Short Report

Joint Risks in a Case-Control Study of Esophageal Cancer in Shanxi Province, People's Republic of China

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SU, W., HAN, X.Y., WANG, Y.P., WANG, Y.L., ZHN, Y.W., SASABA, T., HOSHIYAMA, Y. and TAGASHIRA, Y. Joint Risks in a Case-Control Study of Esophageal Cancer in Shanxi Province, People's Republic of China. Tohoku J. Exp. Med., 1994, 174 (2), 177-181 — A multifactorial analysis on the etiology of esophageal cancer was conducted based on a case-control study conducted in Shanxi. The study analyzed the data of 326 cases and 396 controls. The joint risks of two factors were calculated from dichotomous distributions. Three models of factor combinations were assessed: (1) two risk-enhancing factors, (2) two risk-reducing factors, and (3) a risk-enhancing and a risk-reducing factor. The observed joint risks were in the neighborhood of the multiplicative products of single acting risks of individual factors. This was a uniform pattern across three models.

Epidemiologic study of interactions between etiologic agents presents prospects of gaining a deeper understanding of disease causation and of widening the opportunities for prevention. To pursue these aims, the joint effect of at least two combined factors must first be revealed, but these requirements are met by only a few epidemiologic studies. Accordingly, we undertook an assessment of joint risks in major factor interactions, based on the data by Wang et al. (1992), who identified several risks related to esophageal cancer (EC) in Shanxi.

MATERIALS AND METHODS

Cases, controls, diagnoses, and questionnaire

Forty-three interviewers, who were trained to administer the structured questionnaire, interviewed 326 EC patients in two hospitals: Yangcheng Tumor Hospital and Linfen Tumor Hospital (January 1988—January 1989). All cases (326) had been diagnosed by x-ray and an additional diagnosis was established by biopsy in 247 cases. The majority (184) were squamous cell carcinoma.

Other details were reported previously by Wang et al. (1992).

Data processing and trend assessment

First, odds ratios (ORs) in categories 1, 2, and 3 (with adjustment for areas, sex, and age

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in 3 groups (30–54, 55–64, 65+) were calculated from the distribution for a single factor, with 95% confidence intervals. We then assigned relative values to category 1 (single risks) (tables in Figs. 1 and 2).

Secondly, we classified cases and controls as being either exposed or non-exposed to two factors [non-exposed (−, −), exposed to one factor (+, −), exposed to the other factor (−, +), exposed to both factors (+, +)], having 4 ORs where OR (−, −) = 1.0 (referent), OR (+, +) a joint risk (Khoury et al. 1988).

In addition, scores of 0, 1, and 2 were given to the three levels of consumption frequency (categories 1, 2, and 3), and the trends of joint risks were then assessed.

RESULTS AND DISCUSSION

Wang et al. (1992) revealed that millet gruel and boiled vegetables are major risk-enhancing factors, while soybeans, including soybean products, and cabbage are major risk-reducing factors. Accordingly, we evaluated their joint risks, respectively.

It is easy to understand that the expected joint risk of two factors is equal to the product of a single acting risk factor multiplied by that of another, when no interactions exist between the factors. It can be seen in the figures that most of the observed joint risks were in the neighborhood of the products of single risks.

Fig. 1 shows that joint risks rose nearly linearly with increasing consumption of millet gruel and boiled vegetables, with a significant trend value ($p < 0.01$). The highest joint risk of 22.2 can be found in category (3,3). The multiplicative risk elevation suggests that the risk resulting from the simultaneous action of three or more factors will be extremely high, in the order of more than a 50-fold increase. Notably from the opposite aspect, the joint risks presented by two risk-reducing factors (soybeans and cabbage) displayed a reasonably significant risk decrease (Fig. 2). The lowest joint risk was 0.1 in category (3,3). Combinations of the risk-enhancing factor and the risk-reducing factor are of considerable interest.

![Joint risk graph](image)

**Table 1.** Ratio of odds relative to category 1 (Single risk)

<table>
<thead>
<tr>
<th>Category</th>
<th>Millet gruel</th>
<th>Boiled vegetables</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1,1)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>(2,2)</td>
<td>1.7</td>
<td>5.8</td>
</tr>
<tr>
<td>(3,3)</td>
<td>3.7</td>
<td>5.6</td>
</tr>
</tbody>
</table>

*Category 1: Millet gruel: Less than twice/week
Boiled vegetables: Less than 7 times/week.

Category 2: Millet gruel: 2–6 times/week
Boiled vegetables: 7 times/week.

Category 3: Millet gruel: More than 6 times/week
Boiled vegetables: More than 7 times/week.

$\text{bcd}$ Difference was statistically significant from unity at the levels of 0.05 and 0.01, respectively.
Joint Risks of Two Factors in Esophageal Cancer

Joint risks of soybeans, including soybean products, and cabbage with three exposure levels.

Category 1. Soybeans: Less than once/week
Cabbage: Less than twice/week.

Category 2. Soybeans: 1–2 times/week
Cabbage: 2–3 times/week.

Category 3. Soybeans: More than twice/week
Cabbage: More than 3 times/week.

See Fig. 1.

Fig. 2. Joint risks of soybeans, including soybean products, and cabbage with three exposure levels (for category and the odds ratios of single risk, see Figs. 1 and 2).

A, Millet gruel and cabbage; B, Millet gruel and soybeans; C, Boiled vegetables and cabbage; D, Boiled vegetables and soybeans.

Fig. 3. Joint risks of the risk-enhancing factors and the risk-reducing factors with three exposure levels (for category and the odds ratios of single risk, see Figs. 1 and 2).
Four dose-response relations are given in Fig. 3, which indicates an impressive change. The risks due to exposure to the risk-enhancing factors declined through the risk-reducing factors. In contrast, the reverse was the case for the risks due to exposure to the risk-reducing factors. The statistical significance from unity disappeared in all joint risks. In addition, joint risk trends had no significance. However, with some combinations the risk reduction was insufficient, for example, in the combination of millet gruel and soybeans in category (3,3) (Fig. 3-B). Observed and theoretical values were 1.6 and 0.7 (\(=3.7 \times 0.2\)), respectively. To the contrary, the joint risk in figure 3-C in category (2,2) (4.8) was about 70% of the theoretical value (5.8 \(\times\) 1.2 = 7.0). It is of interest that all joint risks in category (3,3) were less than 2.0, tending to reach unity.

Neuberger and Lynch (1982) proposed a hypothetical model of EC causation with four steps: (1) disruption or breakdown of the mucosal lining of the esophagus, (2) delayed repair of damaged cells and tissues as well as mucosal replacement, (3) stimulation of the exposed cells by carcinogenic substances, and (4) a variety of cancer-prone genotypes. We believe that boiled vegetables and millet gruel play an important role in the first and second steps, respectively. Soybeans appear to contain several potential anticarcinogens (Benjamin et al. 1991; Messina and Barnes 1991), which are important in the third step. Frequent consumption of foods containing vitamin C (especially vegetables of the genus Brassica, e.g. cabbage) has been reported to be associated with a low risk of cancers of the stomach and EC (Lu et al. 1986).

For almost all joint risks, the size of the interaction appears to be in the multiplicative region. The uniform pattern across Figs. 1, 2, and 3 fails to reject the simpler multiplicative hypothesis, probably because these four risk-related factors are acting at different EC causative steps. The conclusions of this paper on the joint risk assessment can be profitable as a model for other studies in this area.

Acknowledgments

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References


