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Rethinking Screening for Breast Cancer and Prostate Cancer

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BREAST CANCER AND PROSTATE cancer account for 26% of all cancers in the United States, with an estimated 386 560 patients diagnosed annually: 194 280 for breast cancer and 192 280 for prostate cancer.¹ For both, there are remarkable differences between outcomes of localized vs advanced disease (breast cancer: 5-year relative survival rates of 98.1% vs 27.1%; prostate cancer: 100% vs 31.7%).² As a result, screening for both cancers has been promoted on the assumption that early detection and treatment is the best way to reduce disease-associated morbidity and mortality.

Effect of Population-Based Screening

A large fraction of the US population participates in screening for prostate cancer and for breast cancer. About 50% of at-risk men have a routine prostate-specific antigen (PSA) test and 75% have previously had a PSA test.^{3,4} About 70% of women older than 40 years reported having a recent mammogram.⁵ Two decades of screening have resulted in a significant increase in detection of early cancers. Prostate-specific antigen testing has nearly doubled the chance that a man will be diagnosed with prostate cancer in his lifetime: In 1980, a white man's lifetime risk of prostate cancer was 1 in 11⁶; today it is 1 in 6.¹ A woman's lifetime risk of breast cancer was 1 in 12 in 1980; today it is 1 in 8.¹ If ductal carcinoma in situ (DCIS) is included, the risk of being

diagnosed with breast cancer, like prostate cancer, has almost doubled as well. The increase in early cancers as a fraction of total cancers detected is not necessarily beneficial. The introduction of an optimal screening test should be followed by an increase in the rate of early disease followed by a decrease in regional disease while the overall detection rate remains constant.⁷ FIGURE 1 illustrates hypothetical optimal, worst-case, and intermediate-case scenarios, using 1980 breast cancer incidence rates as a starting point. In the worst case, screening leads to an increase in local disease detection without a corresponding decrease in regional disease, thereby increasing costs and morbidity due to overdiagnosis and overtreatment of non-life-threatening cancers. Although the scenarios are quite different, the percentage of early cancers detected, as a fraction of total cancers identified, increases from 50% to almost 70% in each case. This type of intermediate metric, often cited as evidence of success for screening programs, is potentially misleading.

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diagnosed with breast cancer, like prostate cancer, has almost doubled as well.

How do breast and prostate cancer screening compare with these hypothetical scenarios? The data for breast cancer and prostate cancer (FIGURE 2) resemble the intermediate-case scenario at best. The incidence of invasive breast cancer (excluding in situ lesions) has increased substantially and remains higher than prescreening rates. SEER data⁸ show that localized (node negative, no skin or chest wall involvement) and regional (node positive, skin or chest wall involvement) breast cancer has declined slightly but far less than the increase in localized disease. The reported rate of advanced disease has decreased substantially for prostate cancer; however, about one-third of patients currently classified as having localized cancer are found to have extraprostatic disease at the time of surgical resection.¹¹ It is disappointing that the absolute numbers of more advanced disease have not decreased nearly as much as hoped for either cancer. Thus, neither screening test is optimal. Although the

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incidence of high-grade cancer has dropped as a fraction of all cancers detected, the absolute numbers have not decreased as much as hoped (Figure 2B).

Mortality has decreased for both cancers over the past 2 decades but the contribution from screening is uncertain. A comparison of prostate cancer incidence rates in the United States and the United Kingdom found that intensive PSA screening in the United States along with dramatic increases in incidence did not result in significant differences in mortality compared with the United Kingdom, where PSA screening was not widely adopted.¹² The 2 prostate cancer screening trials have mixed results: the European trial¹¹ showed a 20% relative decrease in mortality and the US trial¹³ found no effect on mortality. For breast cancer, the relative reduction in mortal-

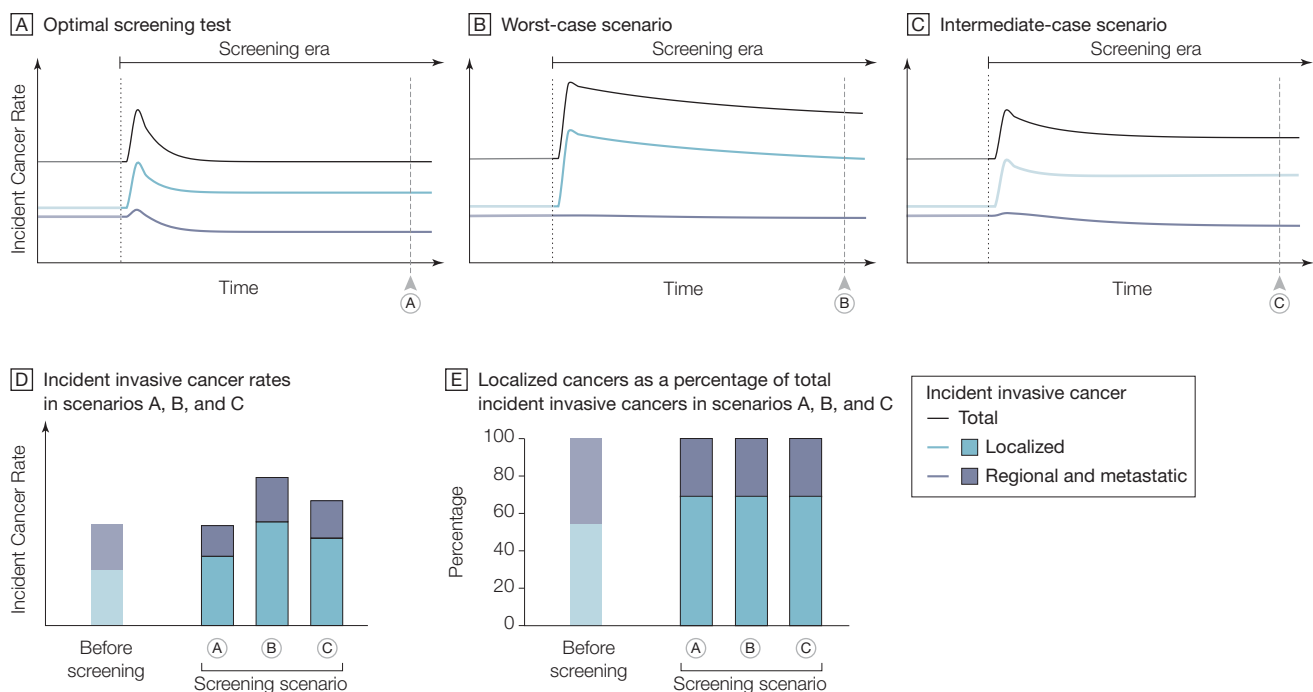
ity from screening in 7 randomized trials ranged from 20% to 30%¹³; meta-analyses estimate the reduction to range from 0% to 20%.¹⁴ The observed decrease in mortality is attributable to both screening and adjuvant therapy, with an estimated decrease of 7% to 23%, and 12% to 21%, respectively.¹⁵

Screening's Limited Effect on Mortality and Significant Effect on Incidence. There are several reasons that may help to explain why screening has not led to a more significant reduction in deaths from these 2 diseases in the United States. First, screening increases the detection of indolent cancers. Second, screening likely misses the most aggressive cancers. In other words, tumor biology dictates and trumps stage, so the basic assumption of these screening programs that finding and treating early stage disease will pre-

vent late stage or metastatic disease may not always be correct.

Periodic screening risks detection of slower growing and potentially indolent tumors (FIGURE 3A and B, length bias), finds some progressive cancer early (Figure 3C) but does not screen patients often enough to detect lethal tumors (Figure 3D) in time to prevent death. Without the ability to distinguish cancers that pose minimal risk from those posing substantial risk and with highly sensitive screening tests, there is an increased risk that the population will be overtreated. This phenomenon was noted in a study comparing prostate cancer incidence and mortality in 2 US sites, Connecticut (low rate of PSA screening) and Seattle, Washington¹⁶ (high rates). Significantly higher prostate cancer incidence and treatment rates in Seattle were unrelated to mortality rates.^{17,18} The

Figure 1. Hypothetical Screening Scenarios



Three hypothetical scenarios of changes over time in stage-specific incidence rates associated with widespread screening usage are presented. The dotted lines indicate the point of screening initiation. The fraction of localized and regional disease before and after screening is shown for each scenario. A, Screening leads to an increase in localized cancers, a decrease in regional cancers, and stable rates of overall invasive cancer (after an initial increase following introduction of screening). B, Screening leads to an increase in the detection of total and early stage cancers but without a decrease in the rate of regional cancers. C, Screening results in an increase in early and overall cancer rates, with some decrease in regional stage disease. This outcome is intermediate between A and B. D, The incidence of localized and regional cancers is shown for the prescreening period and for each of the scenarios. The height of the bars represents total incidence. E, The relative percentage of localized vs regional cancers is shown. Note that all 3 scenarios lead to the same increase in the percentage of detection of localized cancers.

rate of overdiagnosis in national breast cancer screening programs may be as high as 1 in 3 for invasive cancers,¹⁹ and it is possible that some screen-detected cancers might even regress.²⁰ The observed increase in the fraction of molecularly low-risk cancers in a screened population supports this observation.²¹ Screening with a focus on high sensitivity will increase cancer detection rates, which has been demonstrated for other cancers in the setting of population-based screening, including neuroblastoma^{22,23} and now likely lung cancer with the introduction of computed tomographic (CT)-based screening.²⁴

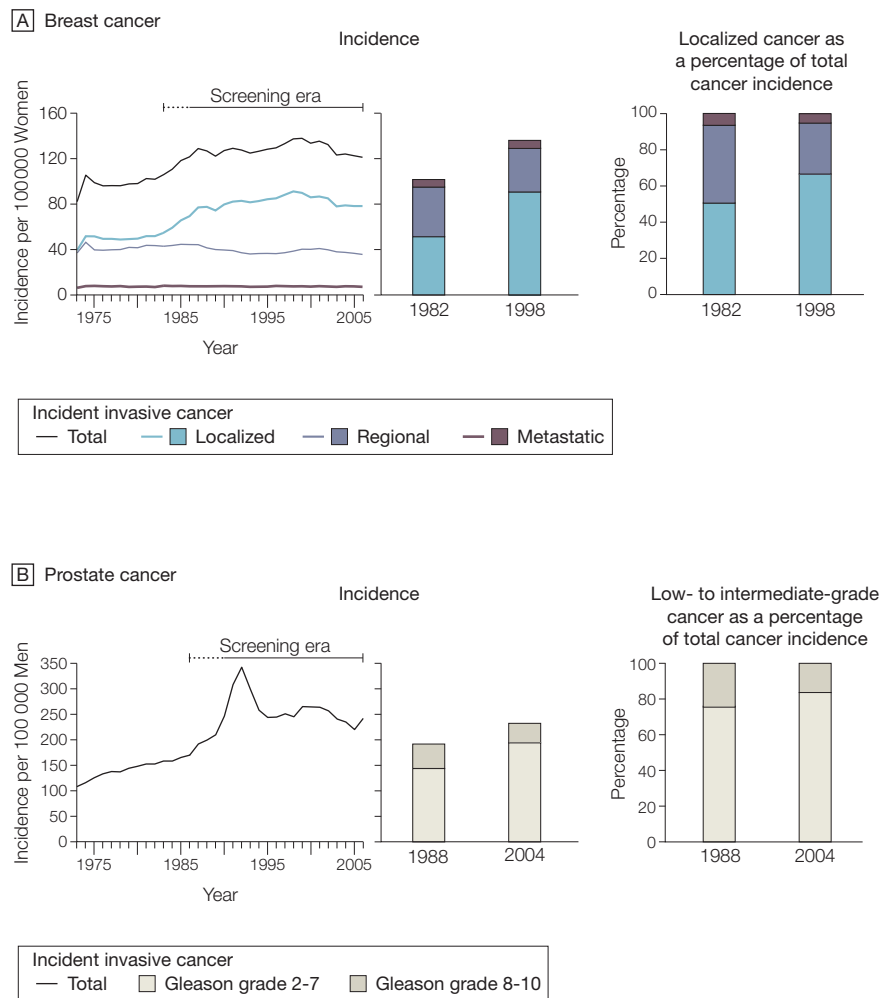
Early detection may not be the solution for aggressive cancers because many may not be detected early enough for cure. Some small “curable” breast cancers, categorized as low risk by National Institutes of Health criteria, have a high mortality risk when analyzed using prognostic molecular profiles such as the NKI 70 gene test.²⁵ Biologically aggressive cancers present with a higher stage despite screening. *Interval cancers*, those that present clinically between routine screens, have a higher growth fraction and are more likely to be lethal compared with screen detected cancers.²⁶ In the neoadjuvant I-SPY (Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging and Molecular Analysis) trial, in which the mean tumor size was 6 cm (accrual 2003-2006 in the United States), 91% had poor prognosis biology²⁷ (using the NKI 70 gene test), which is much higher than the 33% poor prognosis proportion in women undergoing routine screening.²¹ Of women undergoing routine screening in the I-SPY TRIAL, 85% of the malignancies were interval cancers and only 15% were screen detected,²⁸ suggesting that locally advanced cancers reflect the growth curve of line D in Figure 3. Similarly, the most lethal prostate cancers are those with rapidly increasing PSA levels.

Screening is most successful when pre-malignant lesions can be detected and eliminated as in the case of adenomatous polyp removal during colonoscopy screening²⁹ or cervical intraepithelial neoplasia ablation by colposcopy after

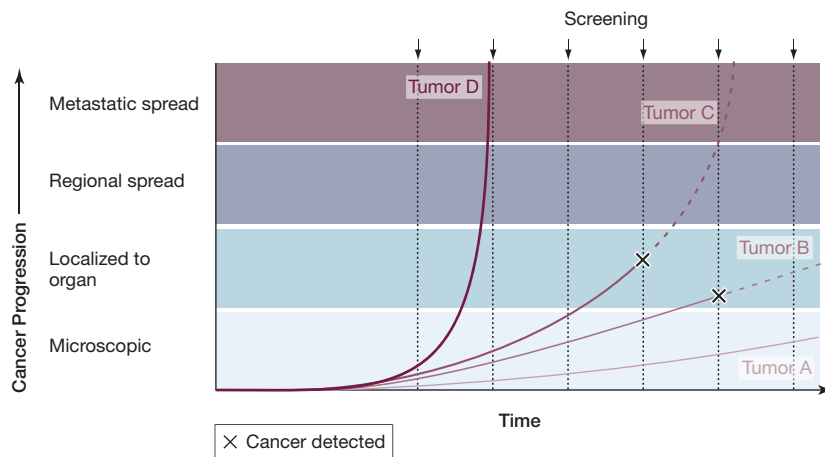
detection by pap smear.³⁰ Perhaps most important is that screening for cervical and colon cancer and the removal of pre-neoplastic lesions have been accompanied by a significant decrease in their invasive cancer counterparts; this has not been seen in breast and prostate cancer. Ductal carcinoma in situ, rare prior to widespread screening, now represents

25% to 30% of all breast cancer diagnoses (>60 000 new case-diagnoses annually are not included in the invasive cancer statistics),¹ the majority of these lesions are low and intermediate grade.³¹ Ductal carcinoma in situ is considered to be a precancerous lesion and standard of care is excision and adjuvant treatment. However, after 2 decades of

Figure 2. Age-Adjusted Incidence Rates of Breast and Prostate Cancer Over Time and by Prescreen and Postscreen Snapshot



A, Age-adjusted incidence rate by stage of invasive female breast cancers for all ages, SEER 1973-2006.⁸ Mammography was introduced in 1983 and more widely used beginning in 1986.⁹ The incidence per 100 000 women of localized, regional, and metastatic breast cancer is shown over time (left), and for the period prior to the uptake of screening (1982) and 16 years after (1998) (middle). Local disease, as a fraction of all cancers reported, is shown on the right. B, Age-adjusted incidence rate of adenocarcinoma of the prostate for men older than 24 years, SEER, 1973-2006. Prostate cancer screening began in 1986 and was more widely used beginning in 1989-1990. Given the degree of missing data for prostate cancer TNM stage in SEER, we chose to show the change in Gleason grade, a significant predictor of outcome since the introduction of screening. The middle panel shows the incidence per 100 000 men of tumors with Gleason grades that were low- and intermediate-grade (2-7) vs high-grade (8-10) tumors, for the period prior to the uptake of screening (1988) and 16 years after (2004). The low- and intermediate-grade tumors as a fraction of all cancers is shown in the panel on the right.¹⁰

Figure 3. Screen Detection Capability Based on Tumor Biology and Growth Rates

Growth rates of 4 tumors are displayed from the time the first tumor cells appear while the tumor is not yet detectable (microscopic); when it can be detected as localized (confined to the organ) and most likely to be curable; regional (after the tumor spreads beyond the organ) where it may not be curable; and to the point when metastases and death occur. Tumor A remains undetectable and without morbidity during the patient's lifetime. Tumor B grows until it becomes detectable but never causes symptoms or leads to death. Both tumors A and B represent low-risk indolent or IDLE (indolent lesions of epithelial origin) tumors. Tumor C is destined to become metastatic and fatal but can be detected while still curable. Tumor D is destined to become metastatic but grows so quickly that by the time it can be detected, it may no longer be curable. Among these 4 tumors, only the patient with tumor C benefits from screening.

detecting and treating DCIS, there is no convincing evidence of substantial reduction in invasive breast cancer incidence. The 2002 decrease in incidence leveled off in 2005 and is attributed to a reduction in postmenopausal hormone therapy use, not DCIS removal.³²

The current quandary stems from the focus of screening programs on improving test sensitivity, leading to potential tumor overdiagnosis and overtreatment. In the Prostate Cancer Prevention Trial,³³ biopsy of all men in this study found that there was no level of PSA below which cancer was not found. Additionally, at the current 4.0 ng/mL cutoff of PSA values, almost 30% of cancers were already potentially incurable. Although lowering the PSA threshold reduced the number of incurable tumors, the risk of detection of insignificant disease increased substantially. That the bulk of tumors found across all levels of risk in the trial³³ met current criteria of "significant cancer" is a testimonial to the inability to discriminate between inconsequential disease and disease that will cause serious illness and death.³⁴ The

European Randomized Study of Prostate Cancer³⁵ screening showed that a very large number of men had been screened to find many prostate cancers, the majority of which will not cause harm during intermediate follow-up.

Surgical and radiation interventions are associated with morbidities that are sometime significant in many men. In the US Prostate, Lung, Colorectal, and Ovarian Cancer study, a large number of excess tumors were detected in the screening group but without a reduction in mortality.³⁶ Even in breast cancer, for which there is evidence and agreement that screening saves lives, the TABLE illustrates that for every breast cancer death averted, even in the age group for which screening is least controversial (age 50-70 years), 838 women must undergo screening for 6 years, generating thousands of screens, hundreds of biopsies, and many cancers treated as if they were life threatening when they are not. Even in the centrally organized European screening programs, where the emphasis on greater specificity has led to fewer interventions,³⁸ the problem remains.

After 2½ decades of screening for breast and prostate cancer, conclusions are troubling: Overall cancer rates are higher, many more patients are being treated, and the absolute incidence of aggressive or later-stage disease has not been significantly decreased. Screening has had some effect, but it comes at significant cost, including overdiagnosis, overtreatment, and complications of therapy, problems likely to be exacerbated as the US population ages. Additional gains are unlikely with the current approach and may inadvertently add to the burden of treatment and diagnosis for relatively indolent disease.

A Shift in Strategy: Options for the Future

To significantly reduce death and morbidity from breast and prostate cancer, a new focus and approach is proposed for early detection and prevention: (1) focus on development and validation of markers that identify and differentiate significant- and minimal-risk cancers; (2) reduce treatment for minimal-risk disease; (3) develop clinical and patient tools to support informed decisions about prevention, screening, biopsy, and treatment and offer treatments tailored to tumor biology; and (4) work to identify the highest-risk patients and target preventive interventions. To accomplish these goals, demonstration projects, that drive innovation in prevention, screening, and management in breast and prostate cancer are needed.

Develop and Validate Biomarkers to Differentiate Significant- and Minimal-Risk Cancers. To help move toward a more effective solution, the first step is a change in mindset in scientific discovery efforts and clinical practice. The approach to screening should follow a multidecision path such as the one shown in FIGURE 4. Beyond merely identifying those most at risk for developing cancer (Figure 4, point 1), individuals at the highest likelihood of having substantial risk disease (Figure 4, point 3) must be identified. Treatment success or failure (point 4) should inform prevention (point 5) and screening (point 6). This will require models to predict those individuals who are likely to de-

velop high-risk cancers and focus studies on this population.

Reduce Treatment Burden for Minimal-Risk Disease. Many diagnosed tumors will follow an indolent course for the patient's lifetime⁴² or are probably cured with surgical excision alone. However, the inability to distinguish the most aggressive from the least aggressive cancers promotes interventions for all patients. For both breast and prostate cancer, methods exist to identify low- and high-risk cancers.^{43,44} Tests for prognosis^{25,44} and prediction⁴⁵ of breast cancer are available and provide better discriminatory information than clinical features alone.^{25,45,46} These and other emerging tools should be used and validated as classifiers at the time of diagnosis. Minimal-risk lesions should not be called cancer. A more appropriate term, such as *indolent lesions of epithelial origin* (IDLE) tumors would help focus on systematically studying how to reduce or eliminate therapeutic interventions while achieving a good outcome. For substantial-risk tumors the focus must be on developing optimal multimodal therapies while concurrently developing preventive strategies.

For prostate cancer, low-volume lesions with low Gleason scores have a low risk of causing death within an intermediate period.⁴⁷ A large US-based trial that randomized men to surgery vs no therapy is nearing completion, a National Cancer Institute (US and Canada)-sponsored trial is beginning to compare immediate vs delayed therapy, and a prospective study of patients on surveillance for prostate cancer is enabling the collection of clinical data and biomarkers to correlate with outcomes.^{48,49} These and other studies will improve the ability to classify lesions as minimal risk. The community should reclassify these low-risk lesions as IDLE tumors and not refer to them as cancer. The in situ precursors of IDLE tumors (IDLE in situ) would then not need to be treated. The scientific community should target the development of classifiers to distinguish IDLE in situ from precursors of more significant lesions, which can then be referred to by the emerging terms, *ductal intraepithelial neoplasia* (DIN) and *prostate intraepithelial neoplasia* (PIN). By doing

Table. Benefit and Burden of Mammographic Screening and Prostate-Specific Antigen Screening in the United States and Europe

Region	Deaths Averted	Cancers Detected, Treated	Biopsies/Recalls	Screening Visits	No. of Individuals Screened	No. of Years of Screening
Breast cancer^a						
United States	1	18 Invasive 6 DCIS	90/535	5866	838	6
Europe	1	15 Invasive 5 DCIS	41/162	3352	838	6
Prostate cancer^b						
United States	0					
Europe	1	48		2397	1410	9

Abbreviations: CI, confidence interval; DCIS, ductal carcinoma in situ.

^aEstimated outcomes of mammographic screening for 6 years for women 50 years and older is taken from the US Preventive Services Task Force.³⁷ The summary relative risk (RR) was 0.78 after 14 years of observation with the number needed to screen of 838 for women older than 50 years (95% CI, 494-1676) to prevent 1 death from breast cancer. For women 40 to 70 years, the number needed to screen is 1224 (95% CI, 665-2564 over 14 years). Assumptions for the United States: screening annual; prevalence round (first screen of previously unscreened population) cancer detection rates 5 to 7/1000 (estimate 6); 3/1000 for incidence rounds; recall rates are 13.5 and 8.4 per 100 mammograms for prevalent and incident rounds, respectively.³⁸ Twenty percent of women will undergo a biopsy after 10 years of screening³⁹ with 2.67 and 1.33 per 100 for prevalent and incident screening rounds, respectively.³⁸ Assumptions for Europe: screening is every 2 years; prevalence round cancer detection rate 6.3/1000 (estimate 6); 3.8/1000 for incidence rounds.⁴⁰ The number of individuals screened is held constant for purposes of comparison. Recall rates are 7.6 and 3.9 per 100 mammograms for prevalent and incident rounds, respectively. Biopsy rates in Europe are significantly lower than those in the United States, approximately 0.5 of US rate over time with 2.4 and 0.8 per 100 for prevalent and incident screening rounds, respectively.³⁸ Assumptions for both: DCIS 25% of all cancers detected⁴¹; 22% of invasive cancer detected by screening would regress.²⁰

^bProstate cancer data are from the United States¹³ and European¹² randomized trials; results from the US trial showed no significant difference in mortality between screened and unscreened participants after 7 years of follow-up.

so and reliably categorizing these lesions with low risk of morbidity or mortality, the burden of therapy can be eliminated in many cases.

Develop Tools to Support Informed Decisions. Information about risks of screening and biopsy should be shared with patients before screening. At the time of cancer detection, risks and benefits of treatment for specific biological subtypes should be shared. Decision support tools should be designed to assist patients and clinicians and facilitate introduction of new data. As risk factors for biologically aggressive cancers are identified, recommendations regarding tools and frequency of screening will need to be tailored to the patient, as in the example of *BRCA* carriers.

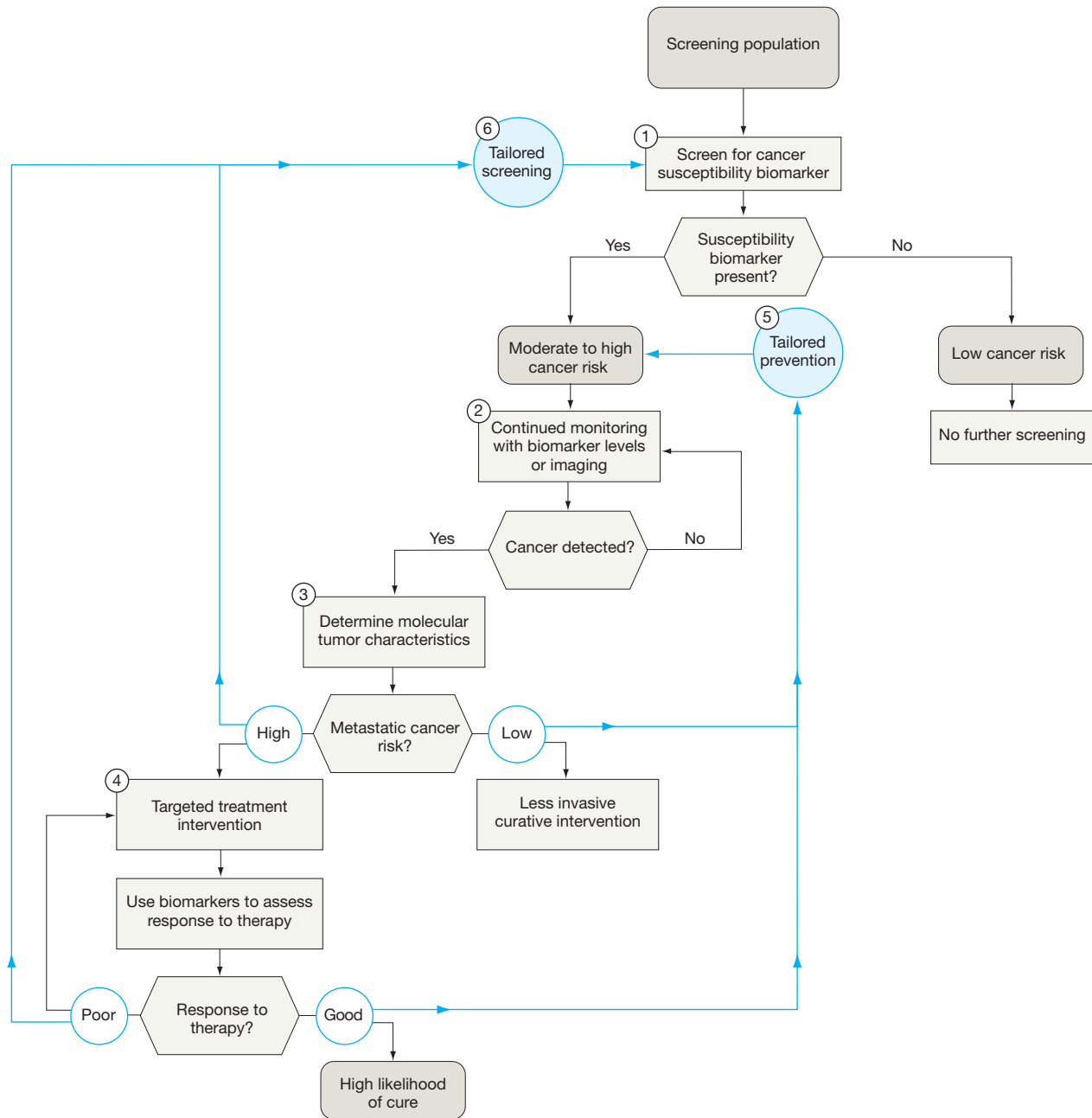
Women recalled after mammography screening are assigned a Breast Imaging Reporting and Data System (BIRADS) classification. BIRADS 4 is considered suspicious but corresponds to a risk that ranges from 3% to 75% for developing cancer.⁵⁰ Less aggressive interventions for women with lowest-risk lesions (BIRADS 4a or <20% risk of cancer) should be developed.⁵¹ For prostate cancer, a risk calculator can integrate multiple risk factors to provide a composite risk estimate that is

often more informative than PSA level alone.⁵² This enables the clinician to recommend biopsies to men at highest risk and avoid biopsies for the lower-risk patients. The risk calculator has the advantage of assessing risk of cancer and risk of high-grade disease; because the latter poses the primary risk of morbidity and death, this level of risk may be most informative as patients decide whether to have a biopsy or a preventive intervention.

Focus on Prevention for the Highest-Risk Patients. Ultimately, prevention is preferable to screening by reducing the risk that a patient will have a diagnosis, experience undesirable effects of treatment, and confront the specter of recurrence. For both breast and prostate cancer, available agents are proven to reduce cancer risk: finasteride⁵³ and tamoxifen or raloxifene.⁵⁴ In the case of prostate cancer, finasteride has been demonstrated to be safe and effective in reducing the risk of cancer regardless of risk stratum.⁵⁵ Finasteride does not increase and may reduce risk of high-grade cancer.⁵⁶⁻⁵⁸ For breast cancer, focus should be on prevention efforts for women for whom the risk and the benefits of intervention have been shown to be highest, eg, in the setting of atypia at a young age

(for which chemoprevention may reduce relative risk by 85%),^{59,60} or breast cancer (*BRCA* gene-mutation carriers at a young age (for which surgical prophylaxis reduces absolute risk by more than 40%-70%).⁶¹⁻⁶³ Chemoprevention may also be an alternative to surgical excision and radiation for minimal-risk cancers.⁶⁴

Figure 4. Framework for Advancing Screening and Detection



At point 1, it would be optimal to find a biomarker for susceptibility (eg, breast density, risk models, gene polymorphisms, immune function) to tailor recommendations for screening. At point 2, higher-risk patients would undergo detection screening with imaging, biomarkers, or both. When a cancer is detected, point 3, molecular profiling determines tumor type, and risk for progression. Minimal-risk disease can be treated less aggressively, and patients with significant risk of metastatic disease should receive tailored interventions, point 4. Biomarkers that predict good response to therapy with targeted agents should provide opportunities to develop tailored prevention interventions with potential biomarkers for measuring response, point 5. Patients with poor response to therapy should provide clues for identifying markers of risk and susceptibility and research should be directed to identify those susceptible (point 6) to aggressive disease that is difficult to treat. Tailored screening might include susceptibility biomarkers or more intensive detection strategies (eg, magnetic resonance imaging for *BRCA* carriers). Biomarkers that characterize tumor type and response should inform prevention and screening efforts (pathways shown in blue).

The timing of progression of cancer is rarely considered but should be a part of decision making and the design of preventive interventions. Premalignant lesions, which are likely to take years to progress, should be seen as an opportunity to study preventive interventions⁶⁵ rather than merely as an opportunity to treat. A high national priority must be to find innovative ways to initiate prevention trials, especially for *aggressive* disease.

Three barriers hinder the acceptance of prevention: failure of physicians to make clear to patients (and patients to understand) their individual risk of cancer, the belief that early detection and “cure” are ensured with screening, and organized medicine’s focus on treatment rather than prevention. It is critical to develop tools to assess the benefit of current preventive interventions for an individual patient (Figure 3, point 2). Preventive interventions will be used if they have few adverse effects, if they are not costly, and if biomarkers identify the patients most likely to benefit and whether the intervention is having an effect.⁶⁶ The human and financial savings of not becoming a cancer survivor for the person’s lifetime makes prevention a better option than treatment.⁵⁵ When risk can be determined with accuracy, patients choose preventive interventions: For *BRCA1* and *BRCA2* gene mutation carriers, prophylactic surgery is cost-effective, lifesaving,⁶⁷ and increasingly selected as reconstruction options improve.⁶⁸

Demonstration Projects: Tactics for the New Strategy. To reduce morbidity and mortality from breast cancer and prostate cancer and to execute the proposed strategy, a comprehensive approach, using large demonstration projects to create a learning system, integrating both clinical care and research is needed. By spanning the spectrum from screening to treatment and survivorship, learning from diagnosis, treatment, and outcomes can be applied to developing tailored strategies for screening and prevention. Critical elements include structured data collection as a byproduct of care and patient engagement in screening and treat-

ment; a database that includes known and proposed risk factors, exposures, and comorbidities, diagnostic interventions, molecular classification of tumors at the time of diagnosis, treatment decisions, short- and long-term outcomes; collection and storage of blood and tissue for research; comparative effectiveness; tools for automated risk assessment; and democratized access to identity-protected information. With this infrastructure, biomarkers to identify minimal-risk cancers can be tested and applied; options can be provided to reduce treatment; shared decision-making tools can be used to update information; and risk assessment tools can be automated, using risk information gathered at the time of screening and diagnostic evaluation to systematically identify, target risk reduction, and track men and women predisposed to developing significant-risk cancers.

Optimizing interventions and tracking outcomes will accelerate the ability to refine treatment and screening strategies, predict risk for specific biological tumor types, and ultimately develop tailored prevention strategies. This is clearly a superior strategy to the fragmented, inefficient, underpowered approach of developing small disease cohorts for each proposed new marker. The demonstration project concept provides opportunity but will require new types of collaborations among industry, academia, government, health care payers, clinicians, and patients. The ATHENA Breast Health Network, an innovative project across the University of California campuses, is an example.⁶⁹

Conclusion

Screening for breast and prostate cancer has increased the number of cancers detected generating expense and morbidity from detection and treatment of cancers that pose minimal risk. To improve screening, a new focus is recommended for research and care to identify markers that discriminate minimal-risk from high-risk disease; identify less aggressive interventions for minimal-risk disease to reduce treatment burden for patients and society; develop deci-

sion support tools to integrate current and emerging knowledge into routine care; and develop effective prevention, screening, and treatment strategies for high-risk disease. About \$20 billion is spent to screen for breast cancer and prostate cancer in the United States.⁷⁰ Highly innovative businesses typically invest 10% to 20% of their sales into research and development for the next new product.⁷¹ A similar investment is needed to improve screening, accelerate prevention research, and reduce harm from breast cancer and prostate cancer deaths.

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Study concept and design: Esserman, Thompson.

Acquisition of data: Esserman, Shieh.

Analysis and interpretation of data: Esserman, Shieh, Thompson.

Drafting of the manuscript: Esserman, Shieh, Thompson.

Critical revision of the manuscript for important intellectual content: Esserman, Shieh, Thompson.

Statistical analysis: Esserman.

Administrative, technical, or material support: Esserman, Shieh.

Study supervision: Esserman.

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