原　著

Proposal of an Improved Relative Risk Measure that Estimates Prevention as well as Promotion of Disease

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Abstract : Background: High relative risk of developing a disease relative to exposure is not equivalent to high disease contraction rate. For example, smoking significantly increases the risk of lung cancer development relative to a non-smoker, but the absolute risk is still low. A new measure is needed to cancel out these apparent differences.

Methods: We assume that the magnitudes of a promoting factor and a preventive factor, p and q; $0<p<1$, $0<q<1$, relative to a disease can be modified by exposure. Since the magnitude contracting the disease without a preventive factor is evaluated to be $\frac{1}{1-q}$, the magnitude of contracting it is represented as $p\times\frac{1}{1-q}=a/(a+b)$; a and b represent the number of affected subjects and the number of non-affected subjects, and since the magnitude of not contracting the disease without a promoting factor is evaluated to be $\frac{1}{1-p}$, the magnitude of not contracting it is represented as $q\times\frac{1}{1-p}=b/(a+b)$. Hence, $p=a^2/(a^2+ab+b^2)$ and $q=b^2/(a^2+ab+b^2)$.

Results: The method is applied for referenced data to analyze the relationship between lung cancer and smoking among men and among women. Since q is extremely larger than p, the magnitude of a preventive factor is even larger than that of a promoting factor. This is the reason why the morbidity of lung cancer of smokers is still very low. The high ratio of p_{men} to p_{women} and the low ratio of q_{men} to q_{women} suggest that men are more liable to be affected by smoking than women.

Conclusions: This new measure could be a better global measure of epidemiological risk.

Key words : case-control study, cohort study, epidemiology, relative risk

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Introduction

Relative risk is defined as the ratio of the probability of a disease occurring in a group exposed to a pathogen, to its probability of occurring in a non-exposed group. Relative risk is used as a variable in many cohort studies. Sobue et al. reported that the relative risk of lung cancer in current smokers to that in non-smokers was 4.1 for men (Table 1)[3]. However, such a high relative risk may appear to be incompatible with the fact that 99.007% of smokers did not contract lung cancer. This is because a relative risk of 4.1 signifies that smoking quadruples the morbidity of lung cancer from 0.24% (in non-smokers) to 0.99% (in smokers), which is still very low. Hence, one could postulate existence of preventive factors leading to low susceptibility to lung cancer that counteract presence of factors quantified traditionally by relative risk. This report examines whether the magnitudes of these two factors can be estimated.

Methods

Model formulation

There are likely multiple preventive factors as well as multiple promoting factors relative to a disease. To keep the model simple, we assume that just one of each of these two types of factors is involved. We assume that the magnitudes of these factors can be modified by exposure. Consider the example in Table 1. The magnitude of a promoting factor which can be modified by smoking is represented by p, the magnitude of a preventive factor which can be modified by smoking is represented by q, the magnitude of a promoting factor without smoking is represented r, and the magnitude of

Table 1.

Men	Lung cancer（+）	Lung cancer（−）	Total
Current smokers	231 [a]	23036 [b]	23267 [a+b]
Non-smokers	26 [c]	10813 [d]	10839 [c+d]
Total	257 [a+c]	33849 [b+d]	34106 [a+b+c+d]

Relationship between smoking and lung cancer in men. The data is cited from Sobue et al.[3].

Table 2.

Women	Lung cancer（+）	Lung cancer（−）	Total
Current smokers	16 [a]	2827 [b]	2843 [a+b]
Non-smokers	78 [c]	44702 [d]	44780 [c+d]
Total	94 [a+c]	47529 [b+d]	47623 [a+b+c+d]

Relationship between smoking and lung cancer in women. The data is cited from Sobue et al.[3].

a preventive factor without smoking is represented by s. These magnitudes are assumed to be between 0 and 1. Since the magnitude of contracting lung cancer without a preventive factor among current smokers is evaluated to be $\frac{1}{1-q}$, the magnitude of contracting lung cancer by smoking is represented as $p\times\frac{1}{1-q}=a/(a+b)$; and since the magnitude of not contracting lung cancer without a promoting factor among current smokers is evaluated to be $\frac{1}{1-p}$, the magnitude of not contracting lung cancer among current smokers is represented as $q\times\frac{1}{1-p}=b/(a+b)$. Hence, $p=a^2/(a^2+ab+b^2)$ and $q=b^2/(a^2+ab+b^2)$. Since $a\neq 0$ and $b\neq 0$, $0<p<1$ and $0<q<1$. These findings satisfy the assumptions that p and q are between 0 and 1. Similarly, the magnitude of contracting lung cancer without smoking is represented as $r\times\frac{1}{1-s}=c/(c+d)$ and the magnitude of non-contracting without smoking is represented as $s\times\frac{1}{1-r}=d/(c+d)$. Hence, $r=c^2/(c^2+cd+d^2)$ and $s=d^2/(c^2+cd+d^2)$. Similarly, $0<r<1$ and $0<s<1$. These findings satisfy the assumptions that r and s are between 0 and 1.

Results

First, the method is applied to analyze the relationship between lung cancer and smoking among men. From Table 1, p=0.0000995, q=0.9899732, r=0.0000058, and s=0.9975955. The ratio of p to r, p/r, gauges risk of contracting lung cancer by increasing the magnitude of the promoting factor with smoking. The magnitude of the promoting factor would be increased to be 17.3 ($=p/r$) times with smoking. The ratio of q to s, q/s, gauges risk of contracting lung cancer by decreasing the magnitude of the preventive factor with smoking. The magnitude of the preventive factor would be decreased to be 0.992 ($=q/s$) times with smoking. Since q is extremely larger than p and s is also extremely larger than r, the magnitude of a preventive factor is even larger than that of a promoting factor without smoking as well as with smoking.

Second, the method is applied to analyze the relationship between lung cancer and smoking among women. Sobue et al. also reported the results for women (Table 2)[3]. From Table 2, p=0.0000319, q=0.9943405, r=0.000003, and s=0.9982551. The magnitude of the promoting factor would be increased to be 10.5 ($=p/r$) times with smoking. The magnitude of the preventive factor would be decreased to be 0.996 ($=q/s$) times with smoking. Since q is extremely larger than p and s is also extremely larger than r, the magnitude of a preventive factor is even larger than that of a promoting factor without smoking as well as with smoking.

Third, the relationship between lung cancer and smoking among men is compared with that among women. The ratio of p_{men} to p_{women} is 3.1, indicating that the magnitude of a promoting factor of male smokers would be 3.1 times as likely as that of female smokers to develop lung cancer. The finding that q_{women} is larger than q_{men} suggests that the magnitude of a preventive factor of female smokers is larger than that of male smokers; the finding that r_{men} is larger than r_{women} suggests that the magnitude of a promoting factor of male non-smokers is larger than that of female non-smokers; and the finding that s_{women} is larger than s_{men} suggests that the magnitude of a preventive factor of female non-smokers is larger than that of male non-smokers.

Discussion

Relative risk is used frequently to examine whether

a suspected exposure causes a disease for which the morbidity is very low. Hence, even if the relative risk is 10 times higher in exposed subjects than in non-exposed subjects, only a small number of subjects contract the disease from exposure, and the greater part of the subjects do not contract it in spite of exposure. Although relative risk is useful, it is considered to be insufficient when taken on its own. Indeed, it may be even more useful to postulate additional existence of a preventive factor associated with low susceptibility to a disease and calculate its effects, as our analysis now allows. Since q is rather larger than p and s is rather larger than r, the magnitude of a preventive factor is even larger than that of a promoting factor without smoking as well as with smoking. This is the reason why the morbidity of lung cancer of smokers is still very low.

Wakai et al. reported that the relative risk of lung cancer for women was less than half of that for men, and surmised that women smoked a smaller amount[4]. On the other hand, Fontham et al. have suggested that women are more susceptible to the carcinogenic compounds of smoking[1]. Freedman et al. suggested that women were not more susceptible than men to the carcinogenic effects of cigarette smoking in the lung[2]. There are many controversies on the relationship between female hormones and lung cancer. The ratio of p_{men} to p_{women} is 3.1, indicating that the magnitude of a promoting factor of male smokers would be 3.1 times as likely as that of female smokers to develop lung cancer. The finding that q_{women} is larger than q_{men} suggests that the magnitude of a preventive factor of female smokers is larger than that of male smokers. These findings suggest that female hormones may protect against lung cancer. It has been first found, calculating both the magnitude of a promoting factor and that of a preventive factor. The suggestion that female hormones are preventive against smoking induced lung cancer is a case in point.

References

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疾患の促進因子のみならずその抑制因子を定量化する新たな相対危険度の考案

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要　　約

ある要因に暴露して発生した疾患の相対危険度が高率であっても罹患率が高いとは言えない。例えば喫煙は非喫煙に比較して肺がん発生のリスクを増加させるが，総体的に見て依然と発生させるリスクは低い。この一見した乖離を埋めるためには新たな指標が必要である。そこで，促進因子，抑制因子の度合いを各々 p と q（$0<p<1$，$0<q<1$）で表し，要因暴露によって修飾されると仮定する。抑制因子がないときに促進因子により罹患する度合いは $p\times\frac{1}{1-q}=a/(a+b)$ で表すことができる［a は罹患者数，b は非罹患者数］。逆に促進因子がないときに抑制因子により罹患しない度合いは $q\times\frac{1}{1-p}=b/(a+b)$ で表すことができる。これより $p=a^2/(a^2+ab+b^2)$，$q=b^2/(a^2+ab+b^2)$ と決定される。この数式を男女別に肺がんと喫煙の関係を報告した代表的な文献のデータにあてはめると，q は p よりかなり大きな値になるため，抑制因子の度合いが促進因子の度合いをはるかに凌駕することが分かる。これが喫煙は非喫煙に比較して肺がん発生のリスクを増加させるが，総体的に見て依然と発生させるリスクが低いことの理由である。p_{men} が p_{women} より大きく q_{men} が q_{women} より小さいことから喫煙により男性が女性より肺がんを発生しやすいことが分かる。

キーワード：症例対照研究，コホート研究，疫学，相対危険度

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