Determinants of Cancer Screening Frequency: The Example of Screening for Cervical Cancer

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Background: **Cancer screening frequency should be based on the rate of progression of the disease and the sensitivity of the screening test. A common misconception is that a person's risk of getting the disease determines how often they should be screened.**

Methods: **We describe algebraically the theoretical interaction of disease progression rate and screening test sensitivity determining the portion of invasive cancers prevented by screening. After discussing the assumptions and limitations of the model, we apply this model to the example of screening for cervical cancer. Actual data from large screening programs assembled by the International Agency for Research on Cancer (IARC) are used to test the assumptions of the model.**

Results: **A simple formula can express the relation between disease progression rate, sensitivity of the screening test, screening frequency, and screening error. Disease prevalence does not figure in this equation. The IARC data suggest that, at least for cervical cancer, as screening frequency increases, incremental sensitivity of the test decreases or remaining undetected cases progress more rapidly so that anticipated benefits from more frequent screening are not realized.**

Conclusions: **Rate of disease progression and sensitivity of the screening test are the proper determinants of cancer screening frequency. Because these factors can vary depending on screening frequency, however, the optimal screening interval for a particular cancer must be determined by clinical trials. (J Am Board Fam Pract 1998;11:87-95)**

Evidence-based preventive medicine guidelines have, in the last decade, become much more widely used and accepted by the medical community. Such authoritative groups as the United States Preventive Services Task Force,[1] The Canadian Task Force on the Periodic Health Examination,[2] The American College of Physicians,[3] and the American Academy of Family Physicians [4] have espoused the principles of evidence-based guidelines that directly link recommendations to specific supporting evidence and grade the quality of that evidence.

Screening recommendations usually have two components. The first is the recommendation to screen for a particular disease using a specific test, questions, or physical examination maneuvers. The second is a statement of how frequently screening should occur. The rate of progression of the disease being detected and the sensitivity of the screening test are the two factors that determine the optimal screening frequency. A common misunderstanding, among both the general public and medical experts, is that the incidence of a disease or a person's risk of acquiring a particular disease determines how often they should be screened for that disease. This misconception is especially common in the debate about how often women should be screened for cancer of the uterine cervix. In this article we will critically examine the interaction of the disease progression rate and the screening test sensitivity predicting the percentage of cancers that will be detected by screening before becoming invasive and potentially incurable. Screening for cervical cancer will be used as a case study to illustrate the general principles.

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Determinants of Screening Frequency

Figures 1 and 2 illustrate the theoretical relationship between the sensitivity of the screening test

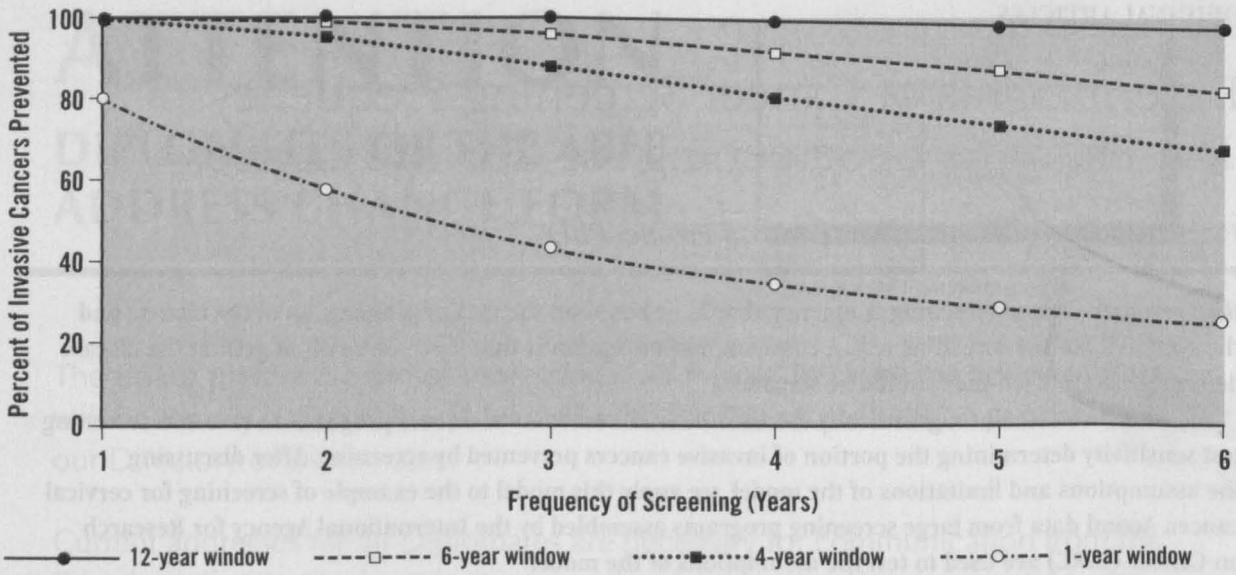

Figure 1. Relation of disease progression rate to invasive cancer prevention, assuming an 80 percent sensitive test.

and the rate of progression of the disease in determining the percentage of cases that will be detected by screening before reaching an incurable stage. The rate of progression of disease is represented by determining a detection window, defined as the period of time that the condition is amenable to detection by the screening test before it becomes potentially incurable.

For cervical cancer the detection window would be the time from the development of early dysplasia (detectable by the Papanicolaou smear) until the development of invasive cancer. For colon cancer the detection window would be the time from the development of adenomatous polyps to the occurrence of Dukes stage B cancer. For hyperlipidemia the detection window would be the time between the development of elevated cholesterol levels and the onset of significant atherosclerotic disease. A shorter detection window represents a more rapidly progressing disease. The goal of cancer screening is to detect and eradicate early precursor lesions so they do not progress and become potentially incurable invasive cancers.

Figure 1 shows the percentage of incurable cases of a hypothetical cancer that would be prevented by an 80 percent sensitive test, varying the screening frequency and length of the detection window. For example, if the detection window is 6 years and screening occurs every 6 years, 80 percent of precursors will be detected before becoming invasive cancer. (One screening test during the window with an 80 percent sensitive test will detect 80 percent of precursors) If screening is done every 3 years, two screening tests occur during the window. The first should detect 80 percent of precursors and the second should detect 80 percent of the remaining 20 percent of precursors missed by the first screening. Accordingly, 96 percent of precursors would be detected after the second screening. A third screening test during the window (screening every 2 years) would detect 80 percent of the 4 percent of precursors missed by the first two screening tests, so that 99.2 percent of precursors would be detected before the occurrence of invasive disease.

This model assumes that the sensitivity of each sequential screening test is independent of the previous screening test having occurred (each screening test detects 80 percent of remaining cases). As will be shown with actual data on cervical cancer, this assumption is not valid. As screening becomes more frequent, sensitivity can decrease. The model also assumes a constant detection window when in reality cancer progression rates are variable. In practice such variability can be dealt with by taking a conservative approach and assigning a detection window on the shorter end of the plausible range. Admitting that the model simplifies reality, it remains that sensitivity of the screening test and rate of progression of the disease are the two factors that determine the screening frequency.

Figure 2 is the converse of Figure 1; the detection window is held constant and the relation of varying the sensitivity of the screening test and the

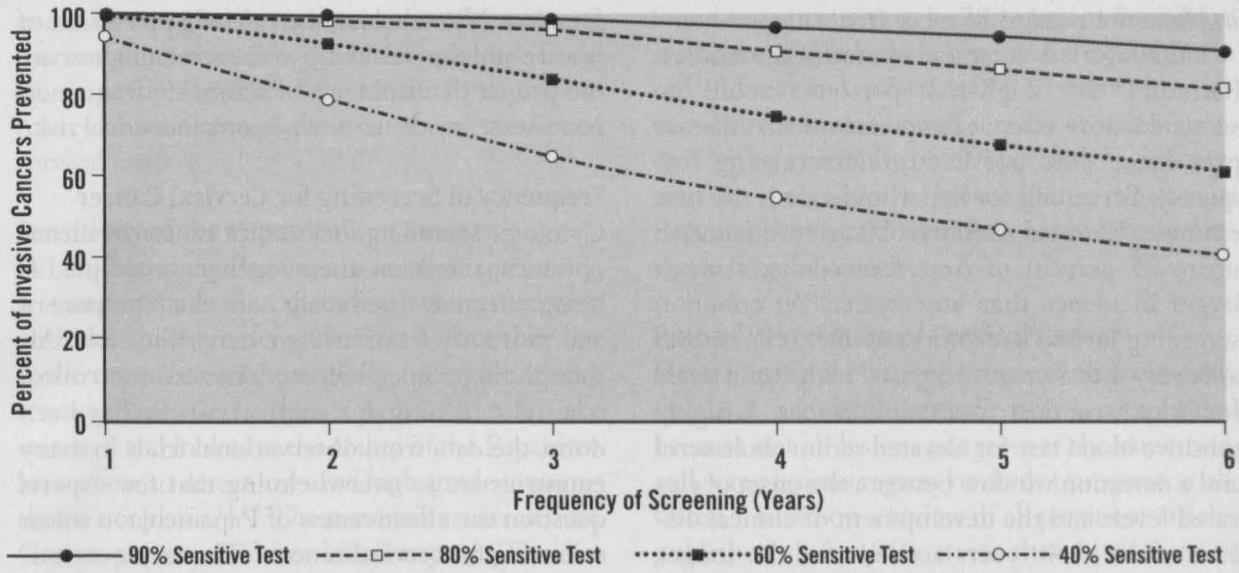

Figure 2. Relation of test sensitivity to invasive cancer prevention, assuming a 6-year detection window.

frequency of screening is shown. Logically, the greater the sensitivity of the screening test, the more precursors will be detected at any given screening frequency. For a large portion of precursors to be detected, screening must be done more often with a less sensitive test than with a highly sensitive test.

This relation between the sensitivity of the screening test, the length of the detection window, and the screening frequency determining the screening error can be expressed mathematically by the formula

$$E = (1 - S)^{W/F}$$

where E is the error or portion of precursors missed by screening, S is the sensitivity expressed as the portion of precursors detected by a single screening test, W is the length of the detection window in years, and F is the screening frequency in years. Multiplying E by 100 gives the percentage of precursors missed by screening. In the previous example of a 6-year detection window, screening every 2 years with a test sensitivity of 0.80 $E = (1 - 0.80)^{6/2}$. Therefore, $E = 0.008$, meaning 0.8 percent of precursors will be missed or 99.2 percent of precursors will be detected by screening.

If actual data are available so that E is known for various values of F, then W can be calculated for actual or assigned values of S by transposing the formula in the following manner:

$$W = \frac{F \ln E}{\ln (1 - S)}$$

W equals F times the natural log (ln) of E divided by the natural log of $(1 - S)$.

The incidence of a disease or a person's risk of acquiring a disease does not appear in this equation and should not be a determinant of how often screening occurs. In the example cited above, 99.2 percent of invasive cancers will be prevented regardless of whether the incidence of the condition is 5 per 100,000 or 500 per 100,000 population.

Disease incidence does influence the cost-effectiveness of screening and can therefore determine whether screening for a given disease is worth the cost and effort. Skin testing for tuberculosis is not currently recommended for the US general population because the incidence of tuberculosis is very low. Tuberculin testing of prison inmates is uniformly recommended because, in addition to meeting other screening criteria, the incidence of tuberculosis is very high in the prison population. Having decided to screen prisoners for tuberculosis, however, the frequency of screening should be determined by the rate of progression of the disease and the sensitivity of the screening test, not by the disease incidence.

It is true that persons at high risk for a particular disease are often the hardest to reach and the most noncompliant with screening recommendations. More intensive outreach efforts often need to be made to involve these people in the screening program and to maintain compliance, but unless the rate of progression of disease is more rapid or the screening test is less sensitive, screen-

ing does not need to be more frequent.

Although it is commonly stated in the medical literature that high-risk persons should be screened more often, examples show that disease prevalence does not determine screening frequency. Screening for hyperlipidemia is the best example. Elevated cholesterol levels are found in up to 25 percent of American adults, a much larger incidence than any cancer. Yet common screening intervals recommended for cholesterol are every 4 to 5 years compared with 1 to 3 years for breast, cervical, and colon cancer. A highly sensitive blood test for elevated serum cholesterol and a detection window between the onset of elevated levels and the development of clinical disease of 20 to 40 years account for the longer screening interval. Thus, even though hyperlipidemia is extremely common, screening does not have to be frequent.

Several caveats should be understood before trying to apply this theoretical model to actual diseases. First, the model assumes that the sensitivity of each sequential screening test is the same: if 80 percent of cases are detected on the first screening test, 80 percent of the remainder will be detected on the second, etc. This assumption is not necessarily true, especially with cancer screening. Incremental sensitivity can decrease with increasing screening frequency. Most clinicians have had experiences in which advanced cancers were diagnosed soon after one or more normal screening test results. Some of these cancers will not be detected by screening tests regardless of frequency.

Second, as will be shown in the example of cervical cancer, the true sensitivity of many screening tests can not be measured directly but must be estimated from indirect data. In addition, that sensitivity is influenced by operational factors, including collection and processing techniques, leads to uncertainty and conflicting estimates of test sensitivity. Finally, diseases do not progress at a uniform rate. Some progress more rapidly than others. Any detection window will necessarily represent an average or best guess of the rate of progression of most cases. There will be outliers on both sides of this approximation.

It is common practice for preventive recommendations to be conservative and err on the side of assigning a shorter detection window or increasing the screening frequency to allow for uncertainty about test sensitivity and disease progression. Nonetheless, the rate of progression of disease and the sensitivity of the screening test are the proper determinants of screening frequency, not disease incidence or a person's individual risk.

Frequency of Screening for Cervical Cancer

Cytologic screening for cervical cancer by means of the Papanicolaou smear is generally accepted as being effective at reducing both the incidence of and mortality from invasive cervical cancer. Although no prospective, randomized, controlled, trial of screening for cervical cancer has been done, the data from observational trials in many countries are so overwhelming that few experts question the effectiveness of Papanicolaou smear screening for cervical cancer.[5] The major controversy with regard to screening is how often Papanicolaou smears should be done.

The United States Preventive Services Task Force[1] recommended Papanicolaou smears at least every 3 years for women who have been sexually active and have a cervix. The American Cancer Society states that all women who have been sexually active should have annual Papanicolaou tests and pelvic examinations. After three or more consecutive negative smear results, the Papanicolaou smear can be performed less frequently at the discretion of the physician.[6] The American College of Physicians recommends Papanicolaou smears every 3 years between the ages of 20 and 65 years.[3] The recommendation of the American College of Obstetricians and Gynecologists is similar to that of the American Cancer Society but also states that high-risk women should be screened more frequently.[7] Many gynecologists and primary care physicians in the United States continue to recommend annual Papanicolaou smears for all women.

Although some authors, such as Knox,[8] recognized as early as 1976 that the frequency of screening should be based on the sensitivity of the screening test and the rate of progression of the disease, many authors, including Richart and Barron[9] (in 1981), Shingleton et al[5] (in 1995), and Lieu[10] (in 1996), as well as the American College of Obstetricians and Gynecologists,[7] continue to recommend that screening frequency should be based on the person's risk of cervical cancer. We propose to show that the concept of risk-based frequencies for screening for cervical cancer is flawed and that screening more frequently than

every 3 years greatly increases costs for minimal increases in prevention of invasive cancer. To do so, we need estimates of the sensitivity of the Papanicolaou smear and the rate of progression of cervical cancer.

Sensitivity of the Papanicolaou Smear

When discussing Papanicolaou smear sensitivity, it is important to note that we are concerned only with the ability to detect lesions before they become invasive and potentially incurable. Some studies have used colposcopy as the reference standard and looked at the ability of the Papanicolaou smear to detect low- and high-grade intraepithelial neoplasia.[11,12] These studies are irrelevant. Cancer precursors never killed anyone. The disease the Papanicolaou smear is designed to prevent is invasive cervical cancer. Detection of precursors, including in situ carcinoma (and even early curable invasive cancer), is a success, not a failure, of screening.

Estimates of Papanicolaou smear sensitivity have ranged from 45 to 94 percent.[5] Reasons for false-negative tests include sampling errors, laboratory errors, and the inherent limitations of the test. Eddy[13] points out that the true way to determine the false-negative rate of a test is to do the test on persons known to have the disease (ie, invasive cervical cancer) and determine the portion of patients with a negative test. Papanicolaou smear sensitivity (or other cancer-screening sensitivity) is not usually determined this way. Rather, authors tend to look at cases of invasive cancer and retrospectively ask whether normal findings were seen on a Papanicolaou smear obtained within 1 to 3 years of the diagnosis.[14]

Gay et al[15] studied false-negative results from Papanicolaou smears obtained at the Mayo Clinic between 1980 and 1983. They looked at tissue-proved cases of invasive or in-situ cervical cancer and defined a false-negative finding as a negative test result obtained within 1 year of the diagnosis of in-situ or invasive cancer. They found the Papanicolaou smear to have an 80 percent sensitivity with most errors the result of inadequate sampling.

Soost and colleagues[16] recently reviewed Papanicolaou smears processed at a central laboratory in Bavaria. Histologic examination was used to confirm positive findings, whereas negative findings were confirmed either by histologic or two subsequent negative cytologic studies. They found test sensitivity to be 78.1 percent for mild to moderate dysplasia, 81.4 percent for carcinoma in situ and severe dysplasia, and 82.3 percent for invasive carcinoma. Overall sensitivity was 80 percent with a specificity of 99.4 percent. Eighty percent is probably a reasonable estimate of Papanicolaou smear sensitivity for in-situ and invasive cervical cancer.

Rate of Progression of Cervical Cancer

Determining the rate of progression from early dysplasia to invasive cervical cancer is complicated because not all lesions progress at the same rate, and some lesions regress or do not progress at all. Ostor,[17] based on a review of all pertinent articles published since 1950, states that 43 percent of grade II cervical intraepithelial neoplasia (CIN II) lesions will regress, 35 percent will persist, 22 percent will progress to carcinoma in situ, and 5 percent will progress to invasive cancer. The important question for screening is determining, for those lesions that do progress, what is the detection window, or average time between early dysplasia and development of invasive cancer.

Direct observation of the progression of dysplasia and carcinoma in situ, if possible, would be the best way to determine the rate of progression, but histologic biopsy of the disease for confirmation often removes the disease and eliminates further progression. Observation without treatment also raises ethical concerns. In the 1960s Richart and Barron,[18] who did an observational study of dysplasia using sequential cytologic smears, found it took 7 years for the average early dysplasia to progress to in-situ carcinoma.

Studies comparing the average age of incidence cases of carcinoma in situ with the average age of incidence cases of invasive cancer have suggested an 11- to 12-year duration for in-situ cancer.[19,20]

More recently, Richart and Barron,[9] using mathematical modeling based on large-population-screening programs, estimated the mean transit time from early dysplasia to carcinoma in situ to be 5.8 years with a mean duration of carcinoma in situ of 10 years; 5 percent of cases of in-situ carcinoma progressed to invasive cancer in less than 3 years, however.

Although these estimates of Papanicolaou smear sensitivity and rate of progression of disease are associated with great uncertainty, they suggest that the Papanicolaou smear might be

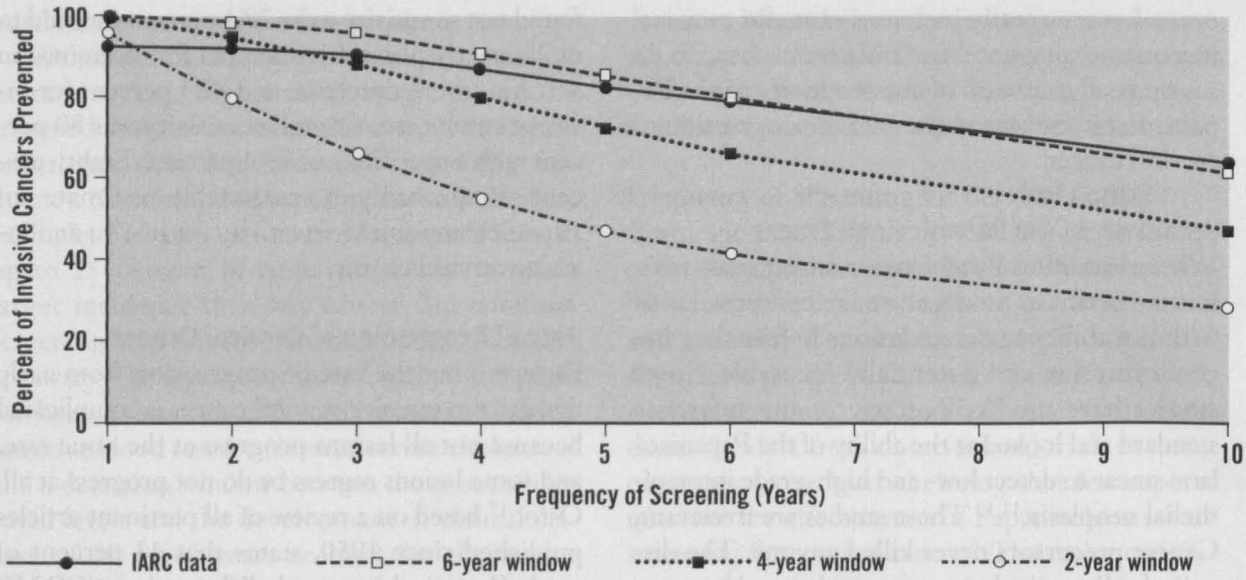

Figure 3. International Agency for Research on Cancer data compared with theoretical cervical cancer progression rats, assuming Papanicolaou smear is 80 percent sensitive.

about 80 percent sensitive for detecting lesions before invasive disease develops and that it takes on average at least 5 to 10 years to progress from early dysplasia to invasive cancer. If these estimates of sensitivity and disease progression rates are correct and the theoretical model holds true, then the curve for a 6-year window in Figure 1 should be a reasonable, conservative approximation of the percentage of cancer precursors that will be detected before they become invasive (and potentially incurable) with different screening frequencies. Screening every 3 years would detect 96 percent of cases, whereas annual screening would detect 99.9 percent of cases while incurring three times the cost.

Fortunately, it is possible to test this model using actual data. The International Agency for Research on Cancer (IARC) has assembled experimental data from large screening programs in eight countries in Europe and North America on the percentage of reduction in the incidence of invasive cervical cancer when patients are screened at different intervals.[21] The combined studies reviewed accounted for more than 1 million women who were screened. The IARC data showed that screening every year prevented 93.5 percent, every 2 years 92.5 percent, every 3 years 90.8 percent, every 5 years 83.6 percent, and every 10 years 64.1 percent of cases of invasive cervical cancer. These data can be used to test the theoretical calculations of disease prevention assuming different Papanicolaou smear sensitivities and rates of disease progression.

Figure 3 shows the IARC data superimposed on theoretical calculations of different disease progression rates assuming an 80 percent sensitive screening test (previously illustrated in Figure 1). At infrequent screening frequencies of 5 and 10 years, the IARC data are highly compatible with a 6-year detection window and an 80 percent sensitive test. At more frequent screening intervals, however, the curves diverge, and the IARC data are compatible with either a more rapid rate of progression of the disease or a decreasing screening test sensitivity.

Figure 4 shows the IARC data superimposed on a graph of different screening test sensitivities assuming a constant 6-year detection window (similar to Figure 2). Again, the IARC data are compatible with an 80 percent sensitive test and a 6-year detection window when 10- or 5-year screening intervals are used, but the incremental sensitivity of the screening test decreases dramatically with more frequent screening. With biannual screening, the IARC data suggest a 60 percent sensitivity, which decreases to 37 percent when screening is done annually.

Both the more rapid progression of disease, illustrated in Figure 3, and the decreasing test sensitivity, illustrated in Figure 4, are plausible explanations for the IARC results not being as good as predicted by the theoretical model at frequent

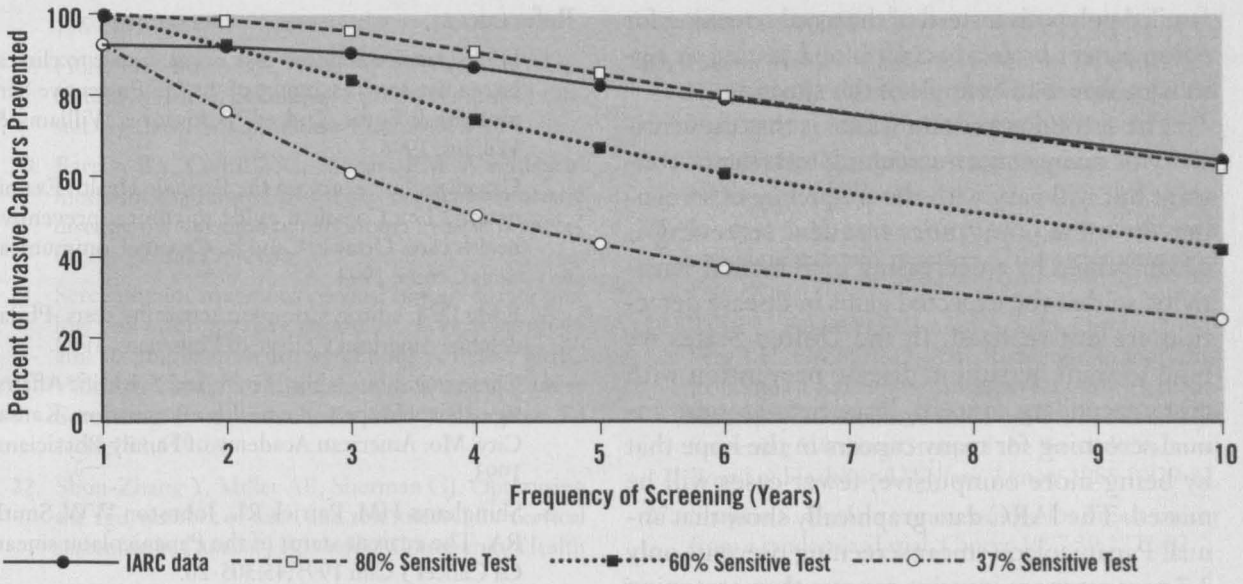

Figure 4. International Agency for Research on Cancer data compared with theoretical test sensitivity and detection rates, assuming a 6-year detection window.

screening intervals. Cancers do not all progress at the same rate. The detection window expresses an average rate of progression. It makes intuitive sense that slower growing cancers will be more likely to be detected during the first few screening tests, leaving a group of more rapidly progressing cancers undetected. Likewise, the characteristics of some cancers make them more amenable to detection by cytologic screening tests than others. Most clinicians are aware of anecdotal cases in which invasive cancer was diagnosed shortly after multiple negative findings on Papanicolaou smears. These cancers would not have been detected by Papanicolaou smear screening no matter how often screening was done. Again, it makes intuitive sense that as screening becomes more frequent, the easy cancers will have been detected, leaving a higher proportion of hard-to-detect cancers undetected. Thus the incremental sensitivity of the screening test can decrease as the screening frequency increases.

Discussion

Several important lessons can be learned from the example of cervical cancer screening that apply to screening for other cancers. First, the incidence of the disease or a person's risk of getting the disease should not influence how often screening is done. Using the IARC data, 90.8 percent of cancers will be detected by screening every 3 years, and 93.5 percent will be detected by screening every year regardless of whether a high- or low-risk population is screened. Only if the rate of progression of the disease is faster or if for some reason the screening test is less sensitive in the high-risk population should this population be screened more frequently. There has been some mention in the literature[22] that cervical cancer progresses more rapidly in younger women, and they therefore need to be screened more often. Data from the Ontario Provincial cancer registry,[23] however, and from the IARC study[21] reflect no difference in the natural history of cervical cancer between younger and older women. Interestingly, a less sensitive screening test and a more rapid progression of disease might explain why mammography screening has not been shown to be an effective screening test for breast cancer in women aged between 40 and 50 years.[23,24]

It is true that screening is more cost-effective in a high-risk or high-prevalence population in that more cases will be detected for any given number of screening tests performed. Women at high risk for cervical cancer often get sporadic medical care and are difficult to involve in a regular screening program. More intensive efforts are needed to reach these women and ensure they receive regular Papanicolaou smears, but they do not need to be screened more often. Also, for some extremely high-risk populations it might be prudent to use a completely different prevention strategy. Recommending prophylactic colectomy for patients with

familial polyposis instead of the usual screening for colon cancer by fecal occult blood testing or sigmoidoscopy is an example of this situation.

The second important lesson is that the sensitivity of many cancer-screening tests is not constant but will vary with the frequency of screening. At some point more frequent screening is accompanied by a decreasing incremental sensitivity, so that the expected gains in disease detection are not realized. In the United States we tend to want maximum disease prevention with cost a secondary concern. Physicians espouse annual screening for many cancers in the hope that by being more compulsive, fewer cases will be missed. The IARC data graphically show that annual Papanicolaou smear screening prevents only 2.7 percent more invasive cancers than screening every 3 years while tripling the cost of screening. A recent study in the author's practice[25] of screening for cervical cancer with biannual Papanicolaou smears during a 20-year period found only one case of invasive cancer that was not prevented by screening, and no woman died of cervical cancer.

Mammography screening for breast cancer should also be critically evaluated to determine the optimum screening interval. The Swedish Two-County study[26] used an average interval of 33 months between screening tests yet achieved results as good as those of the HIP study[27] and others that offered annual mammography. Because of these data the US Preventive Services Task Force recommended mammography should be offered every 1 to 2 years to women aged between 50 and 69 years. The optimum frequency for mammography screening has not been determined.

The frequency of offering a screening test should be based on the sensitivity of the screening test and the rate of progression of the disease, not on a person's risk. An ounce of prevention might be better than a pound of cure, but 2 ounces of prevention is not always better than 1.

Sutherland Frame, chairman of the Mathematics Department at Michigan State University from 1943 to 1960, was an internationally known mathematician. He was also my father. He died 2 weeks after making his invaluable contributions to this paper at the age of 89 years. Any of us would feel blessed to live such a long and creative life.

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