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Special Contribution

Basic Epidemiology
—Methods and Their Application to Epidemiology on Cancer and Radiation (5)

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7. Confounding in radiation epidemiology

Confounding can be caused even if radiation dose is not linearly related to the prevalence of a confounder. The prevalence of the confounder in the lowest (or highest) dose category may have a large effect on the risk estimate when the population size of that dose group is relatively large. In order to illustrate the importance of lowest/highest dose group in ERR estimation, let us consider an example of a cohort study where cancer incidence was examined in relation to radiation dose. Data are shown in Table 20. Here, dose-category specific mean doses and the numbers of cancer cases (Example 1) are those taken from INWORKS[56]. The expected numbers of cancer cases are those calculated using the data shown in a paper reporting the results of INWORKS. Values are rounded for the sake of simplicity. Using the data shown in this table, ERRs were estimated assuming ERR is proportional to radiation dose. The ERR obtained from Example 1 was 0.050 per 100 mGy (90% CI=0.027, 0.074). However, if the cancer cases in the lowest dose category is increased by 5% (Example 2), the ERR became 0.028 per 100 mGy (90% CI=0.006, 0.051). In other words, a 5% increase of cancer incidence in the lowest dose category reduced the ERR per dose by 44%.

Table 21 presents a more simplified example. In Example 2 in this table, the number of cancer cases in the lowest dose category is increased by 5% when compared to Example 1. Other figures in Examplw 2 are the same as those in Examples 1. As shown in this table, dose-category specific ERRs in Example 2 are evidently smaller when compared to Example 1.

In conclusion, an ERR per dose is strongly affected by the cancer risk of a single dose category which has a large "anchor" effect. Confounding may at work even if the prevalence of non-radiation risk factor is not linearly associated with radiation dose.

Table 20. ERRs estimated from fictitious cohort data
– ERR per dose is decreased by more than 50 % by a 5% increase in the number of cancer cases in the lowest dose category

		Example 1	Example 2
Mean dose (mGy)	Expected number of cancer cases	Observed number of cancer cases	Observed number of cancer cases
1	10,230	10,000	10,500
7	2,050	2,100	2,100
14	2,080	2,000	2,000
32	2,110	2,100	2,100
70	1,130	1,200	1,200
122	460	500	500
172	250	300	300
241	250	250	250
414	180	200	200
ERR/100 mGy		0.050	0.028

Mean doses and observed numbers of cases in Example 1 are those taken from INWORKS56). Expected numbers of cases are calculated based on the INWORKS (Table A2). Values are rounded for the sake of simplicity.

In Example 2, the number of cancer cases in the lowest dose category is increased by 5%. The other values of Example 2 are the same as those of Example 1.

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Table 21. ERRs estimated from fictitious cohort data

		Example 1				Example 2			
Mean dose (mGy)	Person-years (thousands)	Cancer cases	Cancer incidence per 10^5	RR	ERR	Cancer cases	Cancer incidence per 10^5	RR	ERR
0	100,000	2,000	2,000	1*	0*	10,000	2,100	1*	0*
50	40,000	820	2,050	1.025	0.025	40,000	820	0.976	-0.024
100	10,000	210	2,100	1.05	0.05	10,000	210	1	0
200	2,000	44	2,200	1.1	0.1	2,000	44	1.048	0.048

* Reference category
In Example 2, the number of cancer cases in the lowest dose category is increased by 5%. The other values of Example 2 are the same as those of Example 1.

XII. Matching

1. Definitions

According to JM Last, matching is the process of making a study group and a comparison group comparable with respect to extraneous factors (DE-IV)[2]. Rothman and Greenland (ME-II)[8] explains the purpose and effect of matching as follows: "Some early views of matching held that its purpose was to enhance validity. It was later shown, however, that the chief importance of matching in observational studies stems from its effect on study efficiency, not on validity. In both cohort and case-controls studies, matching may lead to either a gain or loss in efficiency. Furthermore, in case-control studies, matching can introduce a selection bias that must be accounted for in the analysis via control of the matching factors."

2. Matching in a cohort study

As shown in Tables 22-1 and 22-2, matching on sex in the exposed and unexposed groups in a cohort study can prevent the confounding by sex.

In a cohort study without competing risk or lost-to-follow-up, matching prevents confounding by the matched factor.

Table 22-1. Cohort study without matching on sex

	Men		Women		Total	
	Exposure		Exposure		Exposure	
	+	−	+	−	+	−
Lung cancer death	200	10	10	8	210	18
Population	800	200	200	800	1,000	1,000
Mortality/1,000	250	50	50	10	210	18

Table 22-2. Cohort study with matching on sex

	Men		Women		Total	
	Exposure		Exposure		Exposure	
	+	−	+	−	+	−
Lung cancer death	100	10	50	5	150	15
Population	1,000	200	1,000	200	2,000	400
Mortality/1,000	100	50	50	25	75	37.5

3. Matching in a case-control study

As shown in Table 23, matching on sex in the in a case-control study cannot prevent the confounding by this variable (sex)[8]. Actually, matching in a case-control study introduces a "selection" bias when the matched factor is correlated with the exposure.

Table 23. A case-control study with matching on sex

		Exposure			OR
		+	−	Total	
Men	Lung cancer cases	95	5	100	12.7
	Controls	60	40	100	
Women	Lung cancer cases	40	60	100	12.7
	Controls	5	95	100	
Total	Lung cancer cases	135	65	200	4.3
	Controls	65	135	200	

"The selection bias introduced into the case-control study by the matching process can occur whether or not there is confounding in the source population (the population from which the cases arise). If there is confounding in the source population, the process of matching will superimpose a selection bias in place of the initial confounding. This bias is generally in the direction of the null value of effect, whatever the nature of the confounding in the source population." (ME-II)[8].

4. What is the purpose of matching in a case-control study?

Suppose you conduct a case-control study of thyroid cancer which is several times more common among women than among men. Without matching, the data shown in Table 24 may be obtained.

Table 24. The results of a breast cancer case-control study

	Cases	Controls
Men	20	400
Women	80	400

In this example, there are 100 cases and 800 controls in total. However, the case-control ratio among men is 1:20 among men and is 1:5 among women; the ratio among men is much larger than that among women. It is inefficient to use many controls for such a small number of cases among men. Note that we have to analyze the data stratified by sex in order to avoid confounding by sex.

5. Various matching methods in a case-control study

Individual matching relies on identifying individual subjects for comparison, each resembling a study subject on the matched variable (s) (DE-IV)[2]. On the other hand, frequency matching requires that the frequency of distribution of the matched variable (s) be similar in study and comparison groups (DE-IV)[2]. In Modern Epidemiology (second edition), KJ Rothman and Sander Greenland pointed out that there is no important difference in the proper analysis of individually matched and frequency-matched data (ME-II)[8].

Caliper matching

It is the process of matching comparison group subjects to study group subjects within a specified distance for a continuous variable (DE-IV)[2].

For example, for a case aged 50 years, its control(s) will be selected from subjects aged 48 (=50-2) or older and 52 (=50+2) or younger. Note that you will use a narrower (or wider) age range if the age dependence of risk is stronger (or weaker). The age range should be selected so that the risk of disease of interest is not much different in the selected age range.

Category matching

It is the process of matching study and control group subjects in broad classes, such as relatively wide age ranges or occupational groups (DE-IV)[2]. For example, suppose we use 5-year age categories (0-4, 5-9,,, 50-54, 55-59,,,). In this setting, for a case aged 50 years, its control (s) will be selected from subjects aged 50-54. As opposed to what Last defined, the category is not necessary be broad classes.

Caliper vs category

KJ Rothman and Sander Greenland pointed out that category matching is preferable (ME-II, p103)[8]. The argument is as follows: "if matching on age, it is preferable to match controls from specific age categories rather than by using so called "caliper" matching. To see why, consider a situation in which the size of the population declines with increasing age. Caliper matching will tend to produce a control series younger than the case series because for every case there is a greater probability of getting a younger control than an older control. Category matching may also tend to yield younger controls than cases within the categories, but will at least produce the same age distribution of cases and controls across categories."

6. Overmatching bias in a case-control study

"Matching on factors that are affected by the study exposure or disease is almost never warranted and is potentially capable of irremediably biasing results beyond any hope of repair." "In the most benign situation, case-controls matching on factor affected by exposure but unrelated to disease in any way (except possibly through its association with exposure) will simply reduce statistical efficiency." This is because "case-control matching on a non-confounder associated with exposure but not with disease can turn the factor into a confounder." (ME-II, p157)[8].

XIII. Errors involved in case ascertainment, dosimetry and collecting information on other variables

Measurement errors can be divided into random errors and systematic error.

1. A simple example

Suppose you measured the diameter of a ball with the true diameter of 50mm, which only God knows, using measure sticks A and B. The results of measurement are shown in the Table 25. In the data shown in the left hand panel, the results are inconsistent but the calculated mean is the same as the true value. On the other hand, in the data of the right hand panel, the results are always 0.5 mm less than the true value.

Table 25. The results of 7 measurements of a ball

Measurement	A	B
1	50.3	49.5
2	49.7	49.5
3	49.8	49.5
4	49.9	49.5
5	50.1	49.5
6	50.2	49.5
7	50.0	49.5
Mean	50.0	49.5

Which data set is more useful for us? When we want to know the true value, the results obtained from measurements using stick A is more useful since we can estimate the true value

As shown in the above example, from the data set with random errors, we can obtain the correct estimate of the true value by using a statistical procedure (e.g., taking a mean in this data set). On the other hand, in the presence of a bias, we cannot estimate the true value unless we find out the magnitude of the bias.

Table 26 shows random values with the expected mean of 50. In this data set, measurement errors are so large that each mean value is not always close to the true value (=50). Needless to say, as measurement errors become smaller, mean values are more likely to get closer to the true value. If measurements errors are large, you need to do more measurements to increase the precision of means to be calculated.

Table 26. The results of 7 measurements of a ball by 4 different measure sticks

Measurement	A1	A2	A3	A4
1	80	20	50	90
2	40	40	30	50
3	70	10	20	80
4	40	20	30	90
5	20	30	50	90
6	40	10	30	20
7	40	30	60	90
Mean	47.1	22.9	38.6	72.9

2. Cancer mortality

In Japan, crude cancer mortality rates among men and women in 2010 are estimated to be approximately 750 and 500 per 100,000, respectively (those rates do not include carcinomas *in situ* or benign intracranial tumors). A question is how accurate this estimate is. Some doctors may tend to over-diagnose cancers and some may tend to overlook them. However, as will be described in the next section, the overall probability of over-diagnosis and under-diagnosis of cancer are similar to each other; therefore, the errors involved in the estimate of cancer mortality in this country are not seriously biased. In the case of site specific cancer diagnosis, the situation may be different. It is not always possible to accurately diagnose the primary cancer site, and the metastatic carcinomas tend to occur in the organs such as the lungs and bones. For example, a carcinoma found in the bone may be the metastasis of breast cancer to the bone. On the other hand, a carcinoma found in the breast is unlikely to be the metastasis of a bone carcinoma.

3. Accuracy of diagnosis

Accuracy of underlying cause of death is always a matter of a concern. Several studies addressed this problem[56-59]. One of them is a Japanese study that used autopsy data obtained from the ABCC/RERF autopsy program. This program started in 1950 and ended in 1987. Before 1961, it included cases that did not belong to the LSS cohort as well. Among 46,331 deaths occurring among LSS cohort members, autopsies were performed on 6,613 cases (14%). Researchers examined the accuracy of death certificate for 12 disease categories. The overall percentage of agreement between death certificate and autopsy diagnoses was only 53%. However, in the case of cancer, 75% of cases diagnosed at autopsy were recorded on death certificates. Specificity rates were above 90% for all except the cerebrovascular disease category. Overall agreement was lower among older people and for deaths occurring outside of hospital.

4. Accuracy of exposure

We cannot measure anything without random errors, which are usually called the classical type errors. In this type of errors, a measured value is the sum of a true value and a random error. In epidemiological studies in which designated value of radiation dose are used, the roles of those values and errors are inverted. The designated value (= the "true" value) is a function of the observed value and random errors associated with the measurement. The error associated in this kind of situation is called the Berkson error. Aurore Delaigle explained Berkson type errors as follows: in classical type errors, "the observed value W is the variable X of interest accompanied by a random perturbation, U, (i.e. W = X + U with U and X independent). In many epidemiologic studies, however, the roles of X and W are inverted, and X = W + U, in which the unobservable X that is a random perturbation of W. Here, the errors are rather of Berkson type. Although the two types of errors look similar, the methodology used to estimate a curve with classical errors is not valid in the case of Berkson errors"[59].

XIV. Non-differential miss-classification

1. Introduction

In the cohort study shown in Table 27, case ascertainment is incomplete but the frequencies of missing cases are not different in the exposed and unexposed. Therefore, accurate RR can be estimated, and

RR= (80/1000) / (8/1000) = 10.

As shown in this example, if the magnitude of bias is similar in two groups, a correct result can be obtained from such a comparison.

Table 27. The results of a cohort study

	Exposed	Unexposed
Population at the start of follow-up	10,000	10,000
	After 10-year follow-up	
	↓	↓
Identified cases during 10-year follow-up	80	8
Missed cases during 10-year follow-up	20	2

Suppose the following data are obtained from a case-control study. In this data set, ORs for exposure levels 1 and 2 are 4 and 16, respectively.

Table 28. Results of a case-control study

	Exposure levels		
	0	1	2
Cases	10	40	160
Controls	70	70	70
OR	1(=reference)	4	16

In the following data (Table 29), 90% of cases of the exposure level 2 in Table 28 are misclassified as cases in the exposure level 0. In controls, the same thing happened; 90% of those in the exposure level 2 are misclassified as those in the exposure level 0. In this scenario, ORs for exposure levels 1 and 2 are 0.49 and 1.97, respectively. The OR for the exposure level 1 became a value smaller than 1 although it was larger than 1 in the original data (Table 28). Therefore, non-differential misclassification of exposure does not always bias a true effect toward the null value. This fact was first pointed out by Dosemeci *et al* [60].

Table 29. Results of a case-control study

	Exposure levels		
	0	1	2
Cases	154	40	16
Controls	133	70	7
OR	1(=reference)	0.49	1.97

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