Letters to the Editor

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Computation of Odds Ratios Relative to a Fixed Nonexposed Reference Category: Does It Make a Difference?

To the Editor: The general principle in epidemiologic research on relations between exposure and health effects is to estimate disease rate ratios for an exposed category relative to a nonexposed one (eg, smokers vs nonsmokers). It may be imprudent to apply this principle unrestricted to case-control studies on the relationship between cancer (or any other disease) and occupation. A key question in such studies is how to put together a nonexposed group that can serve as a reference category comparable in any other respect to certain specific occupational categories. Although this is frequently done, it is conceptually incorrect to compare one particular occupation with all other occupations combined (eg, farmers vs nonfarmers; metalworkers vs nonmetalworkers), inasmuch as this approach results in the use of a shifting reference category that might include one or more occupations with an excess risk.[1–2] Such analysis will generally lead to an underestimation of effect.[2] Besides, because the number of subjects in the nonexposure category is not stable, the odds ratios computed for specific occupations are, strictly speaking, mutually incomparable. An alternative approach is to define a reference group as consisting of subjects who were likely to have little or no occupational exposure to carcinogens.[2] Brownson et al. selected in this way a reference group of "low-risk occupations" including professionals, managers, salesmen, and clerical workers.[3] In the analysis, specific occupations were compared with this "low-risk" group to avoid the bias mentioned above. However, this approach suffers from the handicap that it is not feasible to take all possibly risky exposures into account; some occupational risks might still be unknown. For instance, the relationship between occupational physical activity and cancer has received little attention.[4]

Besides, it must be borne in mind that some occupations may be allied with potential risk factors in lifestyle, eg, dietary habits, smoking, consumption of alcohol or drugs. It is possible, therefore, that subjects who are classified as "occupationally low-exposed" still have an excess risk pertinent to the disease under study owing to a higher exposure to lifestyle related risk factors. When one is unable to correct for these factors, use of a "low-exposure" group may lead to an underestimation of effects.

If one concludes that it is not so easy to specify a really "low-exposure" category, it might be preferable to choose an approach in which a "no excess" group is used as fixed reference category. "No excess" occupations can be empirically defined as those for which an odds ratio of about 1 is found in a first analysis of the data set, comparing each occupation with the complementary group of subjects. Obviously, it is arbitrary what is "about 1"; between 0.80 and 1.25 might be a proper choice.

To evaluate the approaches mentioned odds ratios have been calculated in three ways: relative to all others (Table 1, first column), relative to "low-risk occupations" (middle column) and relative to "no-excess occupations" (last column). The analyzed data have been borrowed from a study of ours, in which 345 patients with prostate cancer and 1346 control subjects completed a mailed questionnaire on occupational history (Van der Gulden JWJ, Kolk JJ, Verbeek ALM. Work environment and prostate cancer risk. Prostate [accepted for publication]). Seven occupations were defined as "low-exposed," according to the criteria of Brownson et al.[3] and nine as "no-excess occupations." It is noteworthy that only two occupations were to be classed both in the "low-exposed" and "no-excess" categories.

At first sight it is amazing to observe that the three (or two) odds ratios estimated for specific occupations are almost the same, although computed in different ways. On closer examination the small differences between the odds ratios in the last two columns of Table 1 can be explained by the fact that very similar proportions of cases and controls were assigned to the reference category in both the "low-exposed" approach and in the "no-excess" analysis. Thirty-three percent of the cases and 34% of the controls were classified as "low-exposed." The "no-excess" group consisted—by definition—of comparable proportions of the cases (28%) and controls (27%). The ratio between the denominator of the odds of exposure among the cases and that among the controls is therefore about the same in both approaches. So the numerators (the numbers of cases and controls who held a specific occupation) determine the magnitude of the odds ratios. That the odds ratios in the first column do not differ much from those calculated relative to a nonexposure category can be explained in

TABLE 1
Age-Adjusted Odds Ratios and 95% Confidence Intervals for Prostate Cancer According to Occupation

Occupation	Cases	Referents	Relative to All Other Occupations		Relative to "Low-Risk" Occupations		Relative to "No-Excess" Occupations	
			OR*	95%CI	OR	95%CI	OR	95%CI
Farmer	30	129	0.75	0.49–1.14	0.74	0.47–1.18	0.72	0.45–1.16
Farmworker	6	9	2.51	0.87–7.19	2.43	0.83–7.10	2.35	0.81–6.88
Baker	6	18	1.20	0.47–3.07	1.16	0.44–3.02	No excess	
Butcher	6	14	1.80	0.68–4.78	1.77	0.66–4.76	1.70	0.63–4.59
Carpenter	15	39	1.42	0.76–2.63	1.34	0.70–2.57	1.30	0.68–2.51
Woodworker	6	21	1.05	0.42–2.65	1.03	0.40–2.65	No excess	
Printer	4	14	1.10	0.36–3.39	1.08	0.34–3.38	No excess	
Painter	4	28	0.55	0.19–1.58	0.54	0.19–1.58	0.52	0.18–1.54
Electrician	7	26	1.00	0.43–2.35	0.97	0.41–2.33	No excess	
Metalworker	22	69	1.39	0.84–2.29	1.36	0.80–2.31	1.31	0.76–2.24
Mechanic	11	40	1.22	0.61–2.43	1.21	0.59–2.47	No excess	
Welder	4	12	1.54	0.49–4.84	1.55	0.48–4.96	1.48	0.46–4.77
Construction worker	11	52	0.85	0.44–1.66	0.85	0.42–1.69	No excess	
Production worker	16	51	1.27	0.71–2.27	1.24	0.68–2.28	1.20	0.65–2.22
Driver	5	37	0.54	0.21–1.39	0.54	0.21–1.41	0.52	0.20–1.37
Hotel and catering worker	5	15	1.21	0.43–3.41	1.17	0.41–3.37	No excess	
Military man	11	33	1.36	0.68–2.75	1.33	0.65–2.75	1.29	0.62–2.66
Tradesman	13	71	0.70	0.38–1.29	Low exposure		0.68	0.36–1.28
Manager	39	160	1.02	0.70–1.49	Low exposure		No excess	
Clerical worker	10	55	0.69	0.35–1.38	Low exposure		0.66	0.32–1.36
Bookkeeper	16	33	2.23	1.20–4.13	Low exposure		2.08	1.09–3.98
Civil servant	14	40	1.40	0.75–2.61	Low exposure		1.31	0.68–2.53
Teacher	15	74	0.79	0.44–1.40	Low exposure		0.75	0.40–1.38
Priest/clergyman	7	20	1.23	0.51–2.96	Low exposure		No excess	

* OR, *odds ratio.*

the same way. Because the numbers of subjects with a particular occupation are small in proportion to the total number of subjects, the percentages of cases and controls who held other occupations are comparable as well. For example, 91% of the cases and 90% of the controls were classified as "nonfarmer."

From the above, no definite conclusions can be drawn. Somewhat larger differences might have been found, had some other data set been analyzed in this way. Besides, it was not possible to assess whether larger differences would crop up in odds ratios of about 3 or 4, or even larger, for lack of such large odds ratios in our data. However, considering the small differences between the odds ratios computed in these various ways, we are tempted to conclude that there is little advantage in estimating odds ratios relative to a fixed nonexposure category of occupations.

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Why Are the Occupational and Smoking Risks for Bladder Cancer Not Confounded? An Epidemiologic Puzzle

To the Editor: Exposure to a variety of chemicals, metals, and solvents is a risk factor for bladder cancer. Smoking is highly correlated in the general population with job classifications likely to involve such exposure.[1] Smoking is especially heavy among dye workers and among chemical, aluminum, and petroleum workers exposed to aromatic amines, of whom as many as 60% to 70% smoke.[2] Therefore, there is a strong possibility of confounding between smoking and occupational exposure related to bladder cancer. Any comparison of groups differing by occupation also compares individuals differing by smoking. In a similar way, any comparison of groups differing in smoking habits also compares individuals who differ in their