Women who request or are offered screening mammography should be informed of the following: 1) their age-specific risk of breast cancer, 2) the chance of undergoing a diagnostic procedure, 3) the chance of a false negative, and 4) the evidence that screening mammography reduces the risk of death among screened women in their age group. In addition, health practitioners need to assist women in understanding what factors might influence their choice to undergo or not undergo screening, such as their attitude toward pain, risk, and inconvenience (50).

References


(49) Institute of Public Health. University of Cambridge, Department of Community Medicine, Cancer Intelligence Unit, 1997.


Note

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