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Research Paper

# Sex Disparities in the Association of Lung Adenocarcinoma with Colorectal Cancer

Zhi-Hong Jian[1], Chia-Chi Lung[1,2], Jing-Yang Huang[1], Shih-Yung Su[1], Chien-Chang Ho[3], Yi-Chen Chiang[1,2], and Yung-Po Liaw[1,2]✉

1. Department of Public Health and Institute of Public Health, Chung Shan Medical University, Taichung City 40201, Taiwan;
2. Department of Family and Community Medicine, Chung Shan Medical University Hospital, Taichung City 40201, Taiwan;
3. Department of Health and Leisure Management, Yuanpei University, Hsinchu City 300, Taiwan.

✉ Corresponding author: Yung-Po Liaw, Department of Public Health and Institute of Public Health, Chung Shan Medical University, No. 110, Sec. 1, Chien-Kuo N. Road, Taichung City 40201, Taiwan R.O.C. Phone: +88-642-4730022 ext.11838 Fax: +88-642-3248179 Email: Liawyp@csmu.edu.tw.



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## Abstract

**Background:** Most cancers share common risk factors. It might provide evidence of shared risk factors with cancers by investigating cross-country and cross-township comparisons.

**Methods:** The data were obtained from International Association of Cancer Registries/World Health Organization and the National Cancer Registration Program of Taiwan. Age standardized incidence rates were calculated among gastric cancer, colorectal cancer and lung adenocarcinoma in 19 countries from 1995 to 1998. The Pearson correlations were also compared among 3 types of cancers for both sexes.

**Results:** The incidence rates of gastric and colorectal cancer throughout different countries show male dominance with a male-to-female sex ratio of around 2 and 1.5, respectively. Significant cross-country correlations in colorectal cancer ($r=0.918$, $p<0.001$), gastric cancer ($r=0.985$, $p<0.001$) and lung adenocarcinoma ($r=0.685$, $p=0.001$) were observed between men and women. There was a significant international correlation between colorectal cancer and lung adenocarcinoma in men ($r=0.526$, $p=0.021$), but not in women. In cross-township comparisons of Taiwan, there were significant correlations in colorectal cancer ($r=0.451$, $p<0.001$), gastric cancer ($r=0.486$, $p<0.001$), and lung adenocarcinoma ($r=0.217$, $p<0.001$) between men and women. There were links of lung adenocarcinoma and gastric cancer ($r=0.122$, $p=0.024$) and colorectal cancer ($r=0.128$, $p=0.018$) in women, and lung adenocarcinoma and colorectal cancer in men ($r=0.276$, $p<0.001$).

**Conclusions:** There were associations between lung adenocarcinoma and colorectal cancer between and in both sexes in Taiwan, but not in cross-country comparisons. The results suggest that some factor, like genes, may be important as determinants for the association between lung adenocarcinoma and colorectal cancer.

Key words: Lung adenocarcinoma, Colorectal cancer, Pearson correlation.

## Introduction

Despite an increasing cancer incidence in both genders, the effects of sex on colorectal cancer, lung cancer and gastric cancer incidence are well established and women are less likely to develop cancers than men [1, 2]. In Taiwan, lung (ranked 1st), colorectal (ranked 3rd) and gastric (ranked 6th) cancers were the top 10 of most common cause of cancer death in 2011 [3]. Variable environmental exposures, life styles and comorbidities may contribute to these findings.

Comparisons of International Agency for Research on Cancer / World Health Organization (IARC/WHO) data showed that there were associa-

tions between incidences of lung and colon cancers in men [4, 5]. The incidences of cancers in colon and lung are higher in patients with diabetes [6]. Long-term use of statins was associated with increased risk colorectal and lung cancers [7]. The hormone replacement therapy also has been reported to be associated with reduced incidence of lung and colorectal cancer [8, 9]. In addition, the epidermal growth factor receptors (EGFR) are involved in the pathogenesis and prognostic significance of solid tumors such as cancers of the lung, colon, stomach, bladder, breast, and ovary [10, 11].The cancers of different body sites seem to correlate with one another. Finally, we examined our data to determine the cancer associations with sex disparities.

## Materials and Methods

### Study Population

We compared data through the National Cancer Registration Program in Taiwan and IARC/WHO from 1995 to 1998. The data for Taiwan were obtained directly from Office of Statistics, Department of Health in Taiwan. Since incidence rates for the under 30-year age group are often low, and rates for the over 80-year group might be affected by competitive death effects and incomplete data, only rates for the age range 30 to 79 were enrolled to ensure adequate reliability of the estimates. The involved 19 countries were Australia, Canada, Denmark, England, Estonia, France, Iceland, India, Israel, Italy, Japan, The Netherlands, Poland, Singapore, Slovakia, Spain, Switzerland, United States and Taiwan. We compared age-standardized incidence rates (ASIR) among Taiwan and countries of WHO members. The significance of cross-township and cross-country correlations for gastric cancer, colon cancer and lung adenocarcinoma were evaluated for both sexes.

### Statistical Analysis

ASIR were calculated by using world population for 1976 as the reference [12]. The significance of correlations among tumor types for cross-township and cross-country comparisons was evaluated with the SAS ver. 9.2 software package (SAS Institute, Cary, NC, USA). Correlation coefficients were generated by Pearson correlation coefficients, with $p<0.05$ considered to be significant.

## Results

The ASIR from gastric cancer, colorectal cancer and lung adenocarcinoma per 100000 person-year in 19 countries from 1995 to 1998 are presented in Table 1. The highest incident rates were people in Japan for gastric cancer, men in Slovakia and women in Australia for colorectal cancer, and people in United States for lung adenocarcinoma. The range of male-female sex ratio among countries was 1.8 in India to 2.8 in France for gastric cancer, 1.1 in India to 1.9 in Slovkia for colorectal cancer, and 1.0 in Iceland to 4.7 in Spain for lung adenocarcinoma. These ratios remained relatively constant for gastric and colon cancer, but there were high varieties in sex ratio for lung adenocarcinoma.

**Table 1.** Age standardized incidence rate in the age range 30 to 79 (per 100000 person year) from stomach and colorectal cancer, and lung adenocarcinoma in 19 countries, 1995-1998.

| Country | Colorectal cancer | | | Gastric cancer | | | Lung adenocarcinoma | | |
|---|---|---|---|---|---|---|---|---|---|
| | Male | Female | Ratio | Male | Female | Ratio | Male | Female | Ratio |
| Australia | 98.0 | 65.5 | 1.5 | 19.4 | 8.3 | 2.3 | 21.9 | 10.8 | 2.0 |
| Canada | 81.5 | 55.0 | 1.5 | 16.9 | 7.2 | 2.3 | 29.9 | 23.9 | 1.3 |
| Denmark | 74.4 | 58.6 | 1.3 | 15.2 | 6.9 | 2.2 | 28.2 | 25.1 | 1.1 |
| England | 77.1 | 48.4 | 1.6 | 28.0 | 10.9 | 2.6 | 16.7 | 11.2 | 1.5 |
| Estonia | 65.9 | 42.2 | 1.6 | 68.3 | 29.8 | 2.3 | 10.6 | 3.2 | 3.3 |
| France | 85.7 | 49.6 | 1.7 | 22.0 | 8.0 | 2.8 | 30.7 | 7.0 | 4.4 |
| Iceland | 57.4 | 40.1 | 1.4 | 24.1 | 9.8 | 2.5 | 22.9 | 23.7 | 1.0 |
| India | 11.4 | 9.8 | 1.1 | 17.7 | 9.6 | 1.8 | 4.2 | 2.0 | 2.1 |
| Israel | 75.1 | 61.4 | 1.2 | 23.0 | 12.4 | 1.9 | 14.8 | 8.3 | 1.8 |
| Italy | 85.9 | 55.1 | 1.6 | 45.2 | 22.7 | 2.0 | 34.4 | 8.4 | 4.1 |
| Japan | 90.7 | 50.3 | 1.8 | 123.5 | 47.8 | 2.6 | 27.5 | 14.1 | 2.0 |
| Netherlands | 90.3 | 60.8 | 1.5 | 29.3 | 10.8 | 2.7 | 26.3 | 9.1 | 2.9 |
| Poland | 58.6 | 38.4 | 1.5 | 33.1 | 13.0 | 2.5 | 12.3 | 4.4 | 2.8 |
| Singapore | 85.9 | 60.0 | 1.4 | 46.0 | 22.8 | 2.0 | 34.0 | 18.7 | 1.8 |
| Slovakia | 101.3 | 52.3 | 1.9 | 42.3 | 17.2 | 2.5 | 16.0 | 4.1 | 3.9 |
| Spain | 64.7 | 43.1 | 1.5 | 28.6 | 11.6 | 2.5 | 17.5 | 3.7 | 4.7 |
| Switzerland | 66.0 | 41.2 | 1.6 | 19.1 | 9.3 | 2.1 | 26.1 | 14.5 | 1.8 |
| United States | 77.1 | 54.8 | 1.4 | 14.8 | 6.3 | 2.3 | 39.5 | 29.4 | 1.3 |
| Taiwan | 23.5 | 19.2 | 1.2 | 15.1 | 8.0 | 1.9 | 19.2 | 15.5 | 1.2 |

Cross-country comparisons of cancers between men and women are present in Table 2a. Significant correlations in colorectal cancer, gastric cancer and lung adenocarcinoma were observed between men and women, with Pearson's correlation 0.918 ($p<0.001$), 0.985 ($p<0.001$) and 0.685 ($p=0.001$), respectively. There was a positive correlation between lung adenocarcinoma in men and colorectal cancer in women ($r=0.571$, $p=0.011$). The results for pairs of cancers in 19 countries are listed for men in Table 2b and for women in Table 2c. There was a significant correlation between colorectal cancer and lung adenocarcinoma in men ($r=0.526$, $p=0.021$), but not in women ($r=0.278$, $p=0.250$).

Cross-township comparisons of cancers between Taiwanese men and women are showed in Table 3a. There were significant correlations in colorectal cancer ($r= 0.451$, $p<0.001$), gastric cancer ($r=0.486$, $p<0.001$) and lung adenocarcinoma ($r=0.217$, $p<0.001$) between men and women. Significances between male colorectal cancer and female lung adenocarcinoma ($r=0.280$, $p<0.001$), and male lung adenocarcinoma and female colorectal cancer ($r=0.258$, $p<0.001$) were also observed. The results for significance of correlation coefficients for pairs of cancers in Taiwan are presented for men in Table 3b and for women in Table 3c. There were links of lung adenocarcinoma and gastric cancer ($r=0.122$, $p=0.024$) and colorectal cancer ($r=0.128$, $p=0.018$) in women, and lung adenocarcinoma and colorectal cancer ($r=0.276$, $p<0.001$) in men. There was a trend between cancers of stomach and colorectum in men, but it did not reach significance ($r=0.101$, $p=0.062$).

**Table 2a.** Cross 19 country correlations of cancers between men and women.

| Site and tumor type | Female | | |
|---|---|---|---|
| Male | Colorectum | Stomach | Lung adenocarcinoma |
| Colorectum | | | |
| r | 0.918 | 0.263 | 0.110 |
| *p* | <0.001 | 0.276 | 0.651 |
| Stomach | | | |
| r | 0.107 | 0.985 | -0.202 |
| *p* | 0.662 | <0.001 | 0.406 |
| Lung adenocarcinoma | | | |
| r | 0.571 | 0.010 | 0.685 |
| *p* | 0.011 | 0.966 | 0.001 |

**Table 2b.** Cross 19 country correlations between cancers in men.

| Site and tumor type | Colorectum | Stomach | Lung adenocarcinoma |
|---|---|---|---|
| Colorectum | | | |
| r | 1 | 0.301 | 0.526 |
| *p* | | 0.209 | 0.021 |
| Stomach | | | |
| r | | 1 | 0.012 |
| *p* | | | 0.960 |
| Lung adenocarcinoma | | | |
| r | | | 1 |
| *p* | | | |

**Table 2c.** Cross 19 country correlations between cancers in women.

| Site and tumor type | Colorectum | Stomach | Lung adenocarcinoma |
|---|---|---|---|
| Colorectum | | | |
| r | 1 | 0.095 | 0.278 |
| *p* | | 0.700 | 0.250 |
| Stomach | | | |
| r | | 1 | -0.216 |
| *p* | | | 0.374 |
| Lung adenocarcinoma | | | |
| r | | | 1 |
| *p* | | | |

**Table 3a.** Cross 346 township correlations of cancers between male and female Taiwanese.

| Site and tumor type | | | Female |
|---|---|---|---|
| Male | Colorectum | Stomach | Lung adenocarcinoma |
| Colorectum | | | |
| r | 0.451 | -0.035 | 0.280 |
| *p* | <0.001 | 0.518 | <0.001 |
| Stomach | | | |
| r | -0.027 | 0.486 | -0.045 |
| *p* | 0.616 | <0.001 | 0.402 |
| Lung adenocarcinoma | | | |
| r | 0.258 | -0.007 | 0.217 |
| *p* | <0.001 | 0.902 | <0.001 |

**Table 3b.** Cross 346 township correlations between cancers in male Taiwanese.

| Site and tumor type | Colorectum | Stomach | Lung adenocarcinoma |
|---|---|---|---|
| Colorectum | | | |
| r | 1 | -0.035 | 0.276 |
| *p* | | 0.512 | <0.001 |
| Stomach | | | |
| r | | 1 | 0.101 |
| *p* | | | 0.062 |
| Lung adenocarcinoma | | | |
| r | | | 1 |
| *p* | | | |

**Table 3c.** Cross 346 township correlations between cancers in female Taiwanese.

| Site and tumor type | Colorectum | Stomach | Lung adenocarcinoma |
|---|---|---|---|
| Colorectum | | | |
| r | 1 | 0.020 | 0.128 |
| *p* | | 0.717 | 0.018 |
| Stomach | | | |
| r | | 1 | 0.122 |
| *p* | | | 0.024 |
| Lung adenocarcinoma | | | |
| r | | | 1 |
| *p* | | | |

## Discussion

We found that the sex ratio in cancers varied geographically. The incidences of gastric and colorectal cancer throughout different populations show male dominance with a constant male-to-female ratio. This sex ratio cannot be completely attributed to the disparities in the prevalence of known risk factors between the sexes [13, 14]. Recent advances in the molecular biology of gastric and colorectal cancer have led to greater understanding of the effect of estrogen in carcinogenesis. Estrogen has a potentially protective effect against the development of colorectal cancer [15] and invasions of gastric cancer [16], and may be the cause of improved prognosis of colorectal cancer in premenopausal women [17]. Also, women on hormone replacement therapy seem to have a decreased risk of gastric and colorectal cancer [18]. However, use of tamoxifen, an antagonist of the estrogen receptor, in women seems to increase their risk of gastric cancer [19].

Moore et al. conducted cross-country comparisons for cancer incidence in men [4, 5] and concluded that some factors could be involved in the association between lung adenocarcinoma and colorectal cancer. Cigarette smoke contains many carcinogens, and the gastrointestinal tracts are exposed to these compounds through the circulation or direct ingestion of saliva [20]. The relationships between smoking and increased risks of gastric and colorectal cancer have been established [21, 22]. However, few studies examining the effects of passive smoke exposure on risk of gastric cancer report inconsistent results [23, 24]. Passive smoke exposure on risk of colorectal cancer shows no association among women [25]. In Taiwan, lung adenocarcinoma and colorectal cancer were correlated in both sexes and between sexes, but not in the cross-country comparisons. Most of the female lung cancer patients in Taiwan were non-smokers and the proportion was more than 90% [8]. The relationship with passive smoking and smoking might be limited and incompatible with the observed association between lung adenocarcinoma and colorectal cancer so that other factors must be operating.

Obesity and overweight have become a global problem in the last decade. Given its documented promoting effects on colon carcinogenesis, insulin resistance and hyperinsulinaemia are certainly key biological mechanisms involving in tumor development [26]. The data from Taiwan National Health Insurance showed that the incidences of the most common cancers, such as liver, colon, lung, and prostate cancer increased independently in diabetic patients with hypertension, dyslipidemia, and gout [6]. Use of insulin was also reported to be associated with higher risks for liver, colorectal, lung, stomach, and pancreas cancer in type 2 diabetes in Taiwan [27]. The use of anti-diabetes drugs also has been reported to decrease the risk of lung cancer in diabetes patients [28]. Insulin resistance might play a role in the association between lung adenocarcinoma and colorectal cancer in Taiwanese, but it was not consistent with cross-country comparisons.

In Taiwan, the incidence of lung cancer is increasing and lung adenocarcinoma is the most common histological subtypes of lung cancer [29]. Among lung cancer patients without traditional risk factors, a substantial proportion of patients are found to have oncogene-driven malignancies, such as EGFR. It has been reported that mutations in genes encoding EGFR pathway proteins result in multiple aberrations in the signal-transduction pathways and dysregulation of the tyrosine kinase activity, and lead to tumor cell proliferation, inhibition of apoptosis, and dissemination [30]. More than 60% of non–small-cell lung cancers show EGFR overexpression [31], which is negatively prognostic [32]. The frequency of tumor EGFR mutations was found to be higher in East Asian ethnicity, such as Taiwan [33, 34].

Luo et al. found that multiple primary malignancies occurred more frequently in patients with lung adenocarcinoma and classic EGFR mutation [35]. Amplification and overexpression of EGFR also have been involved in development of numerous types of human cancer [36]. EGFR is widely expressed in colonic tissues and EGFR genes have gender-specific prognostic significance in colon cancer [37]. Wang et al. reported that low EGFR expression in patients with colorectal cancer was associated with low tumor metastasis and better survival [38]. Besides, amplification or overexpression of EGFR is present in gastric carcinomas with independent prognostic value [39, 40]. EGFR mutations and overexpression have been intensely pursued as extremely valuable for treatment of lung adenocarcinoma patients in Asian countries

including Taiwan, where the EGFR mutation rate is higher than in the rest of the world.

One of the strengths of our study was the use of registered database, which was population-based and highly representative. A number of important limitations warrant discussion. First, we did not obtain basic information on smoking rate, air pollution, physical inactivity, incidence of diabetes, and dietary habits and rate of Helicobacter pylori infection. Second, as a result of modernization and life style changes globally, the incidence of the studied countries may have changed. The results from data collected between 1995 and 1998 could be established as a reference or model to which future studies could compare.

## Conclusions

International and cross-township comparisons of tumor incidences can provide information on risk factors shared by different tissue sites. The main finding of our study is that link between lung adenocarcinoma and colorectal cancers may be associated with the increased risk in adenocarcinoma. To find shared candidate genes will lead to an understanding of the genetic associations and sex disparities among cancers, the development of more effective treatments, and better guiding future risk-stratification efforts , especially Taiwanese susceptible to adenocarcinoma.

## Abbreviations

ASIR: Age-standardized incidence rates; EGFR, epidermal growth factor receptors; IARC/WHO: International Agency for Research on Cancer / World Health Organization.

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### Authors' contributions

YPL was responsible for designing the study. ZHJ was responsible for drafting the manuscript. CCL, JYH, SYS, CCH and YCC did the statistical programming and helped with manuscript revisions. All authors read and approved the final manuscript.

## Competing Interests

The authors declare that they have no competing interests.

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