# Secondary Primary Cancer after Primary Gastric Cancer

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Advances in cancer screening and early detection, as well as improvements in surgical techniques and therapeutics, have contributed to decreasing gastric cancer mortality. The number of gastric cancer survivors continues to rise; however, long-term follow-up has revealed an increase in the risk of post-gastrectomy symptoms or other health problems, such as extra-gastric secondary primary cancer (SPC), in these survivors. The characteristics of SPC are of increasing interest to both treatment providers and gastric cancer survivors.

gastric cancer secondary primary cancer

## 1. Introduction

Cancer research and advances in cancer treatment modalities have increased the rates of overall survival in cancer patients. After completion of cancer treatment, cancer survivors return to pre-treatment life, but their quality of life is not the same as before treatment. Patients face financial burden, psychological difficulty, work-related problems, and physiological changes in the body after organ resection [1]. Along with providing emotional support and explaining the disease to patients, health care providers should also be aware that secondary primary cancers (SPCs) can develop in cancer survivors.

In gastric cancer, the development of new chemotherapeutic agents and advances in surgical techniques have resulted in more survivors in recent decades [2][3][4][5][6]. In East Asian countries, the advent of national screening programs has resulted in more than half of all gastric cancer patients being diagnosed with early stage tumors, and their 5-year survival rate exceeds 90% [2][7][8]. SPCs affect the long-term survival of cancer survivors, and several national and institutional database studies have been published previously.

## 2. Epidemiology of SPCs

Previous studies on the incidence of SPCs can be divided into two categories according to their scope, namely single institution- and nationwide population-based studies. Single institution-based studies with more than one thousand patients are summarized **Table 1** [9][10][11][12][13][14][15][16][17][18][19]. Most studies on SPCs were performed in regions with a high prevalence of gastric cancer. The incidence of SPC in gastric cancer patient survivors varies between 1.0% and 6.6%. Synchronous tumors were defined as those with a time interval between SPC and gastric cancer diagnosis of less than 6 months, and metachronous tumors were defined as those with more than 6

months. The development of SPCs after gastric cancer mainly occurred within 2 years of diagnosis including synchronous tumor [15][17][18].

**Table 1.** List of single institutional-based studies on the incidence of secondary primary cancer (SPC) after gastric cancer.

| Authors | Country | Publication Year | Number of Patients | Incidence of SPC | Synchronous/ Metachronous | Common SPCs |
|---|---|---|---|---|---|---|
| Takekuni K et al. [9] | Japan | 1999 | 1925 | 127 (6.6%) | N/A | Lung, liver, colorectum, esophagus, and pancreas |
| Dinis-Ribeiro M et al. [10] | Portugal | 2002 | 2268 | 78 (3.4%) | 21/57 | Colorectum, breast, uterus, urinary tract, and lymphoma |
| Ikeda Y et al. [11] | Japan | 2003 | 2250 | 95 (4.2%) | 48/47 | Colorectum, lung, liver, esophagus, and breast |
| Ikeda Y et al. [12] | Japan | 2005 | 1070 | 54 (5.0%) | 0/54 | Lung, colorectum, esophagus, breast, and liver |
| Park YK et al. [13] | Korea | 2005 | 2509 | 65 (2.6%) | 17/48 | Colorectum, breast, hepatobiliary, esophagus, and uterus |
| Lee JH et al. [14] | Korea | 2006 | 3291 | 111 (3.4%) | 111/0 | Colorectum, lung, esophagus, liver, and breast |
| Molinero M et al. [15] | Spain | 2006 | 1170 | 23 (1.96%) | 11/12 | Colorectum, multiple myeloma, prostate, lung, and kidney |
| Ha TK et al. [16] | Korea | 2007 | 10,090 | 96 (1.0%) | 96/0 | Colorectum, liver, kidney, pancreas and gallbladder |
| Eom BW et al. [17] | Korea | 2008 | 4593 | 159 (3.4%) | 49/110 | Colorectum, lung, liver, kidney, and lymphoma |
| Kim JY et al. [18] | Korea | 2012 | 5778 | 214 (3.70%) | 0/214 | Colorectum, lung, liver, ovary, and cervix |
| Kim C et al. [19] | Korea | 2013 | 3066 | 70 (2.5%) | 32/38 | Colorectum, lung, liver, gallbladder, and head and neck |

Nationwide population-based studies in Japan, Taiwan, United States of America, Portugal, and Sweden are available and listed in **Table 2** [20][21][22][23][24]. The incidence of SPCs in patients with gastric cancer ranges from

SPC, secondary primary cancer; N/A, not applicable.

4.4% to 5.5%. In most studies, the risk of SPC in patients with gastric cancer was estimated using standardized incidence ratio (SIR), which is defined as the number of observed cancer occurrences divided by the expected number. The expected number of cancers was calculated by multiplying the first primary cancer incidence by the person-years after first primary cancer diagnosis in the general population. The SIR for all SPCs in gastric cancer patients ranges from 0.91 to 1.46. The most common SPC site after gastric cancer is the gastrointestinal tract, such as esophagus, small intestine, and colon. Some studies showed increased incidences of SPCs in thyroid, pancreas, bone and soft tissues, ovaries, bladder, kidney, liver, and intrahepatic bile duct, and non-Hodgkin's lymphoma. By contrast, the incidence of SPCs in lung, breast and prostate, melanoma, and myeloma decreased after a diagnosis of gastric cancer.

**Table 2.** List of nationwide population-based studies on the incidence of secondary primary cancer (SPC) after gastric cancer.

| Country of Study | Publication Year | Number of Patients | Statistical Significance | SPC Site |
|---|---|---|---|---|
| Japan [20] | 2014 | 174,477 | 3225 (1.8%) patients had SPC. | SIR for all cancers, 1.09.<br>SIR for esophagus cancer, 1.70<br>SIR for colorectum cancer, 1.35 |
| Taiwan [21] | 2016 | 47,729 | 2110 (4.42%) patients had SPC.<br>SIR for all cancer, 1.46 | SIR for head and neck, 1.34.<br>SIR for esophagus, 2.16.<br>SIR for colon and rectum, 1.37.<br>SIR for bones and soft tissues, 1.95.<br>SIR for ovaries, 2.89.<br>SIR for bladder, 1.47.<br>SIR for kidneys, 1.44.<br>SIR for non-Hodgkin's lymphoma, 5.56. |
| the United States [22] | 2016 | 33,720 | 1838 (5.45%) patients had SPC with O/E ratio of 1.11. | Gastrointestinal O/E ratio, 1.71.<br>Biliary O/E ratio, 1.30,<br>Pancreatic O/E ratio, 1.60.<br>Thyroid O/E ratio 2.00. |
| Portugal [23] | 2017 | 7427 | 331 (4.5%) patients had SPC (26.9% synchronous and 73.1% metachronous).<br>10-year cumulative incidence of SPC, 4.8%<br>SIR for all cancer, 1.30 (male) and 1.20 (female) | SIR for esophagus, 4.99 (male) and 8.03 (female).<br>SIR for small intestine, 11.04 (male) and 13.08 (female).<br>SIR for colon, 2.42 (male) and 2.58 (female).<br>SIR for non-Hodgkin's |

| Country of Study | Publication Year | Number of Patients | Statistical Significance | SPC Site |
|---|---|---|---|---|
| | | | | lymphoma, 2.53 (male). SIR for liver and intrahepatic bile duct, 5.18 (female). |
| Sweden [24] | 2021 | 23,137 | 1042 (4.5%) patients had SPC. | SIR for esophagus, 2.15. SIR for small intestine, 4.12. SIR for kidney, 1.62. |

SPC, secondary primary cancer; O/E, observed/expected; SIR, Standardized Incidence Ratio.

oma after
l bladder, whereas in women, the incidences of SPCs were elevated in bone and soft tissue, ovaries, kidneys, liver and intrahepatic bile ducts. The incidence of SPCs in gastric cancer survivors was higher in men than in women [12][19][21][23].

## 3. Biology of SPCs

Several risk factors for gastric cancer have been documented, namely *Helicobacter pylori* infection, male sex, old age, low socioeconomic status, smoking, alcohol consumption, salted food intake, preserved food, genetic factors, and familial predisposition [25]. These factors often overlap with risk factors for other cancers.

Consumption of preserved foods increases the risk of gastric cancer, hepatocellular carcinoma, nasopharyngeal carcinoma breast cancer, and prostate cancer [26][27][28][29][30][31]. By contrast, low intake of vegetables is known to lead to gastric cancer, lung cancer, hepatocellular carcinoma, and nasopharyngeal cancer [25][32][33][34]. Smoking is the major risk factor for cancers at several sites, such as stomach, oropharynx, larynx, esophagus, and lung [25][35][36][37][38][39]. In a previous study, seven out of nine patients (77.7%) with SPCs after gastric cancer consumed tobacco [40]. A synergy between smoking and alcohol consumption was also identified as contributing to carcinogenesis [41][42].

Chemo/radiotherapy has been proposed to contribute to the development of SPCs. Treatments for the first malignancy may contribute to the development of SPCs by causing damage to specific regions of DNA, chromosomal rearrangements, or chromosome loss [43][44]. Some genetic factors have been found to be associated with the development of gastric and other cancers. Microsatellite instability is closely associated with gastric and sporadic colorectal carcinoma [45][46][47]. Lynch syndrome, an autosomal dominant inherited cancer predisposition syndrome, is a risk factor for tumors of gastric, colorectal, small bowel, gallbladder, and biliary tract, and is also associated with microsatellite instability [48][49][50]. In addition, several hereditary diseases, such as Li-Fraumeni syndrome, breast-ovarian cancer syndrome, multiple endocrine neoplasia, Peutz-Jegher syndrome, and Cowden syndrome, increase the risk of gastric and other cancers [40][51].

## 4. Predisposing Factors for SPCs

A Taiwanese population-based study employing multivariate logistic regression analysis demonstrated that age over 70 years, male sex, and comorbidities, such as diabetes mellitus, chronic obstructive pulmonary disease, and liver cirrhosis are risk factors for developing SPCs [21]. Several single institution-based studies found several risk factors for developing SPCs after gastric cancer, such as age over 60 years, differentiated histology, earlier stage gastric cancer, and multiplicity of lesions [14][19].

## 5. Prognosis of Patients with SPCs

The long-term outcomes of gastric cancer patients with SPCs have not been reported by national population-based studies. However, several single-institutional retrospective studies have reported the long-term survival outcomes of gastric cancer patients with SPCs. In a Korean study, the 5-year overall survival rate according to gastric cancer stage regardless of SPC site was as follows; 61% for stage I, 39% for stage II, 30% for stage III, and 0% for stage IV [16]. In studies comparing the survival outcomes of patients with and without SPCs, the 5-year survival rates of patients with SPCs were statistically poorer than those of patients without SPCs [18][19]. In addition, the 5-year survival rate of patients without SPCs was 76.5%, that of patients with metachronous SPC was 67.5%, and that of patients with synchronous SPC was 34.1%, which were statistically significant ($p < 0.001$ for metachronous SPC vs. no SPC and $p < 0.001$ for synchronous SPC vs. no SPC). In a Japanese study analyzing 10-year survival rates, the survival rate of patients with metachronous SPC was higher than that of patients without SPC or with synchronous SPC (75.2% for metachronous SPC; 69.3% for no SPC; and 40.1% for synchronous; $p < 0.01$) [11]. The 5-year survival of metachronous SPC patients was significantly superior to that of synchronous SPC patients in a Korean retrospective study (77.9% for metachronous SPC and 55.2% for synchronous SPC; $p = 0.002$) [17]. However, in a Spanish study, no significant differences in survival rates were found between patients with synchronous and those with metachronous SPC [15].

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