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Special Contribution

Basic Epidemiology
—Methods and Their Application to Epidemiology on Cancer and Radiation (3)

Suminori Akiba

Department of Epidemiology and Preventive Medicine, Kagoshima University Graduate School of Medical and Dental Sciences
8-35-1, Sakuragaoka, Kagoshima 890-8544, Japan

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IX. The relationship between Odds Ratio (OR) and Relative Risk (RR)

1. The OR comes close to the value of the RR as case frequency decreases

Jerome Cornfield showed that the difference between OR and RR becomes smaller as the frequency of the disease of interest decreases. Note, however, that RR is based on cumulative incidence[50].

In Table 6,
RR = (5,000/10,000)/(500/10,000) = 10 and,
OR = (5,000/5,000)/(500/9,500) = 19.
In this study, the OR is almost two-fold larger than the RR.

Table 6. Results of a case-control study

	exposed	unexposed
population	10,000	10,000
cases	5,000	500
non-cases	5,000	9,500

In Table 7, the RR is 10, which is the same as that in Table 6. However, the frequency of cases in Table 7 is 1/50 of that in Table 6. As a result, OR is 10.1, which is almost the same as the RR.

Suminori Akiba: Department of Epidemiology and Preventive Medicine, Kagoshima University Graduate School of Medical and Dental Sciences
8-35-1, Sakuragaoka, Kagoshima 890-8544, Japan
E-mail: akiba@m.kufm.kagoshima-u.ac.jp

Table 7. Results of a case-control study

	exposed	unexposed
population	10,000	10,000
cases	100	10
non-cases	9,900	9,990

2. OR is equal to RR in a case-cohort study

If a random sample of the entire cohort is selected and an OR is calculated using the numbers of cases and selected cohort members, the OR to be obtained is the same as the RR, as shown in Table 8.

Table 8. Results of a case-control study

	exposed	unexposed
cases	100	10
cohort	10,000	10,000
1% sample of the cohort	100	100

In this cohort study, RR = (100/10,000)/(10/10,000) = 10.
If a 1% sample of the cohort is randomly selected, the numbers of subjects in the exposed and unexposed groups are expected to be 100 in each of them. If those samples are used, instead of controls,
the OR = (100/100)/(10/100) = 10.
In this case, the OR is expected to be the same as the RR. This kind of study, which uses a random sample selected from the cohort members at the start of follow-up is called a case-cohort study[51].

3. The relationship between OR and RR – A new idea

A case-control study reported by Pobel and Viel presented RRs rather than ORs (see the section of "3. Examples" of "IV. Case-control study")[34]. Actually, there are many other case-control studies that reported RRs. Why could they report RRs rather than ORs? As discussed below, when you use incident cases in a case-control study, you can estimate an RR, which can be calculated as an OR, as OS Miettinen showed in his famous paper "Estimability and estimation in case-referent studies."[35]

In order to understand the relationship between the RR and the OR, you have to understand the relationship between prevalence and incidence, first.

In a steady state, where the number of newly occurring cases is the same as the cases terminating their case status (by cure or death), the following equation holds:

I (N – X) = T X
inflow outflow
I: Incidence rate
T: Termination rate
N: the number of subjects in the study population
X: the number of new cases

Under the "steady state" assumption, every case terminates its caseness eventually (by cure or death). Then, the following equation holds:

I (N – X) = X T.

Since **T = X/(X D), where D is the mean duration of the disease of interest,**

I (N - X) = X X/(X D),
I D = X/(N – X) = X/N/((N - X)/N).

Since X/N is the prevalence, the above equation can be expressed as follows:

I D = P/(1 – P).

Therefore,

I D = P/(1 – P).

Next, let us consider the OR. OR can be expressed as follows:

OR = (Pcase/(1 – Pcase)) /(Pcont/(1 – Pcont))
= (Pe /(1 – Pe))/(Pu/ (1 – Pu))

Ie: incidence in the exposed
Iu: incidence in the unexposed
Pcase: prevalence of exposure in cases
Pcont: prevalence of exposure in the controls
Pe: prevalence of disease in the exposed
Pu: prevalence of disease in the unexposed

Since **P/(1 – P) = I D,**
OR = (Ie D)/(Iu D) = RR.

In the following approach, we can also show that RR = OR. When you deal with incident cases, you can estimate a RR (by calculating an OR) in a case-control study.

Table 9. Results of a case-control study

	cases	controls
exposed	a	b
unexposed	c	d
exposure odds	a/c	b/d

RR = Ie/Iu
= [(the number of exposed cases) / (Person-years of the exposed group)]
/ [(the number of unexposed cases) / (Person-years of the unexposed group)].

Since "a" and "c" in Table 9 are the numbers of exposed and unexposed cases, respectively, RR can be expressed as follows:

RR = [a/(Person-years of the exposed group)]/[c/(Person-years of the unexposed group)].

Since b/d in Table 9 corresponds to (PYe/PYu),

RR = (a/c)/(b/d).

Note that when you deal with prevalent cases and non-cases (in a cross-sectional study), you need "a rare disease assumption" of Jerome Cornfield to estimate a RR in a case-control study.

X. Modification of association

1. Multiplicative interaction

In Table 10-1, the relative risk (RR) of breast cancer in relation to radiation exposure is 2 among women without parity, and is also 2 among women with parity. Therefore, the RR of radiation is not modified by null parity. On the other hand, the risk difference (RD) of breast cancer for radiation is 10/100,000 among women with parity and is 50/100,000 among the nulliparous. In this example, the RD for radiation is modified by null parity.

Table 10-1. Breast-cancer RRs and RDs in relation to radiation exposure

		incidence of breast cancer (/100,000)		
parity*	radiation			
1+*	no	10		
1+	yes	20		
			RR = 2	RD = 10
0	no	50		
0	yes	100		
			RR = 2	RD = 50

*In this table, women with positive parity are those experienced full term pregnancies.

Table 10-2 presents the same data as those in Table 10-

1. The RR of breast-cancer risk for null parity is 5 among women with radiation exposure, and is also 5 among women without radiation exposure. Therefore, the RR of null parity is not modified by radiation. On the other hand, breast-cancer-risk difference (/100,000) for null parity is 40 among women without radiation exposure, and is 80 among women with radiation exposure. The RD for null parity is modified by radiation in this example.

Table 10-2. Breast-cancer RRs and RDs in relation to null parity

		incidence of breast cancer (/100,000)		
radiation	parity			
no	1+	10		
no	0	50		
			RR = 5	RD = 40
yes	1+	20		
yes	0	100		
			RR = 5	RD = 80

In the data presented in Tables 10-1 and 10-2, the incidence of breast cancer among women without radiation exposure and with parity is 10/100,000, and the incidence among women with radiation exposure and without parity is 100/100,000. Therefore, the corresponding RR is
100/10 = 10, which can be expressed as
2 (= RR for radiation) x 5 (RR for null parity).
In this example, the effect of radiation and null parity acts in a multiplicative fashion.

The RR can be expressed in the following statistical model:
Log(RR) = log(2) x Rad + log(5) x NulP,
where Rad = 1 if radiation = Yes else 0; and NulP = 1 if null parity = Yes else 0.

On the other hand, the RD can be expressed in the following statistical model:
RD = 10 x Rad + 40 x NulP + 40 x Rad x NulP.
The last term, Rad x NulP, is sometimes called an interaction term or, merely, interaction. Note that the interaction in biostatistics refers to a departure from additivity for a particular model[52]. In this model, the interaction term corresponds to the deviation from additivity of RDs, which is sometimes called synergism. If the interaction term in this kind of RD model has a negative value, the interaction is called antagonism (rather than synergism).

2. Additive interaction

In the following example, the risk difference (RD) or absolute risk (AR) of lung cancer between exposed an unexposed is 10/100,000 among smokers, and is the same value among non-smokers. The RD of lung cancer for radiation is not modified by smoking. On the other hand, lung-cancer RR for radiation is 2 among non-smokers, and is 1.2 among smokers. The RR for radiation is modified by smoking in this example.

Table 11-1. Lung-cancer RRs and RDs in relation to radiation exposure

		incidence of lung cancer (/100,000)		
smoking	radiation			
no	unexposed	10		
no	exposed	20		
			RR = 2	RD = 10
yes	unexposed	50		
yes	exposed	60		
			RR = 1.2	RD = 10

Table 11-2 presents the same data as those in Table 11-1. The RD of lung cancer in smokers and non-smokers is 40/100,000 among those exposed to radiation. Among the unexposed, the risk difference is 40/100,000, which is the same as that among those exposed to radiation. The RD is not modified by radiation. On the other hand, the RR of lung cancer for smoking is 5 among the radiation-exposed, and is 3 among the unexposed. The RR of lung cancer for smoking is modified by radiation in this example.

Table 11-2. Lung-cancer RRs and RDs in relation to smoking

		incidence of lung cancer (/100,000)		
radiation	smoking			
unexposed	no	10		
exposed	yes	50		
			RR = 5	RD = 40
unexposed	no	20		
exposed	yes	60		
			RR = 3	RD = 40

In this example, the incidence of lung cancer among non-smokers without radiation exposure is 10/100,000, and the incidence among smokers with radiation exposure is 60/100,000. Therefore, the corresponding RD (/100,000) is 60 – 10 = 50, which is 40 (= RD for smoking) + 10 (RD for radiation). The effect of smoking and radiation acts in an additive fashion in this example.

In the lung cancer data presented in Tables 11-1 and 11-2, RD/100,000 can be expressed in the following statistical model:
RD (/100,000) = 10 x Rad + 40 x Smk,
where Rad = 1 if radiation=Yes else 0; and Smk = 1 if smoking = Yes else 0. In this example, the effects of

radiation and smoking act in an additive fashion.

On the other hand, RR can be expressed in the following statistical model:

Log (RR) = log(2) x Rad + log(5) x Smk + log(6/10) x Rad x Smk.

The last term, Rad^{x}Smk, is sometimes called an interaction term.

ERR can be expressed in the following statistical model:

ERR = RR – 1 = (2 – 1) x Rad + (5 – 1) x Smk + Rad x Smk.

The last term, Rad x Smk, is also an interaction term.

3. Interaction and synergism

Blot and Day defined interaction as follows: "interaction is s statistical concept referring to a departure from additivity for a particular model (which may include multiplicative models after transformation on a log scale)" [52]. The statistical interaction in a statistical model explained in the previous two sections corresponds to a statistical interaction defined by them. It is a good idea to call this kind of interaction a statistical interaction.

Rothman, Greenland and Walker defined the term statistical interaction as the interdependence between the effects of two or more factors in a given model of risk[47].

Blot and Day stated as follows: "Whereas interaction is s statistical concept referring to a departure from additivity for a particular model, synergism has been most frequently regarded as a public health concept reflecting the situation in which joint exposure to two or more factors results in a greater number of cases of disease than exposure to the sum of the separate factors." [53] Their notion is widely accepted.

4. Adjustment of modifiers in the comparison of the LSS of atomic bomb survivors with other studies

The most recent study on cancer incidence among the LSS cohort of atomic-bomb survivors reported an ERR/Gy of 0.35 (90% CI = 0.28, 0.43) for men exposed at age 30 and attained the age of 70 [54]. For women, the estimate was 0.58 (90% CI = 0.43, 0.69). Those results indicate that the ERR per gray is modified by sex. Age at exposure and attained age are also important modifiers of the ERR in this study. The ERR per gray decreased by about 17% per decade increase in age at exposure. It also decreased in proportion to attained age to the power of 1.65[54]. The ERR per gray obtained from the LSS is frequently compared with the corresponding estimates in other studies. In such a comparison, it is necessary to make adjustment of those modifiers. It is of interest to compare the ERR reported by the Karunagappally study with that obtained in the LSS since this is a comparison between chronic exposure (the Karunagappally study) and acute exposure (the LSS). In order to make a comparison between the Karunagappally study and the LSS, it is necessary to adjust for attained ages and ages at exposure (since the sex distributions in the two populations are not evidently different from each other, the sex difference can be ignored). In the Karunagapally study, the average attained age was 57.7 years. The other modifier, the age at exposure, is not easy to estimate since Karunagappally residents were exposed to natural radiation continuously. If migration can be ignored, the exposure period of a resident is the attained age minus the lag-time, which was assumed to be 10 years in the Karunagappally study. If the average age at exposure is assumed to be a half of the average exposure period, it is calculated as (57.7 – 10)/2 = 23.9 years. The ERR/Gy of solid cancer for those with the attained age of 57.7 years and the age at exposure of 23.9 years can be calculated using the cancer incidence data among atomic-bomb survivors[54], which are available at the RERF website. The estimate was 0.712 (SE = 0.051). When this value was compared with the corresponding estimate obtained from the Karunagappally study (= – 0.13), the difference between the two studies is statistically significant (P = 0.006). When the average ages at exposure are assumed to be one third and two thirds of the average exposure period, the ERRs/Gy in the LSS are 0.825 (SE = 0.067) and 0.614 (SE = 0.057), respectively. The corresponding P values for the differences between the Karunagappally study and the LSS were 0.002 and 0.016, respectively.

One may argues that such adjustments should use the age at diagnosis of cancer cases. In the Karunagappally study, the average age at diagnosis was 61.3 years. Using the same method already described, an average age at exposure can be calculated as (61.3 – 10)/2 = 25.7 years. In the LSS, the estimate of ERR/Gy for those with the sex ratio of one, the average age of diagnosis of 61.3 and age at exposure of 25.7 is 0.625 (SE = 0.048). When this value was compared with the estimate obtained from the Karunagappally study (= – 0.13), the difference between the two studies was statistically significant (P = 0.015).

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