

- (25) Imperiale TF, Ransohoff DF, Itzkowitz SH, Turnbull BA, Ross ME. Fecal DNA versus fecal occult blood for colorectal-cancer screening in an average-risk population. *N Engl J Med* 2004;351:2704–14.
- (26) Sidransky D, Tokino T, Hamilton S, Kinzler K, Levin B, Frost P, et al. Identification of ras oncogene mutations in the stool of patients with curable colorectal tumors. *Science* 1992;256:102–5.
- (27) Ahlquist DA, Shuber AP. Stool screening for colorectal cancer: evolution from occult blood to molecular markers. *Clin Chim Acta* 2002;315:157–68.
- (28) Traverso G, Shuber A, Levin B, Johnson C, Olsson L, Schoetz DJ Jr, et al. Detection of APC mutations in fecal DNA from patients with colorectal tumors. *N Engl J Med* 2002;346:311–20.
- (29) Traverso G, Shuber A, Olsson L, Levin B, Johnson C, Hamilton SR, et al. Detection of proximal colorectal cancers through analysis of faecal DNA. *Lancet* 2002;359:403–4.
- (30) Ahlquist DA, Skoletsky JE, Boynton KA, Harrington JJ, Mahoney DW, Pierceall WE, et al. Colorectal cancer screening by detection of altered human DNA in stool: feasibility of a multitarget assay panel. *Gastroenterology* 2000;119:1219–27.
- (31) Dong SM, Traverso G, Johnson C, Geng L, Favis R, Boynton K, et al. Detecting colorectal cancer in stool with the use of multiple genetic targets. *J Natl Cancer Inst* 2001;93:858–65.
- (32) Boynton KA, Summerhayes IC, Ahlquist DA, Shuber AP. DNA integrity as a potential marker for stool-based detection of colorectal cancer. *Clin Chem* 2003;49:1058–65.

NOTES

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Prostate Specific Antigen Levels in the United States: Implications of Various Definitions for Abnormal

H. Gilbert Welch, Lisa M. Schwartz, Steven Woloshin

Background: The finding that some men with a normal prostate-specific antigen (PSA) level (i.e., less than 4 ng/mL) nonetheless have microscopic evidence of prostate cancer has led to some suggestions that the threshold defining abnormal should be lowered to 2.5 ng/mL. We examined the effect of this lower threshold on the number of American men who would be labeled abnormal by a single PSA test. **Methods:** We obtained PSA data on a nationally representative sample of American men 40 years of age and older with no history of prostate cancer and no current inflammation or infection of the prostate gland (n = 1308) from the 2001–2002 National Health and Nutrition Examination Survey. We obtained data on the 10-year risk of prostate cancer death in the pre-PSA era from DevCan, the National Cancer Institute's software to calculate the probability of dying of cancer. **Results:** Based on NHANES data, approximately 1.5 million American men aged 40 to 69 years have a PSA level over 4.0 ng/mL. Lowering the threshold to 2.5 ng/mL would label an additional 1.8 million men as abnormal, if all men were screened. For men aged 70 years or older, the corresponding numbers are 1.5 and 1.2 million. The proportion of the population affected by different thresholds would vary with age. Among men in their 60s, for example, 17% have a PSA level over 2.5 ng/mL, 5.7% have a PSA level over 4.0 ng/mL, and 1.7% have a PSA level over 10.0 ng/mL. For context, only 0.9% of men in their 60s are expected to die from prostate cancer in the next 10 years. **Conclusion:** Lowering the PSA threshold to 2.5 ng/mL would double the number of men defined as abnormal, to up to 6 million. Until there is evidence that screening is effective, increasing the number of men recommended for prostate biopsy—and the number

potentially diagnosed and treated unnecessarily—would be a mistake. [*J Natl Cancer Inst* 2005;97:1132–7]

Several studies have demonstrated that a substantial number of men have microscopic evidence of prostate cancer despite having a prostate-specific antigen (PSA) level below the standard threshold used to define abnormal, i.e., 4.0 ng/mL (1–3). These findings have led some physicians to advocate a lower PSA threshold of 2.5 ng/mL (4,5). A lower threshold inevitably means that more men would be labeled as abnormal, have a prostate biopsy, and be treated for prostate cancer. However, because clinically insignificant disease (also known as pseudodisease) is a well-known problem in prostate cancer (6), others are concerned that a lower PSA threshold will lead to more overdiagnosis and have urged caution in pursuing a diagnosis of prostate cancer in men who have a PSA level of 4.0 ng/mL or lower (7).

Although some data on the number of men who would be identified as abnormal with various PSA thresholds are available from invitational studies of prostate cancer screening (8,9), population-based data on the distribution of PSA levels among men in the United States have not been previously available.

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We use newly released data from the 2001–2002 National Health and Nutrition Examination Survey (NHANES) on the distribution of PSA levels in American men to investigate how many men would be labeled as having abnormal PSA levels if the threshold were to change.

We first determined the distribution of PSA levels for screen-eligible American men and the number of these men who would be labeled abnormal using various PSA thresholds (assuming that all such men were screened). To put these numbers in perspective, we attempted to estimate the true burden of clinically important disease using the risk of prostate cancer death.

METHODS

Distribution of PSA Levels

Data on the distribution of PSA levels for American men were obtained from the National Center for Health Statistics' most recent NHANES (2001–2002 data release). These surveys, which have been conducted periodically since the 1970s, involve household interviews and standardized medical examinations that include a variety of blood tests (10). The sampling design, data collection methods, and weighting approach of NHANES have been described elsewhere (11,12). The 2001–2002 NHANES data are based on a randomly selected, nationally representative sample of approximately 11 000 people of all ages. This survey was the first NHANES to include a PSA test for men aged 40 years or older as part of the medical examination.

Figure 1 shows the selection process recommended by NHANES that we used to identify a representative PSA screen-eligible population of men aged 40 and years or older (23). Men who had a history of prostate cancer were excluded, as were those who had an examination or condition that might spuriously elevate PSA level (i.e., prostate biopsy or cystoscopy during the previous month, rectal examination during the previous

week, or current inflammation or infection of the prostate). We also excluded men who had missing data for any of these eligibility criteria or for their PSA level. Our final sample included 1308 men.

10-year Risk of Prostate Cancer Death

Data on the risk of prostate cancer death for American men were obtained by using DevCan 5.2 software from the National Cancer Institute (13). DevCan allows users to calculate the age-specific chance of developing or dying from specific cancers for a given time frame. These probabilities are based on cancer incidence data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute, mortality data from the National Center for Health Statistics, and population estimates from the U.S. Bureau of the Census. We chose a 10-year time frame to examine the risk of dying from prostate cancer because it is an intermediate interval (i.e., somewhere between an annual and a lifetime risk) during which annual screening could plausibly affect clinical diagnosis and mortality. We obtained the 10-year risk of death due to prostate cancer for men at each year of age and then averaged these 10-year risks within each decade of life. For example, to obtain the 10-year risk of death due to prostate cancer for men in their 40s, we first determined the 10-year risk of death for men at each year of age (e.g., 10-year risk for a 40 year old, 10-year risk for a 41 year old, and so on) and then averaged the 10-year risks for men aged 40 years, men aged 41 years, and so on through men aged 49 years.

Because prostate cancer mortality has declined somewhat since the introduction of PSA screening, it is possible that some of the decline is due to PSA screening itself. If so, 10-year risks based on current mortality data would underestimate the 10-year risks expected in the absence of screening. To avoid this problem, we used prostate cancer mortality data from 1984 through 1986 (i.e., before the advent of PSA screening). In addition, because the risk data are based on the entire U.S. population (a small fraction of which already has clinically evident prostate cancer), they may actually overstate the risk of death in the screen-eligible population reported here.

Statistical Analysis

We examined results for five age groups: 40–49 years, 50–59 years, 60–69 years, 70–79 years, and 80 years or older. For each age group, we first calculated the number and proportion of men whose PSA level exceeded the following threshold values: 2.5 ng/mL, 4.0 ng/mL, 6.0 ng/mL, 8.0 ng/mL, and 10.0 ng/mL. We then compared the number of men whose PSA level exceeded each of those threshold values with the number of men who were expected to die of prostate cancer in the next 10 years without undergoing PSA testing.

To make national estimates from the NHANES sample, all analyses incorporated the sampling variable (WTMEC2YR) which weights the sample up to the 2000 census as well as accounting for differential probability of selection across subjects and nonresponse. The analyses also incorporated design effects variables (variable names: SDMVPSU and SDMVSTRA) to account for the survey's complex multistage sampling strategy when calculating 95% confidence intervals. All analyses used the SVY series of commands in STATA statistical software (version 8.0; College Station, TX).

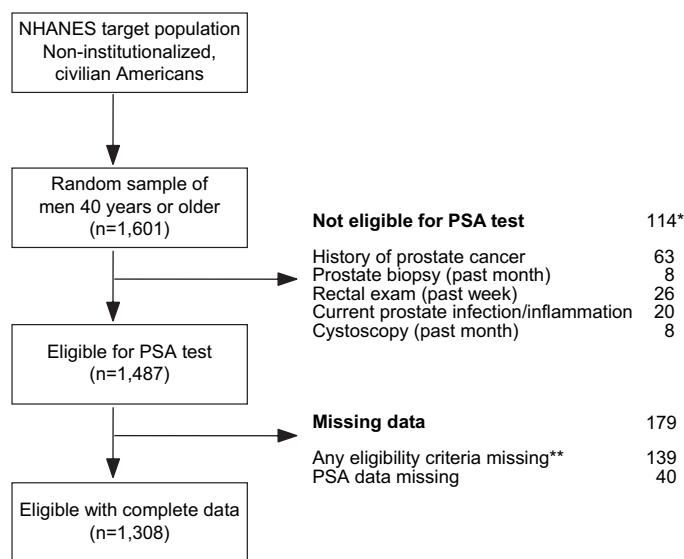


Fig. 1. Cohort selection of screen-eligible men. *Because some men were ineligible on more than one criterion, this number (114) is smaller than the sum of the five items below. **The most common reason for missing data on eligibility was that men did not attend the physician examination. PSA = prostate-specific antigen; NHANES = National Health and Nutrition Examination Survey.

RESULTS

Figure 2 illustrates the estimated distribution of PSA levels among American men in each of five age groups, and Table 1 shows the estimated number of men in the general screen-eligible population in each age group who would be labeled abnormal using various PSA thresholds if all men were screened. Among men typically thought of as being of screening age (i.e., 40–69 years old), approximately 1.5 million would have a PSA level greater than 4.0 ng/mL. Lowering the threshold to 2.5 ng/mL would label an additional 1.8 million men as abnormal. For men aged 70 years or older, the corresponding numbers are approximately 1.5 million and 1.2 million.

Table 1 also shows the number of men who are expected to die from prostate cancer. Among men aged 50–59 years, for example, approximately 35 000 are expected to die from prostate cancer in the next 10 years. This number of men contrasts sharply with the 1.5 million men aged 50–59 years who would be labeled abnormal using a PSA threshold of 2.5 ng/mL. For each age group, even at the highest PSA threshold (i.e., 10 ng/mL), considerably more men are labeled abnormal than are expected to die from the disease in the next 10 years.

Figure 3 and Table 2 illustrate the effect of PSA threshold on the proportion of screen-eligible men who, if screened, would be labeled as abnormal. For example, among men aged 50–59 years, 10.7% have a PSA level greater than 2.5 ng/mL, 5.3% have a PSA level greater than 4.0 ng/mL, and 1.6% have a PSA level greater than 10.0 ng/mL. To put these proportions in context, only 0.3% of men aged 50–59 years are expected to die from prostate cancer in the next 10 years. Among men aged 60–69 years, 17% have a PSA level greater than 2.5 ng/mL, 5.7% have a PSA level greater than 4.0 ng/mL, and 1.7% have a PSA level greater than 10.0 ng/mL, but only 0.9% of men in this age group are expected to die from prostate cancer in the next 10 years. Almost half of men age 70 years or older have a PSA level greater than 2.5 ng/mL, yet even in this age group, the 10-year risk of death from prostate cancer is less than 3%.

DISCUSSION

The PSA test was developed as an assay for an immunologic marker that corresponded well with clinical stage in patients known to have prostate cancer (14) and was subsequently found to be able to identify prostate cancer in men not known to have the disease (15). However, PSA screening was widely adopted in the United States before there was any evidence of its effectiveness in reducing prostate cancer mortality. Although many adjustments have been suggested to define abnormal (e.g., PSA density, PSA velocity, age-specific PSA norms, free PSA) (16), the PSA threshold used in the seminal article that advocated PSA screening (15)—4.0 ng/mL—remains, for practical reasons, the standard to define abnormal. This threshold value was selected not on the basis of a randomized trial but arbitrarily (2). Although there is still no evidence that screening reduces prostate cancer mortality, there are now calls (4,5) to lower the PSA threshold to 2.5 ng/mL simply because more prostate cancer would be found.

Just because a lower PSA threshold allows more prostate cancer to be detected does not mean it is a better threshold than the current one. The logic behind the call for a PSA threshold

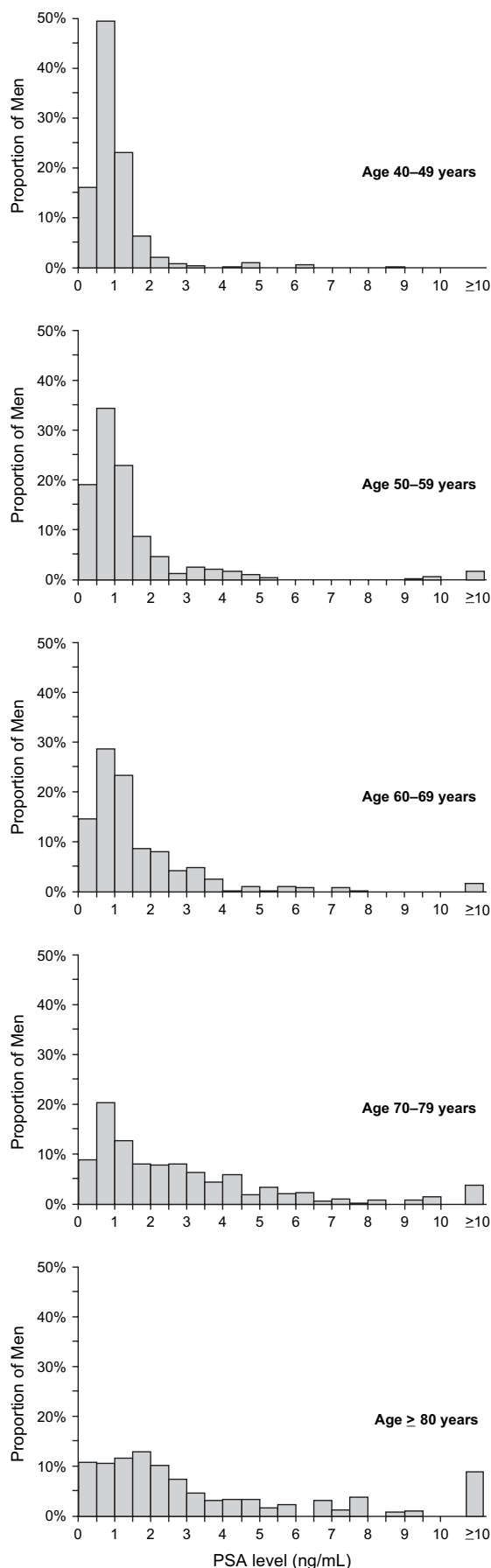


Fig. 2. Distribution of prostate-specific antigen (PSA) levels among screen-eligible American men by age group.

Table 1. Number of American men who would be labeled abnormal using three PSA thresholds*

Age group (years)	PSA>2.5 ng/mL	PSA>4 ng/mL	PSA>10 ng/mL	No. of prostate cancer deaths in next 10 years†
40–49	506 900	323 200	Insufficient sample	7000
50–59	1 523 700	747 000	232 900	34 400
60–69	1 213 800	407 300	118 600	67 200
70–79	2 019 600	1 056 000	162 000	109 500
≥80	713 800	461 700	129 500	49 200

*Total screen-eligible population is 49 million. All values rounded to the nearest 100. PSA = prostate-specific antigen.

†Calculated using age-specific death rates from 1984 through 1986 (i.e., before the introduction of PSA testing).

of 2.5 ng/mL is that there are men who have PSA levels between 2.5 and 4.0 ng/mL who have prostate cancer. But the same logic could be extended to argue that any PSA level is abnormal and that all men should have a prostate biopsy, given the finding that more than 10% of those with PSA levels less than 2.5 ng/mL nonetheless have prostate cancer (1).

There are several limitations to our analysis. Our data are only as good as our data sources. Fortunately, NHANES and DEVCAN are among the most credible nationally representative sources for information on the distribution of laboratory tests and cancer mortality. Nevertheless, both have missing data and may not be perfect estimates. In addition, the PSA data from NHANES is limited by the small number of younger men with elevated PSAs. To deal with this uncertainty, we provide confidence intervals in Table 2. Nevertheless, these data make it possible to examine the likely effect of lowering the PSA threshold.

If all men were screened using the current threshold of 4.0 ng/mL, 1.5 million American men aged 40 to 69 years would be labeled abnormal. Lowering the PSA threshold to 2.5 ng/mL would more than double this number, such that approximately

1.8 million additional men aged 40 to 69 years would be labeled abnormal and face negative consequences of the test result (i.e., biopsy or a cycle of repeated testing and anxiety as long as the uncertainty about whether or not they have prostate cancer persists). If all 1.8 million men had a biopsy, more than 1.35 million men would undergo the procedure unnecessarily (i.e., their PSA test results would be considered false positives). The remaining men, approximately 450 000, would be diagnosed with prostate cancer (1). Whether the lower PSA threshold would have any benefit on morbidity or mortality is not known, but its burden is clear. If all of these men underwent radical prostatectomy, approximately 180 000 men would be expected to be made impotent, approximately 40 000 men would be expected to have at least moderate incontinence (17), and approximately 1000 men would be expected to die from the procedure alone (18). The problem is that although it is easy to diagnose more prostate cancer, it is not easy to know who has clinically important disease.

The overdiagnosis of prostate cancer reflects the fact that the cellular abnormality that pathologists call prostate cancer is far

Fig. 3. Proportion of screen-eligible American men of different age groups who would be labeled abnormal by prostate-specific antigen (PSA) threshold.

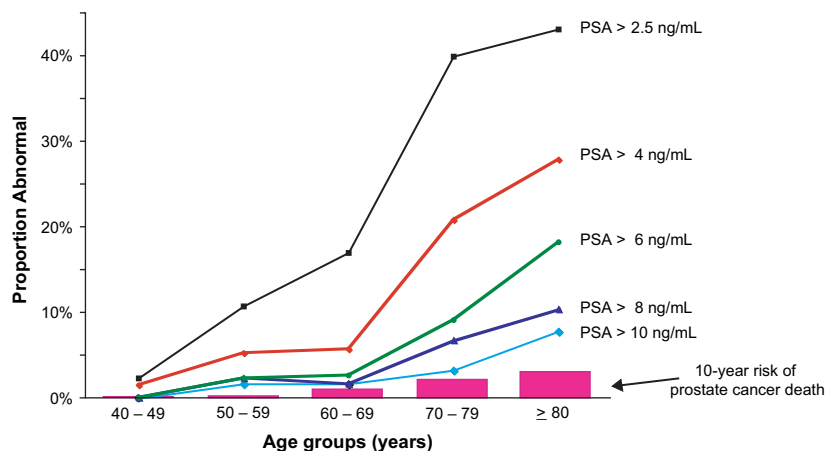


Table 2. Proportions and 95% confidence intervals for the proportion of screen-eligible American men labeled abnormal using various PSA thresholds (from 2000–2001 NHANES)*

Age group (years)	PSA>2.5 ng/mL	PSA>4 ng/mL	PSA>6 ng/mL	PSA>8 ng/mL	PSA>10 ng/mL
40–49	2.4% (1.0% to 5.5%)	1.5% (0.5% to 4.6%)	0.1% (0.01% to 0.8%)	0.1% (0.01% to 0.8%)	Insufficient sample
50–59	10.7% (6.7% to 16.7%)	5.3% (3.1% to 8.9%)	2.4% (0.9% to 6.2%)	2.4% (0.9% to 6.2%)	1.6% (0.5% to 5.1%)
60–69	17.0% (12.1% to 23.5%)	5.7% (3.8% to 8.5%)	2.7% (1.2% to 5.8%)	1.7% (0.6% to 4.8%)	1.7% (0.6% to 4.8%)
70–79	40.0% (35.1% to 45.2%)	20.9% (16.0% to 26.8%)	9.2% (5.3% to 15.3%)	6.6% (3.9% to 11.1%)	3.2% (1.1% to 8.7%)
≥80	43.1% (31.4% to 55.6%)	27.9% (18.4% to 39.8%)	18.3% (13.0% to 25.1%)	10.3% (5.9% to 17.4%)	7.8% (4.4% to 13.4%)

*PSA = prostate-specific antigen; NHANES = National Health and Nutrition Examination Survey.

too prevalent to be consistently clinically important. How much prostate cancer is found seems to be directly related to how hard it is looked for. Consider the prostate biopsy process: because generally there is no obvious lump to remove, urologists sample cells from different portions of the organ. Historically, six needle biopsy samples were taken; now, many urologists are advocating taking 12 or more biopsy samples—noting that the more samples that are taken, the more cancer is found (19). Some researchers have even advocated the use of “saturation biopsy” (a procedure involving from 32 to 38 needle biopsy samples) because this procedure has demonstrated that microscopic cancers can still be found in men who have had been cancer free on three or more prior biopsy procedures (20). Furthermore, when pathologists systematically searched the prostate glands removed from older men who were not known to have the disease, they found that at least half had microscopic evidence of prostate cancer (21).

In the absence of data on the effectiveness of screening, we believe that it would be inappropriate to select the PSA threshold simply to maximize how much prostate cancer is found. The choice of a threshold should be equally informed by how many men would be drawn unnecessarily into the process of prostate cancer diagnosis and treatment. That is, the PSA threshold should be selected to target the number of men who are expected to develop clinically important disease. In other words, given that the effectiveness of the PSA screening test is not known, the threshold selected should not result in many more men labeled abnormal than could conceivably benefit from early detection.

To apply this principle, we considered the risk of prostate cancer death over 10 years—a time period during which annual PSA screening could plausibly affect mortality. Because more than two-thirds of men diagnosed with metastatic prostate cancer in the SEER data ultimately die of the disease (22), the risk of death also captures most men who develop symptomatic metastatic disease—a group of men who certainly warrant the label of having “clinically important” disease. Using the 10-year risk of death as the standard for clinically important disease, we found that roughly 10 times more men had an abnormal PSA level using the current PSA threshold of 4.0 ng/mL than would be expected to die from the disease in the next 10 years. Our results, from a population of screen-eligible men (i.e. those without symptoms of prostate cancer), suggest that raising the threshold—perhaps to 10 ng/mL—would identify a number of men that more closely approximates the number at risk for prostate cancer death. Furthermore, because screening always has benefits and harms, it is possible that raising the PSA threshold would enhance the net effect of PSA screening by identifying the people at highest risk of clinically significant disease and thereby limiting the number of healthy people harmed. Although it is possible that a higher PSA threshold could cause some cases of clinically important disease to be missed (some of which may benefit from earlier therapy), it is incumbent on those who would argue for keeping the current PSA threshold of 4 ng/mL to demonstrate that finding such cases outweighs the inevitable harms of involving millions of men in the screening process.

We recognize that many clinicians will find the suggestion of higher PSA thresholds both radical and difficult to accept. Ideally, randomized trials that test a variety of thresholds should be performed to inform the choice of threshold. However, no such trials are in progress. In the meantime, it does not make sense to

adopt a PSA threshold that causes the number of men identified as abnormal to move yet further away from the number of men who are destined to develop clinically important disease. We believe that lowering the PSA threshold to 2.5 ng/mL would be a mistake.

REFERENCES

- (1) Thompson IM, Pauler DK, Goodman PJ, Tangen CM, Lucia MS, Parnes HL, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level ≤ 4.0 ng per milliliter. *N Engl J Med* 2004;350:2239–46.
- (2) Raaijmakers R, Blijenberg BG, Finlay JA, Rittenhouse HG, Wildhagen MF, Roobol MJ, et al. Prostate cancer detection in the prostate specific antigen range of 2.0 to 3.9 ng/ml: value of percent free prostate specific antigen on tumor detection and tumor aggressiveness. *J Urol* 2004;171:2245–9.
- (3) Catalona WJ, Smith DS, Ornstein DK. Prostate cancer detection in men with serum PSA concentrations of 2.6 to 4.0 ng/mL and benign prostate examination. Enhancement of specificity with free PSA measurements. *JAMA* 1997;277:1452–5.
- (4) Kolata G. It was medical gospel, but it wasn't true. Available at: <http://www.nytimes.com/2004/05/30/weekinreview/30kola.html>. [Last accessed: May 30, 2004.]
- (5) Szabo L. Change in prostate cancer testing urged. Available at: http://www.usatoday.com/news/health/2004-04-06-prostate-usat_x.htm. [Last accessed: April 6, 2004.]
- (6) Yao SL, Lu-Yao G. Understanding and appreciating overdiagnosis in the PSA era. *J Natl Cancer Inst* 2002;94:958–60.
- (7) Carter HB. Prostate cancers in men with low PSA levels—must we find them? *N Engl J Med* 2004;350:2292–4.
- (8) Smith DS, Catalona WJ, Herschman JD. Longitudinal screening for prostate cancer with prostate-specific antigen. *JAMA* 1996;276:1309–15.
- (9) Schroder FH, van der Maas P, Beemsterboer P, Kruger AB, Hoedemaeker R, Rietbergen J. Evaluation of the digital rectal examination as a screening test for prostate cancer. *J Natl Cancer Inst* 1998;90:1817–23.
- (10) National Health and Nutrition Examination Survey [database on the internet]. Hyattsville (MD): National Center for Health Statistics. Available at: <http://www.cdc.gov/nchs/about/major/nhanes/nhanes01-02.htm>. [Last accessed: July 1, 2005.]
- (11) NHANES Data Release. Sample Weights To Use with Particular Data Files. NHANES—National Health and Nutrition Examination Survey—NHANES 2001–2002. Available at: http://www.cdc.gov/nchs/data/nhanes/nhanes_01_02/weights_to_use.pdf. [Last accessed: July 1, 2005.]
- (12) NHANES 1999–2000 Addendum to the NHANES III Analytic Guidelines. NHANES—National Health and Nutrition Examination Survey—NHANES 2001–2002. Available at: <http://www.cdc.gov/nchs/data/nhanes/guidelines1.pdf>. [Last accessed: July 1, 2005.]
- (13) DevCan—Probability of developing or dying of cancer. National Cancer Institute. Cancer Control and Population Sciences. Statistical Research and Applications Branch. Available at: <http://srab.cancer.gov/devcan/>. [Last accessed: July 1, 2005.]
- (14) Stamey TA, Yang N, Hay AR, McNeal JE, Freiha FS, Redwine E. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. *N Engl J Med* 1987;317:909–16.
- (15) Catalona WJ, Smith DS, Ratliff TL, Dodds KM, Coplen DE, Yuan JJ, et al. Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. *N Engl J Med* 1991;324:1156–61.
- (16) Brawer MK. Prostate-specific antigen: current status. *CA Cancer J Clin* 1999;49:264–81.
- (17) Stanford JL, Feng Z, Hamilton AS, Gilliland FD, Stephenson RA, Eley JW, et al. Urinary and sexual function after radical prostatectomy for clinically localized prostate cancer: the Prostate Cancer Outcomes Study. *JAMA* 2000;283:354–60.
- (18) Ellison LM, Heaney JA, Birkmeyer JD. The effect of hospital volume on mortality and resource use after radical prostatectomy. *J Urol* 2000;163:867–9.
- (19) Arnold PM, Niemann TH, Bahnson RR. Extended sector biopsy for detection of carcinoma of the prostate. *Urol Oncol* 2001;6:91–3.

- (20) Fleshner N, Klotz L. Role of "saturation biopsy" in the detection of prostate cancer among difficult diagnostic cases. *Urology* 2002;60:93-7.
- (21) Montie JE, Wood DP, Pontes JE, Boyett JM, Levin HS. Adenocarcinoma of the prostate in cystoprostatectomy specimens removed for bladder cancer. *Cancer* 1989;63:381-5.
- (22) Surveillance Research Program. National Cancer Institute SEER*Stat software (version 5.3.0). Available at: <http://www.seer.cancer.gov/seerstat>. [Last accessed: July 1, 2005.]
- (23) NHANES 2001-2002 Data Release. Documentation for Laboratory Results. NHANES-National Health and Nutrition Examination Survey. Available at: http://www.cdc.gov/nchs/data/nhanes/nhanes_01_02/111psa_b_doc.pdf. [Last accessed: July 1, 2005.]

NOTES

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American Joint Committee on Cancer Tumor-Node-Metastasis Stage After Neoadjuvant Chemotherapy and Breast Cancer Outcome

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Background: Response to neoadjuvant chemotherapy is used as an intermediate endpoint for breast cancer relapse and survival. Most breast cancer response classification systems use pathologic complete response, either alone or in conjunction with clinical assessments, to categorize response. We examined the ability of the revised 2003 American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system, which considers both the number of involved axillary lymph nodes and the extent of tumor in the breast to predict patient survival after neoadjuvant chemotherapy for breast cancer. **Methods:** We assessed the pathologic stage of residual tumor in 132 patients with nonmetastatic breast cancer after they had undergone neoadjuvant chemotherapy and examined the association between AJCC TNM stage and subsequent distant disease-free survival and overall survival. All statistical tests were two-sided. **Results:** At a median follow-up of 5 years, pathologic stage in the surgical specimens after neoadjuvant chemotherapy using the revised AJCC system was strongly associated with both distant disease-free survival and overall survival. A higher pathologic stage of residual tumor after neoadjuvant chemotherapy was associated with a statistically significant lower rate of distant disease-free survival (stage 0: 95%, stage I: 84%, stage II: 72%, and stage III: 47%; $P_{\text{trend}} < .001$). The 5-year distant disease-free survival for patients with residual stage IIC tumors was only 18% (95% CI = 0% to 36%). **Conclusion:** Classification of residual tumor in the breast and axillary surgical specimens after neoadjuvant chemotherapy using the revised AJCC TNM system is useful for predicting distant relapse and survival. [*J Natl Cancer Inst* 2005;97:1137-42]

The extent of residual tumor after neoadjuvant chemotherapy is a well-established intermediate endpoint for breast cancer relapse and survival (1-3). Different methods have been used to categorize

residual tumor, but they generally provide only limited prognostic categories, often do not include assessments of both the primary breast tumor and axillary lymph nodes, or require both pathologic and clinical assessments. A revision of the American Joint Committee on Cancer tumor-node-metastasis (AJCC TNM) staging system was implemented in January of 2003 (4). This revision included several important modifications to the breast cancer classification system, such as a designation for response after neoadjuvant treatment and incorporation of the number of involved axillary lymph nodes into the nodal categories.

In this study, we examined the ability of the revised AJCC TNM staging system to predict patient survival after neoadjuvant chemotherapy for breast cancer.

METHODS

All breast cancer patients diagnosed with clinical stage II or III disease according to the 1988 AJCC TNM system who were treated at the University of North Carolina at Chapel Hill with neoadjuvant chemotherapy from January 1992 through December 2000 were eligible for this study. Most of these patients were treated in one of two neoadjuvant chemotherapy trials that were open during that time. In one trial, patients were treated first with

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See "Notes" following "References."

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