Radon and Lung Cancer: A Cost-Effectiveness Analysis

ABSTRACT

Objectives. This study examined the cost-effectiveness of general and targeted strategies for residential radon testing and mitigation in the United States.

Methods. A decision-tree model was used to perform a cost-effectiveness analysis of preventing radonassociated deaths from lung cancer.

Results. For a radon threshold of 4 pCi/L, the estimated costs to prevent 1 lung cancer death are about \$3 million (154 lung cancer deaths prevented), or \$480 000 per life-year saved, based on universal radon screening and mitigation, and about \$2 million (104 lung cancer deaths prevented), or \$330 000 per life-year saved, if testing and mitigation are confined to geographic areas at high risk for radon exposure. For mitigation undertaken after a single screening test and after a second confirmatory test, the estimated costs are about \$920 000 and \$520 000, respectively, to prevent a lung cancer death with universal screening and \$130000 and \$80 000 per life-year for high risk screening. The numbers of preventable lung cancer deaths are 811 and 527 for universal and targeted approaches, respectively.

Conclusions. These data suggest possible alternatives to current recommendations. (Am J Public Health. 1999;89:351-357)

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Residential radon exposure has been estimated to cause 7000 to 30 000 deaths each year in the United States.1 About one third of these deaths are due to residential exposure in excess of 4 pCi/L (the recommended action level for radon mitigation in the United States) and thus are potentially preventable. In 1986 the Environmental Protection Agency (EPA) and the Department of Health and Human Services recommended radon screening for most homes in the United States, and in 1992 the recommendation was revised to include a 2-step strategy for measuring residential radon: a short-term screening measurement followed by a confirmatory measurement if the screening measurement was 4 pCi/L or greater.2,3 However, in recent years, it has been suggested that testing and mitigation recommendations should be targeted to households in geographic areas with elevated radon levels.4 Some remain unconvinced that residential radon exposure represents a major threat to the US population.⁵ Because the costs of residential radon testing and remediation are high, examining various options for lowering the risk for individual and population exposure to radon is important.

At least 11 economic analyses of radon reduction programs have been reported.^{1,4,6-14} EPA's analysis concluded that preventing a radon-associated lung cancer death would cost about \$700 000.¹ Several analyses have concluded that targeted screening programs are more cost-effective than programs aimed at all home occupants.^{12,14} Differences in assumptions and analytic design, however, make these analyses difficult to compare. In addition, most of the analyses have not incorporated medical, productivity, or program costs. Because of the inconsistency in previous economic analyses, we conducted a costeffectiveness analysis that incorporated newer data.

Methods

We developed a decision tree¹⁵ that included 5 major scenarios: (1) a no action program; (2) a universal screening program based on EPA recommendations3; (3) a targeted screening program similar to the universal program, except that it is targeted at homes in areas considered to be at risk for elevated radon levels; (4) a modified universal screening program whereby radon mitigation of a household is allowed after the completion of a single radon test; and (5) a modified targeted screening program (Figure 1). For options 2 and 3, we modeled the decision tree in accordance with EPA recommendations for radon testing and mitigation, except that the recommendation to mitigate was based on the results of 2 consecutive short-term tests' being above a certain threshold or on positive results of a confirmatory long-term test instead of the average result of two successive short-term tests. For options 4 and 5, we modified the decision tree to allow mitigation after a single positive short-term radon test. In addition to the analyses for the entire population, we also conducted separate analyses by smoking status and age. All models incorporated probabilities for compliance.

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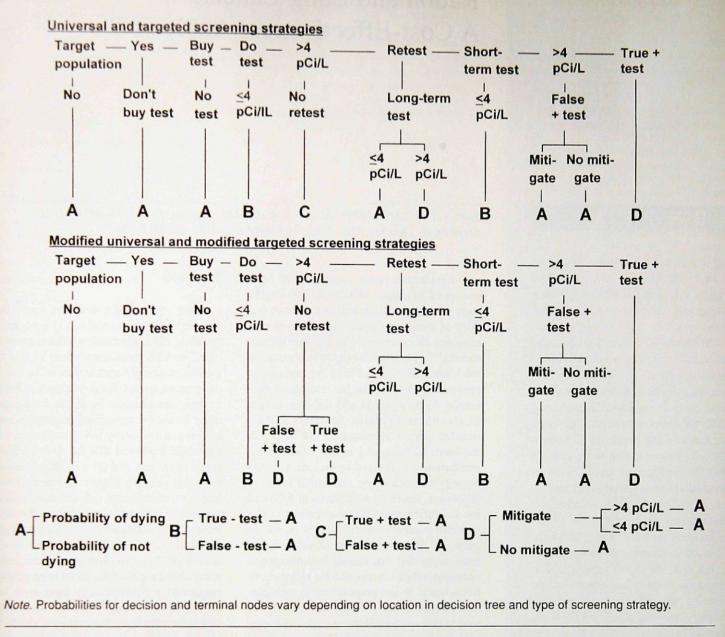


FIGURE 1—Simplified decision tree presenting various options of radon testing and mitigation.

The analysis examined the lifetime costs and effects of these approaches to reducing exposure to radon and prevention of lung cancer in a stationary population of about 250 million people whose age structure reflected the 1990 US Census. The societal approach included all costs and benefits. To facilitate modeling and comparisons of differences among strategies, we assumed a 2-year period during which an intervention would occur and decisions and actions about radon testing and mitigation would be performed and implemented.

Costs

The costs are presented in 1993 dollars and include those associated with both the intervention (program, testing, and mitigation costs) and radon-related lung cancer deaths (direct medical costs and productivity losses from lung cancer morbidity and mortality). In order to convert future costs to 1993 dollars, they were discounted 4% per year.

The universal screening program cost used in this analysis was \$18 776 000 (50% of the 5-year average of EPA funding of \$18 000 000 along with \$9 776 000 in nonfederal funds related to residential radon exposure) (F. Marcinowski, US EPA, e-mail, April 1994).¹⁶ The cost for a very intensive targeted program (\$28 500 000) was based on a community radon intervention in the Washington, DC, area¹⁷ and then applied to counties having high potential for residential radon exposure nationwide. The testing and mitigation costs used in this analysis were based on 1992 estimates adjusted to 1993 dollars.¹ The per individual costs were \$41.66 for a long-term test and \$11.66 for a short-term test. The cost of mitigation, adjusted to 1993 dollars and discounted at 4%, was \$1801.72 per person.

The total cost due to lung cancer included direct medical costs and productivity losses from lung cancer morbidity and mortality. Data were aggregated by gender. We used the weighted average of the excess medical expenditures related to lung cancer for male and female smokers of \$2554 to estimate the excess medical expenditures for radon-related lung cancer over a 3-year course of illness.¹⁸ For productivity losses from morbidity, we estimated that 9% of those with lung cancer would be 100% disabled by their disease, 20% would be 80% disabled, 40% would be 50% disabled, and 31% would be 20% disabled (M. Siegel, written communication, 1994),¹⁹ for an average productivity cost of \$12 159. We estimated that productivity losses from mortality totaled \$85 196. Thus, the average total cost of a radon-related lung cancer death used in this analysis was \$99910.

Probabilities and Risks

We estimated compliance probabilities (best estimate probabilities) for purchasing a radon test, completing the test, retesting, and mitigating (Table 1). Alternative sets of probabilities were based on either published data from a community intervention radon program in the Washington, DC, area²⁰ or the assumption of full compliance with testing and mitigation recommendations.

Using national data when available, we estimated that an average of about 1.7% of dwellings in the United States would be tested each year,^{21,22} 55.8% of people who obtained a test kit would complete the testing process,¹⁷ 3.05% of occupants of dwellings would purchase a radon test each year, 40.7% of homes would be retested,²¹ 22% of homes testing positive would be mitigated,^{21,22} and 95% of mitigation efforts would be successful.¹

We used the BEIR IV model to estimate the risk of dying from radon-associated lung cancer for the US population, assuming that the risk for exposure to 1.25 pCi/L of radon, the national mean, is equivalent to the baseline risk calculated from mortality data.²³ We calculated lung cancer and all-cause mortality rates for 1990 using national vital statistics and census data. (An appendix summarizing the lifetime risks used for the various radon thresholds is available from the first author.)

Using a 1-year alpha track detector as the referent (long-term test), we calculated that the sensitivity rates of a 2-day charcoal canister test (short-term test) were 83.1%, 84.5%, 88.2%, 74.0%, and 60.0% and that specificity rates were 71.9%, 90.9%, 96.9%, 98.0%, and 99.5% for radon thresholds of 2 pCi/L, 4 pCi/L, 8 pCi/L, 10 pCi/L, and 20 pCi/L, respectively (F. Marcinowski, US EPA, written communication, August 1994).

The prevalence of dwellings with radon levels above various thresholds for both the universal and targeted screening approaches and average radon concentrations were derived from the National Residential Radon Survey conducted in 1989/90.²⁴ Radon levels by radon risk level and by dwelling testing criteria were also calculated.

We based the universal screening option on the 1990 Census estimate of 100 480 000

	Best Estimate	Doyle et al.17	Full Compliance
Being a member of the target population	0.83	0.83	0.83
Purchasing short-term test	0.0305	0.065	1.0
Using short-term test if purchased	0.558	0.558	1.0
Probability of retesting	0.407	0.071	1.0
Purchasing a short-term test for retest	0.91	0.91	0.91
Using long-term test if purchased	0.558	0.558	1.0
Mitigating	0.22	0.25	1.0
Postmitigation radon test >4 pCi/L	0.05	0.05	0.05

dwellings with a population of 248 710 000.¹ For the targeted approach, we used a recent map, assigning each county to 1 of 3 zones of radon exposure.²⁵ Approximately 25.9 million homes with a population of about 71 million people are located in the high risk (zone 1) counties.

We calculated smoking-specific estimates of lifetime risk for lung cancer death^{26,27} using relative risks from the American Cancer Society's Cancer Prevention Study^{28,29} and agespecific estimates of smoking prevalence from the 1990 National Health Interview Survey Health Promotion and Disease Prevention Supplement.³⁰ In calculating the radon-associated risk for lung cancer, we used models that assumed that radon and smoking risks were multiplicative. A submultiplicative model is available from the authors.³¹

Sensitivity analyses examined the impact of the possible ranges of probability estimates and costs on the cost-effectiveness estimates. Lower and upper bound limits of sensitivity parameters were derived from either published literature or various reports. Upper bound limits for behavioral probabilities reflected full compliance. We calculated the incremental costs associated with lowering incrementally the radon action threshold from 20 pCi/L to 2 pCi/L and the incremental costs for switching from one scenario to another. Because costs were discounted to reflect the time preference for money, deaths from lung cancer were also discounted at 4%.

Results

No Program

Almost 13.5 million people would be expected to die from lung cancer in a cohort of 250 million people over the lifetime of the cohort.

Universal Screening

Using best estimate probabilities, the lowest cost-effectiveness ratio is achieved at the 4 pCi/L threshold (Table 2). We estimate that it would cost about \$3 million to prevent 1 death from radon-associated lung cancer, or about \$480 000 per life-year (Table 2). About 154 lung cancer deaths would be prevented during the lifetime of the population, estimated to be about 75 years. Using probabilities from the Washington, DC, study,¹⁷ we estimate that it would cost about \$9.4 million to prevent 1 lung cancer death and that 65 lung cancer deaths would be prevented. If all home occupants could be convinced to comply with current recommendations, the model shows that about 182 000 deaths could be prevented at a savings of about \$91 000 each.

Targeted Screening

The most cost-effective ratios are achieved at the 4 pCi/L threshold; about 104 lung cancer deaths would be prevented at a cost of about \$2 million for each death, or about \$330 000 per life-year. In comparison, use of the Washington, DC, compliance results¹⁷ suggests that about 49 lung cancer deaths would be prevented at a cost of about \$4.9 million each. Using the full compliance scenario, about 122 000 deaths would be preventable at a cost of about \$35 000 each at the 4 pCi/L threshold.

Modified Universal Screening

In this scenario, in which occupants could mitigate after a single positive radon test, about 811 lung cancer deaths would be prevented at a cost of about \$920000 each, or about \$130000 per life-year, according to best estimate probabilities for the 4 pCi/L threshold. However, the best cost-effectiveness estimates are achieved for the 8 pCi/L threshold. Use of compliance estimates from the Washington, DC, study¹⁷ leads to a cost-effectiveness estimate of \$710000 and 2042 lung cancer deaths prevented. Using full compliance probabilities, the model yields results identical to those for the universal screening option.

Modified Targeted Screening

This scenario predicts that 527 lung cancer deaths would be prevented at a cost

TABLE 2—Summary Results of Cost-Effectiveness Analysis of Radon and Lung Cancer Deaths Using Best Estimate Probabilities

	2 pCi/L	4 pCi/L	8 pCi/L	10 pCi/L	20 pCi/L
No. of lung cancer deaths averted					Contraction of the second
Universal screening	292	154	70	00	teo firkithinaid
Targeted screening	152	104	70 55	32	4
Modified universal screening	1048	811		24	1
Modified targeted screening	546	527	528	349	105
		527	316	181	10
Cost per lung cancer death prevented, inc	cluding				
medical costs and productivity losses,					
Universal screening	3 050 000	3 030 000	4 420 000	9 100 000	68 440 000
Targeted screening	2 500 000	2 040 000	2 220 000	4 430 000	148 670 000
Modified universal screening	1 660 000	920 000	600 000	790 000	2 550 000
Modified targeted screening	1 180 000	520 000	300 000	460 000	9 470 000
Cost per lung cancer death prevented, ex	cludina				
medical costs and productivity losses,	\$				
Universal screening	3 360 000	3 340 000	4 720 000	9 410 000	00 740 000
Targeted screening	2 800 000	2 340 000	2 530 000	4 740 000	68 740 000
Modified universal screening	1 970 000	1 230 000	910 000		148 980 000
Modified targeted screening	1 490 000	830 000	610 000	1 100 000	2 850 000
	1 400 000	030 000	610 000	770 000	9 780 000
Cost per life-year, \$					
Universal screening	700 000	480 000	690 000	1 440 000	1 380 000
Targeted screening	570 000	330 000	360 000	730 000	580 000
Modified universal screening	380 000	130 000	110 000	150 000	500 000
Modified targeted screening	220 000	80 000	70 000	100 000	2 410 000

of about \$520000 each, or about \$80000 per life-year, for the 4 pCi/L threshold. On the basis of compliance estimates from the Washington, DC, study,¹⁷ we estimated that it would cost \$320000 to prevent a death from lung cancer and that 1317 deaths would be prevented. Assuming full compliance, the results are similar to the targeted screening option. Potential savings are achieved at thresholds of 8 and 10 pCi/L.

Smoking

Using the universal screening scenario, best estimates of the probabilities, and a multiplicative model, we found that performing an intervention in the homes of smokers was more cost-effective than performing one in the home of someone who had never smoked (Table 3). The same pattern held for the other scenarios, but the cost-effectiveness estimates differed. Although the estimates for former, light, and heavy smokers remained relatively unchanged when a submultiplicative approach was used (data not shown), the cost-effectiveness estimate for lifetime nonsmokers was substantially lessened. Nevertheless, even under this approach to calculating cost-effectiveness estimates, it remains more costly to prevent a lung cancer death among never smokers than among people who have ever smoked.

Age

From the first decade through the fourth decade of life, the cost-effectiveness estimates for the universal and targeted scenarios decrease, after which they progressively increase with increasing age (particularly after age 79). For the third through sixth decades of life, the cost-effectiveness estimates are less than \$2 million to prevent a lung cancer death for the universal scenario and less still for the targeted scenario.

Sensitivity Analyses

For the universal scenario, increasing the probability of retesting for the presence of elevated radon levels, the probability of mitigating, or the probability of successfully mitigating improved the cost-effectiveness estimates (Table 4). In addition, maximizing the probabilities of completing 2 radon tests together reduced the cost-effectiveness estimate. Increasing the costs associated with lung cancer also led to a lowering of the cost-effectiveness estimates. Changes in these probabilities substantially affected the number of lung cancer deaths prevented as well. Whereas increasing the probability of purchasing a radon test did not greatly affect the cost-effectiveness

TABLE 3-Cost-Effectiveness Analysis, Stratified by Smoking Status, for Radon Threshold of 4 pCi/L

	Universal Screening	Targeted Screening	Modified Universal Screening	Modified Targeted Screening
No. of lung cancer deaths prevented		San Start Start	ready of shores	and a statistical and
Never smoked	16	11	90	58
Former smoker	46	33	255	165
Light smoker	58	41	322	209
Heavy smoker	25	18	142	92
Cost per lung cancer death prevented, \$				
Never smoked	15 750 000	10 310 000	5 240 000	3 440 000
Former smoker	2 470 000	1 530 000	650 000	340 000
Light smoker	1 450 000	850 000	300 000	100 000
Heavy smoker	870 000	470 000	100 000	30 000

TABLE 4—Sensitivity of Cost-Effectiveness Estimates and Number of Lung Cancer Deaths Prevented to Varying Probabilities Using 4 pCI/L Threshold

	Value	Universal Best Estimate		Modified Universal Best Estimate	
		Cost-Effectiveness, \$ per Lung Cancer Death Prevented	No. of Deaths	Cost-Effectiveness, \$ per Lung Cancer Death Prevented	No. of Deaths
Base scenario	Best estimate	3 031 176	154	919 577	811
Purchasing STT	0.0305 → 0.27	2 785 072	1 368	872 717	7183
Processing STT	0.558 → 1	2 231 014	277	767 223	1454
Processing second STT	0.558 → 1	2 311 229	264	970 998	921
Processing LTT	0.558 → 1	2 800 207	167	1 006 266	671
Processing STT, second STT, LTT	0.558 → 1	1 758 335	496	896 436	1399
Retesting	0.407 → 0.071	11 598 330	27	780 154	843
	0.407 → 1	1 957 656	380	1 194 295	755
Mitigating	0.22 → 0.13	5 320 681	91	1 355 508	479
	0.22 → 0.64	860 916	449	506 350	2360
Postmitigation >4 pCi/L	0.05 → 0.40	4 954 928	98	1 567 204	531
Cost of lung cancer, \$	99 910 → 49 955	3 184 918	154	1 073 319	811
	99 910 → 199 820	2 723 692	154	612 092	811

estimate, it did result in a large increase in the number of lung cancer deaths that could be prevented. However, in no case was more than a fraction of the theoretical number of preventable deaths achieved.

The results from the sensitivity analyses were generally similar for the modified universal scenario. The biggest departure was that decreases in the probability of retesting resulted in decreases in the cost-effectiveness estimate and in the number of lung cancer deaths that could be prevented. The choice of a discount rate can strongly influence costeffectiveness estimates; these estimates were \$1.8 million for the universal scenario and \$1.4 million for the targeted strategy at a 0% discount rate and \$4.8 million for the universal scenario and \$3.3 million for the targeted strategy at a 7% discount rate.

Incremental Cost-Effectiveness Analysis

Incremental costs increased as the radon threshold was lowered from 20 pCi/L to 2 pCi/L, and especially when the threshold was lowered from 4 pCi/L to 2 pCi/L (Table 5).

Depending on the radon threshold, either the targeted or modified targeted scenario had the lowest total cost, and either the universal or modified universal scenario had the highest total cost. At 4 pCi/L, the incremental costs were \$150 000 for moving from a targeted to a modified targeted scenario and \$1.66 million for moving from a modified targeted to a modified universal scenario.

Discussion

The issue of radon testing and mitigation has been contentious owing to the potentially high costs that would be borne by homeowners and to the lingering controversy over the magnitude of the risks from residential radon exposure. Assuming that excessive exposure to radon elevates the risk of dying of lung cancer, how best to implement a radon testing and mitigation program becomes an important consideration. The differences in cost-effectiveness among models raise the question of model superiority. The universal model using the best estimate of probabilities suggests that only about 4000 homes would be mitigated annually, whereas the modified universal model suggests that about 45 000 homes would be mitigated annually. The latter is more consistent with results from the first

From Lung Cancer No. of Lung Cancer Radon Level, pCi/L **Deaths Prevented** Total Cost, \$ Incremental Cost, \$ Universal screening 2 95 289 520 000 3 070 000 4 50 152 170 000 1 880 000 8 23 100 830 000 540 000 10 10 94 040 000 340 000 20 1 90 940 000 . . . Modified universal screening 2 340 566 030 000 4 210 000 4 264 242 450 000 1 510 000 8 171 103 090 000 220 000 10 113 90 100 000 40 000 20 34 86 930 000 . . . Targeted screening 2 49 123 200 000 3 490 000 4 34 68 640 000 1 830 000 8 18 39 490 000 490 000 10 8 34 600 000 260 000 20 0 32 620 000 . . . Modified targeted screening 2 177 209 190 000 19 348 712 4 171 89 030 000 850 000 8 103 31 000 000 90 000 10 59 26 990 000 -50 000 20 3 29 660 000

TABLE 5—Incremental Cost Analysis for Preventing Radon-Associated Deaths

Note. Lung cancer deaths were discounted and rounded. Costs were rounded to nearest \$10 000.

and second Radon Risk Communication Studies of the Conference of Radiation Control Program Directors. Consequently, many people may mitigate on the basis of a single radon test, although only limited data support this possibility.³²

We explored three possibilities for focusing radon screening efforts: screening all homes vs screening homes in geographically defined high radon risk areas, screening homes of smokers vs those of nonsmokers, and screening homes of all age groups vs those of selected age groups. When best estimates of compliance are used, a geographical approach aimed at screening about one third of the country with predicted elevated radon levels produces more favorable costeffectiveness estimates than do universal approaches. In addition, targeted approaches prevent about 50% to 80% the number of predicted lung cancer deaths of comparable universal approaches, because the positive predictive value of the test is substantially improved in a setting where a higher prevalence of dwellings contain radon levels above a particular threshold.

Most lung cancer deaths from radon exposure occur among current and former smokers.¹⁰ In a multiplicative model about 10% of radon-associated lung cancer deaths would occur among nonsmokers, while in a submultiplicative assumption about 30% of these deaths would be predicted to occur among nonsmokers.³¹ As a result, the costeffectiveness estimate for nonsmokers under a submultiplicative model is substantially lower than under a multiplicative model. Nevertheless, preventing lung cancer deaths among nonsmokers is still more expensive than preventing such deaths among smokers.

The age-specific analysis suggests that few lives would be saved (at increasingly high costs) from testing and mitigating radon from homes inhabited only by people more than 70 years of age because of the declining remaining lifetime risk for lung cancer among people of advanced age. Although partitioning the total housing stock according to the age distribution may have introduced some error into the analyses, it is unlikely to have affected the results in a significant way.

Using the Finnish radon distribution, Castren suggested that cost-effectiveness decreased as the action level was raised but increased when estimates were based on a theoretical radon distribution.⁷ Both the EPA and the Department of Energy analyses produced a shallow U-shaped curve with the lowest cost-effectiveness ratios at 8 pCi/L and 10 pCi/L, respectively.^{1,11} Our analysis suggests that, depending on the scenario, either 4 or 8 pCi/L is a reasonable threshold. Sensitivity analyses show the large improvements in cost-effectiveness that could be achieved if adherence to existing recommendations were increased. Costeffectiveness can be improved by increasing the proportion of people who would retest their homes and mitigate if necessary. To prevent the maximum number of lung cancer deaths, compliance with all of the recommendations needs to be maximized. Similar conclusions were reached by Bierma.⁸

A number of methodological limitations must be borne in mind when evaluating these data. Because data for many of the variables were sparse, frequently dated, and of questionable generalizability, we often modeled data from national surveys. We also used probabilities for decision nodes that were based on probabilities for 4 pCi/L in estimating the cost-effectiveness estimates for other radon thresholds. Risk estimates were based on formulas developed from mining studies. Extrapolation of these data to the residential environment is uncertain.33,34 Because the total lung cancer and all-cause mortality rates were disaggregated on the basis of summary relative risk and prevalence estimates, some error may have been introduced into the resulting estimates. The average radon exposures for each terminal node were also estimates. For example, for people who failed to mitigate sufficiently, we assigned (using data from the National Residential Radon Survey) the average level of radon exposure that was above the action threshold for the entire population that tested above that threshold. If, in fact, mitigation had had some effect, but not enough to lower the reading below the action level, we would have underestimated the number of deaths that would have been prevented. Different techniques to model the relationship between short-term and longer term radon measurements are possible.

Recent research has demonstrated that residential mobility has a significant impact on cumulative lifetime exposure to radon and on an individual's risk for lung cancer.³⁶ Our model does not include mobility. However, assumptions about the population's risk remain unchanged. Modeling a dynamic population is likely to produce different costeffectiveness estimates.

Our analysis, as well as those by others, did not factor in potential benefits, such as delayed onset of lung cancer, prevention of nonfatal lung cancer, and benefits to future generations from modifications of existing housing units, that would result in more favorable cost-effectiveness ratios. Furthermore, the present analysis did not attempt to examine the impact of construction guidelines for new homes. Our assumption that preventable lung cancer deaths would be equally spaced in time, starting at a certain age, is likely to have underestimated costeffectiveness estimates. In addition, the cost estimated for the targeted program was based on an intensive program in Washington, DC, and may have overestimated the true costs of an effective targeted program. However, an overestimation of these costs would have tended to narrow the differences in cost-effectiveness estimates between universal and targeted programs, making the findings of our analysis even more robust.

In conclusion, more cost-effective residential radon mitigation programs can be developed by focusing on geographically defined areas where the risk of exposure to elevated levels of radon is high. Our analysis shows that it is more cost-effective to prevent radon-associated lung cancer deaths among people who smoke; from a public health perspective, however, helping smokers to quit smoking is obviously more desirable. Smoking cessation programs are more costeffective.37-39 Substantial improvements in compliance are needed to maximize the number of lung cancer deaths that can be prevented. Experience has shown that actual compliance with recommendations falls far short of expectations, ^{21,22,40} and increasing compliance may prove a difficult task. Therefore, examination of regulatory and behavioral options is needed. In addition, our analysis underscores the need for more current data on most of the decision nodes that we modeled in our decision tree. Finally, new cost-effectiveness estimates may need to be developed when additional data from residential case-control studies of radon exposure and lung cancer become available.

Contributors

E. S. Ford took the lead in performing the analyses and writing the paper. A. E. Kelly assisted with the analyses and the writing of the paper. S. M. Teutsch supervised data analysis and contributed to the writing of the paper. S. B. Thacker was instrumental in the conception of the paper and contributed to the writing of the paper. P. L. Garbe contributed to the writing of the paper. All authors are guarantors for the integrity of the research.

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