Adjusting for Selection Biases in Referral Populations

Paul Froom, MD, and Jack Froom, MD
Maagan Michael, Israel, and Stony Brook, New York

Current medical literature provides guidelines for acceptable medical practice. Much of this literature emanates from referral centers, where selected patients referred from primary sources are seen. Yet these research studies frequently influence physician behavior on unselected patients in primary care settings.[1]

It can be difficult to decide whether to refer an asymptomatic patient because of an abnormal test result. The prevalence of the suspected disease may be low, but if a positive finding is ignored, the consequent delay in diagnosis can have adverse consequences. Although rates,[2] reasons,[3] and even risks[4] of referral by primary care physicians have been reported, the decision process that governs these referrals is not well understood. A selection process, nevertheless, is operative with the likelihood that the referred patient population will have a greater prevalence of the suspected disease than the population of patients not selected for referral. The use of data derived from the study of selected patients to decide a course of action on unselected patients is therefore questionable.

The problem is that studies on less selected populations are often not available. Nevertheless, calculations from prevalence and morbidity and mortality data can estimate the probability of disease in patients with an abnormal finding. Such calculations can put studies on selected patients into perspective and predict the outcome of studies on less selected cohorts. In patients with an abnormal finding (ie, gallbladder stones), the maximum probability for an adverse outcome (ie, carcinoma of the gallbladder) can be calculated by dividing the number of patients with the adverse consequence by all patients with the abnormal finding.

In this report, prevalence and morbidity and mortality data are used to calculate the expected incidence of adverse outcomes in asymptomatic patients with thyroid nodules, gallbladder stones, and microhematuria. The results are contrasted with data derived from studies on selected groups of patients with the same abnormalities.

THYROID NODULES

In the past thyroid nodules were thought to represent an absolute indication for surgery because 4 to 17 percent[5] of surgical specimens revealed malignancy. In the Framingham study, however, 4 percent of the population in a nongoiterous region had nodules.[6] As the incidence of thyroid cancer is low (2 to 5/100,000/yr,[7]) the incidence of cancer in those with nodules should be no more than 1/1,000/yr (2 to 5/100,000/yr divided by 4000/100,000/yr) (Table 1). In fact, none of the 218 patients with asymptomatic nodules in the Framingham cohort developed symptomatic cancer during a ten-year follow-up period.[5]

The high rates of cancer in thyroid nodules reported previously were probably the result of the ability of the referring physician to select those at high risk for cancer.[5] That patients with asymptomatic thyroid nodules are at low risk for thyroid cancer could have been predicted given the 4 percent prevalence of the abnormal finding and the rare morbidity and mortality of thyroid cancer. Confirmation was provided by the study of unselected patients followed in a prospective longitudinal manner.

GALLBLADDER STONES

For many years it has been recommended that patients with asymptomatic gallbladder stones have them re-

Submitted, revised, March 25, 1986.

From Maagan Michael DN Menashe, Israel, and the Department of Family Medicine, State University of New York at Stony Brook, New York. Requests for reprints should be addressed to Dr. Paul Froom, Maagan Michael DN Menashe, Israel 37805.

TABLE 1. CALCULATED PROBABILITIES OF ADVERSE CONSEQUENCES FROM THYROID NODULES, GALLBLADDER STONES, AND MICROHEMATURIA IN THE GENERAL POPULATION COMPARED WITH REPORTS ON SELECTED PATIENT POPULATIONS

A Abnormality	B Prevalence of Abnormality No./100	C Adverse Consequence	D Incidence of Adverse Consequence No./100,000/yr	E* Calculated Probability of Adverse Consequence in Persons with Abnormality No./1,000/yr	F Reported Incidence of Adverse Consequence of Selected Patients with Abnormality No./1,000/yr	G** Extent of Selection Bias
Thyroid nodule	4.0	Cancer	2.0-5.0	0.5-1.3	90-240	100.0
Gallstones	7.5	Cancer	2.0	0.3	4	13.0
		Cholecystitis	30.0	4.0	25	6.3
		Death	4.5	0.06	2	3.3
Microhematuria Men aged 40 yr	5.0	Cancer of the bladder	6.0	1.0	60	60.0
Men aged 50 to 60 yr	20.0	Cancer of the bladder	23.0	1.0	60	60.0

*E = D/B
**G = F/E

moved because of the high incidence of cholecystitis (2.5 percent per year) and cancer (0.4 percent per year), and the resultant mortality of 1.2 percent per year.[8,9] The prevalence of gallbladder stones in the general population, however, has been demonstrated to be 7.5 percent in men and even higher in women.[10,11] From morbidity and mortality figures[12] it can be calculated that the incidence of complications in the general population is lower than reported from studies of patients seen at referral centers (Table 1). Although these data have been available for many years, experts have continued to recommend elective cholecystectomy in persons with asymptomatic gallbladder stones.[13] Recently a long-term follow-up study of a less selected and unreferred population found minimal morbidity and no mortality in a group of patients with asymptomatic gallbladder stones,[14] supporting conclusions based on calculations using morbidity and mortality data.

MICROHEMATURIA

Cancer of the bladder has been reported in 1.8 to 11 percent of patients referred for microhematuria.[15-18] Based on these findings, it is generally recommended that patients with microhematuria and no obvious explanation undergo cystoscopy.[19]

Asymptomatic microhematuria, however, is a common finding. In young men the prevalence of 2 to 4 red blood cells per high-power field is 5 percent,[20,21] whereas the incidence of bladder carcinoma is extremely low (Table 1).[7] The probability of significant pathology in younger men with asymptomatic microhematuria is therefore much lower than predicted by the above-mentioned studies. In a recent study of 1,000 men in the Israeli Air Force,[21] recurrent microhematuria was found in 161 men; yet only one case of bladder carcinoma developed over a seven-year follow-up period. The only case of bladder carcinoma occurred in a patient with gross hematuria, whose urinalysis just prior to diagnosis was normal.

In elderly men the increased prevalence of microhematuria with aging[22] is accompanied by an increased prevalence of urothelial malignancies.[7] Because the degree of microhematuria has been shown not to differentiate those with and without neoplasms,[15] the probability of bladder carcinoma in the elderly man with microhematuria is also low (Table 1).

CONCLUSIONS

The above examples emphasize the need for caution in regard to the generalization from studies on referred patients as well as the need for collaborative studies by groups of family physicians and other primary health care providers to provide information on a nonreferral population. Studies in primary care populations can define the prevalence of abnormalities and clarify referral practices. Follow-up studies of patients with specific abnormalities are needed to determine their natural history. Until these data are available, prevalence of abnormal findings, coupled with incidence figures of adverse consequences, can give rough estimates of the probability of adverse outcomes in primary care populations.

References

1. Gehlbach SH: Selection bias in clinical research: The land outside the tower. J Fam Pract 1985; 20:433-434
2. Geyman JP, Brown TC, Rivers K: Referrals in family practice: A comparative study by geographic region and practice setting. J Fam Pract 1976; 3:163-167
3. Brook C: Consultation and referral patterns of family physicians. J Fam Pract 1977; 4:1129-1134
4. Froom J, Feinbloom RI, Rosen MG: Risks of referral. J Fam Pract 1984; 18:623-626
5. Sokal JE: The problem of malignancy in nodular goiter recapitulation and challenge. JAMA 1959; 170:405-412
6. Vander JB, Gaston EA, Dawber TR: Significance of solitary nontoxic thyroid nodules. Preliminary report. N Engl J Med 1954; 251:970-973
7. Cutler SJ, Young JL Jr: Third national cancer survey: Incidence data. Natl Cancer Inst Monogr 1975; 41:1
8. Comfort MW, Gray HK, Wilson JM: The silent gallstone, a ten to twenty year follow-up study of 112 cases. Ann Surg 1948; 128:931-937
9. Lund J: Surgical indications in cholelithiasis, prophylactic cholecystectomy elucidated on the basis of long term follow-up on 526 nonoperated cases. Ann Surg 1960; 151:153-161
10. Wilbur RS, Bolt RJ: Incidence of gallbladder disease in "normal" men. J Gastroenterology 1959; 36:251-255
11. Bainton D, Davies GT, Evans KT, Gravelle IH: Gallbladder disease; prevalence in a South Wales industrial town. N Engl J Med 1976; 294:1147-1149
12. Vayda E: A comparison of surgical rates in Canada and England and Wales. N Engl J Med 1973; 289:1224-1229
13. Binder SC, Katz B: The benefits of surgery for asymptomatic gallstones. Am Fam Physician 1978; 18:171-173
14. Gracie WA, Ransohoff DF: The natural history of silent gallstones. N Engl J Med 1982; 307:798-800
15. Carson CC, Segura JW, Greene LF: Clinical importance of microhematuria. JAMA 1979; 241:149-150
16. Green LF, O'Shaughnessy ET, Hendricks ED: Study of five hundred patients with asymptomatic microhematuria. JAMA 1956; 161:610-613
17. Golin AL, Howard RS: Asymptomatic microscopic hematuria. J Urol 1980; 124:389-391
18. Burkholder GV, Dotin LN, Thomason KWB, Beach PD: Unexplained hematuria. JAMA 1969; 210:1729-1733
19. Maffly RH: Asymptomatic urinary abnormalities, tubulointerstitial diseases, and cystic diseases, vol 6. In Rubinstein E, Federman DD (eds): Scientific American Medicine 1985 Update. Scientific American 1985; vol 2, sect 10, pp 1-6
20. Sanders C: Clinical urine examination and incidence of microscopic hematuria in apparently normal males. Practitioner 1963; 191:192-197
21. Froom P, Ribak J. Benbassat J: Significance of microhematuria in young adults. Br Med J 1984; 288:20-22
22. Freni JC, Delderup LM, Oudegeest JJ, Sensveen N: Erythrocyturia, smoking and occupation. J Clin Pathol 1977; 30:341-344