Epidemiology of Esophageal Squamous Cell Carcinoma

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Abstract

Esophageal cancer is the eighth most common cancer worldwide and the sixth most common cause of death from cancer. More than 80% of esophageal cancer cases and deaths occur in developing countries, and approximately 80–90% are squamous cell carcinomas in the high-incidence regions. The incidence rates of esophageal cancer show wide variation internationally. It has been shown to be more common among men than women in general. Of note, it is approximately five times more common among males in Japan. Both incidence and mortality are on the rise in number since 1960 due to the aging of Japanese population, while age-adjusted mortality rates are decreasing in both males and females. Convincing risk factors for esophageal squamous carcinoma include tobacco smoking and alcohol consumption, while suggestive protective factors are fruit and vegetable intake. Likewise, intake of high-temperature beverages and foods show high probability of increasing risk through heat damage in the esophagus. Approximately 88% of male esophageal cancer (52% for females) in Japan is thought to have been avoidable by lifestyle improvements such as refraining from smoking of tobacco and alcohol use, while maintaining sufficient fruit and vegetable intake.

Keywords

Esophageal cancer · Time trend · Risk factor · Tobacco smoking · Alcohol consumption

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1.1 Esophageal Cancer in the World and Japan

1.1.1 Esophageal Cancer in the World: Burden, Geographical Difference, and Trends

1.1.1.1 Global Burden and Geographical Difference (Global Cancer Observatory, https://gco.iarc.fr/)

Esophageal cancer is the eighth most common cancer worldwide, with 572,000 new cases (3.2% of the total) estimated in 2018, and the sixth most common cause of death from cancer with 508,600 deaths (5.3% of the total). These figures encompass both adenocarcinoma and squamous cell carcinoma types. More than 80% of esophageal cancer cases and deaths occur in developing countries.

The incidence rates of esophageal cancer vary internationally more than tenfold in men (Age-standardized incidence rate to the World population (ASR) 17.9 per 100,000 in Eastern Asia compared to 1.6 in Western Africa/ Central America), and almost 15-fold in women (ASR 7.1 per 100,000 in Eastern Africa compared to 0.46 in Central America) (Fig. 1.1). The incidence rate in China is one of the highest, (19.7 in men and 8.2 in women), while also relatively high in Japan (9.3 in men and 1.9 in women).

Esophageal cancer is more common among men than women in general. Of note, it is approximately five times more common among men in Japan and 13 times more common among men in Korea. These differences in sex ratio may suggest different etiologies by region. In Japan and Korea, tobacco smoking and alcohol drinking are assumed to be major causes of esophageal cancer and the predominant incidence rate among males is associated with a much higher prevalence of smoking of tobacco and alcohol use among men versus women. In China and Southern Africa, an important risk factor, in addition to tobacco smoking and alcohol drinking, is thought to be nutrient deficiency such as vitamins and micronutrients, which occurs equally in both men and women. However, the apparent reason for geographic variations is unspecified.

1.1.1.2 Histological Type [1]

In those high-incidence regions that provide information on histological type, approximately 80–90% are squamous cell carcinomas (Fig. 1.2). This is in contrast to some lower-risk populations, such as Caucasian Americans and Europeans, where adenocarcinomas are predominant. For example, in the United States, SEER (Non-Hispanic White) indicated ASR 5.5 in men where 75% of cases are coded as adenocarcinoma as opposed to 17% squamous cell carcinoma. In contrast, Japan, Nagasaki indicated ASR 11.6 in men where only 6% as adenocarcinoma as opposed to 91% squamous cell carcinoma.

1.1.2 Esophageal Cancer in Japan (Cancer Information Service, https://ganjoho.jp)

In 2017, 9580 men and 1988 women died from esophageal cancer, representing 4.3% and 1.3% of total cancer death in men and women, respectively. Mortality

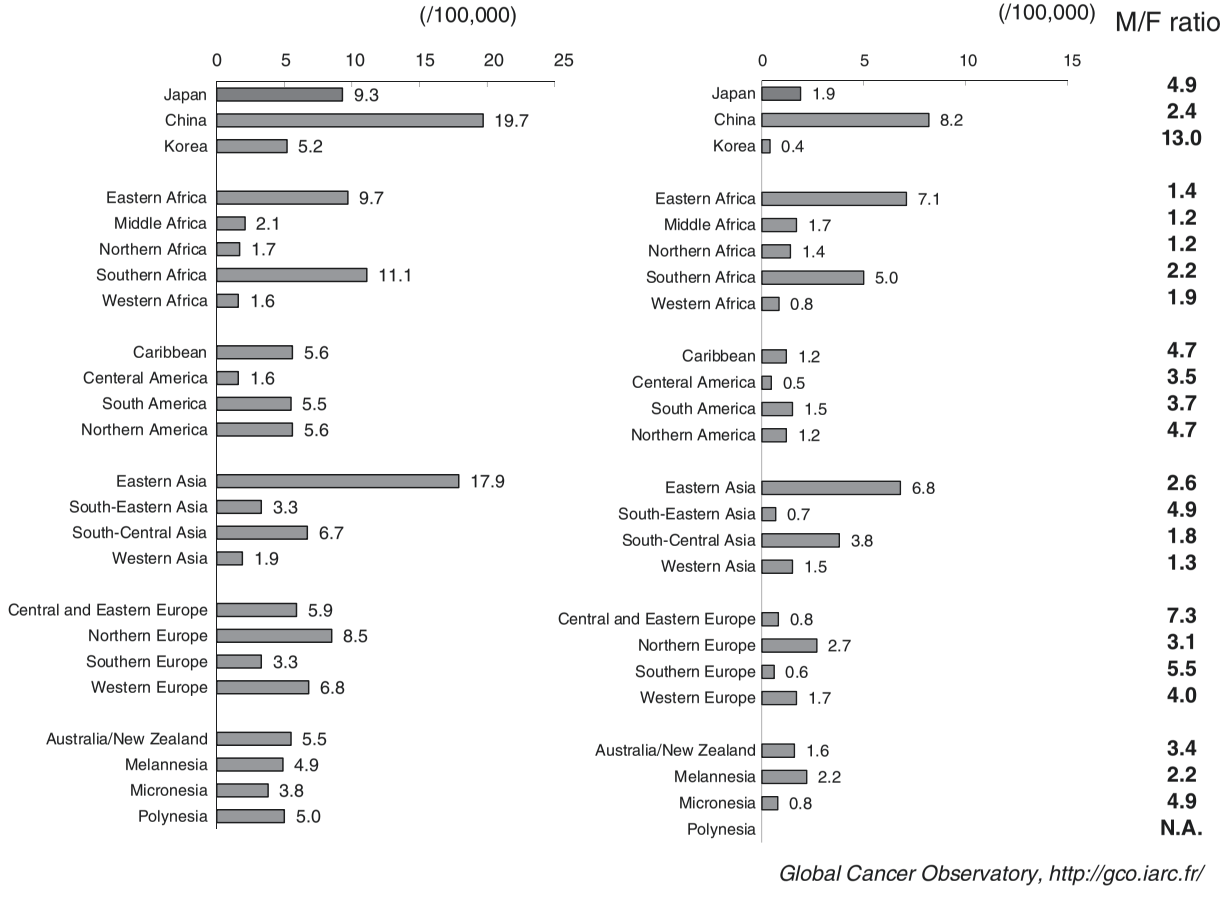
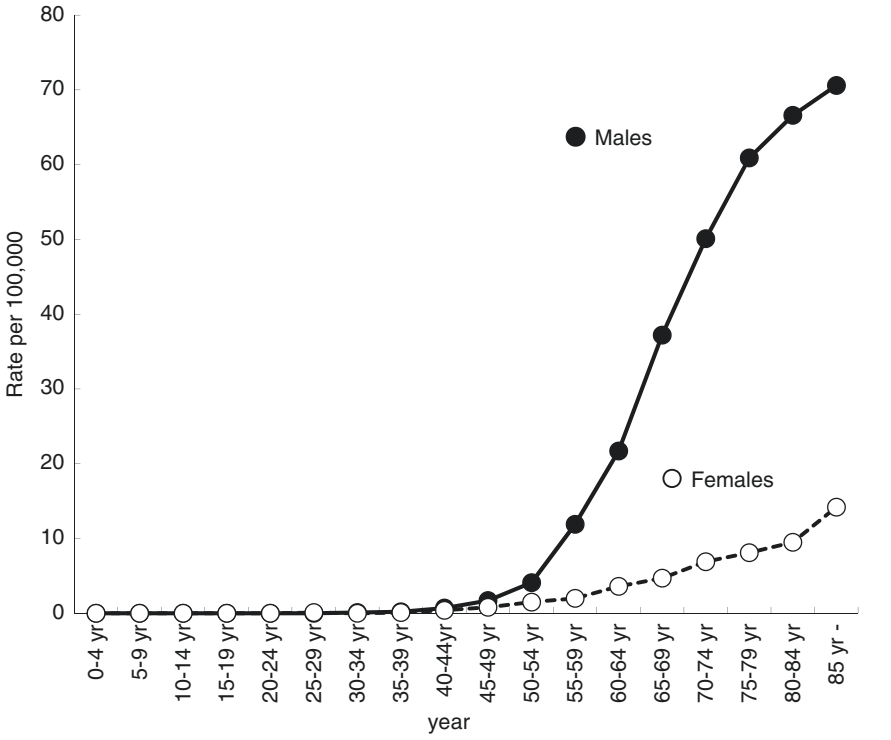


Fig. 1.1 Age-standardized incidence rate (World population) of esophageal cancer in the world (2018)

Fig. 1.2 Esophageal cancer—histological distribution percentage (2008–2012) [1]

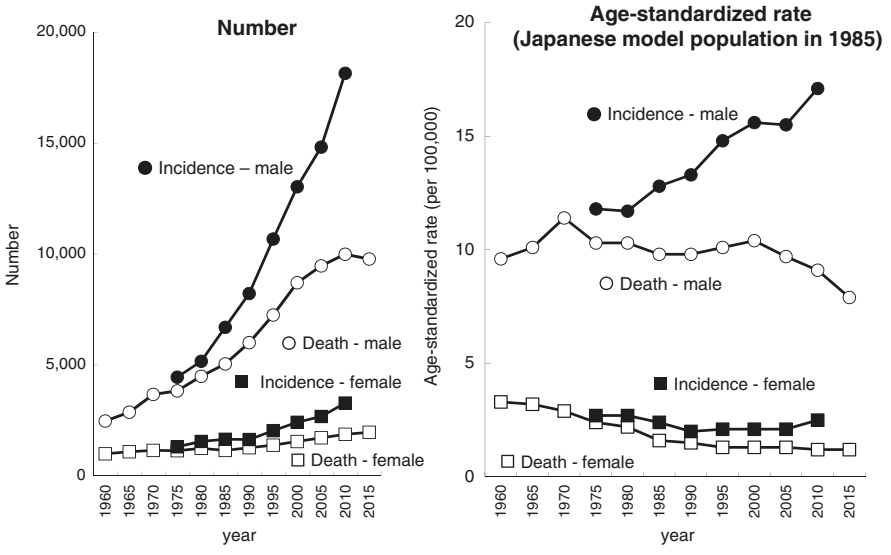
rates increased with age rapidly after 40 years (Fig. 1.3). The mortality rate of esophageal cancer is estimated to be 0.55% in men and 0.09% in women up to 75 years, increasing to 1.06% in men and 0.20% in women over a lifetime. Regarding incidence, 19,233 men and 3551 women were estimated to be diagnosed with esophageal cancer in 2014 and probability of esophageal cancer diagnosis was 1.36% in men and 0.23% in women up to 75 years, increasing to 2.28% in men and 0.46% in women for lifetime. Five-year survival rates were 36.0% in men and 43.9% in women who were diagnosed with esophageal cancer in 2006–2008 based on the population-based cancer registry.

Both incidence and mortality are observed to have increased in number since 1960 due to the aging of Japanese population (Fig. 1.4, Left), while age-standardized mortality rates tended to have been decreasing in both males and females (Fig. 1.4, Right). Histological distribution trends were analyzed using 8 population-based cancer registries with high level of reliability from 1993 to 2001 [2] and the Miyagi Prefectural Cancer Registry from 2000 to 2010 (Fig. 1.5). Squamous cell carcinoma was the predominant type of esophageal cancer in Japan, and a remarkable increase in adenocarcinoma was not observed until 2010. Disparity in the



Source: Center for Cancer Control and Information Services, National Cancer Center, Japan

Fig. 1.3 Age-specific mortality rate of esophageal cancer in Japan (2017)



Source: Vital statistics and Estimates from the population-based cancer registry

Fig. 1.4 Time trends in the incidence and mortality of esophageal cancer in Japan

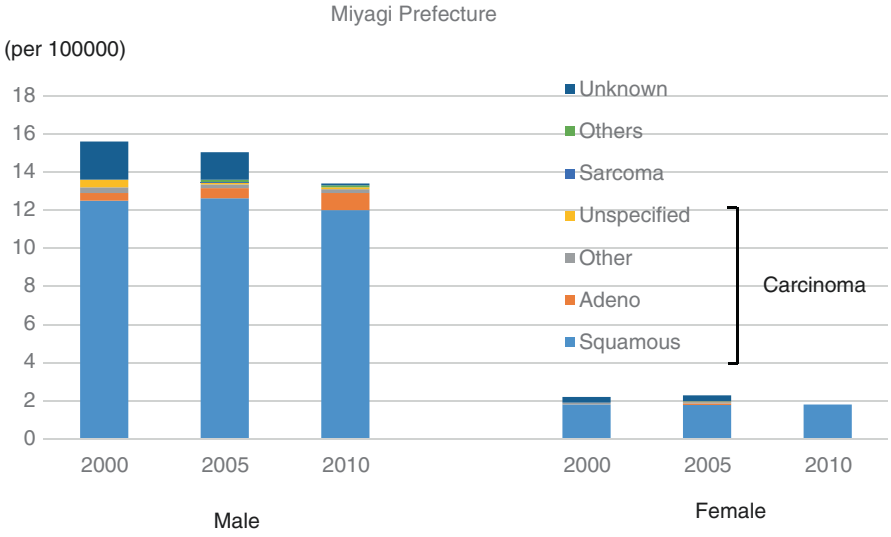


Fig. 1.5 Time trends in the age-standardized (world population) incidence of esophageal cancer by histological subtype in Japan [1]

classification of esophageal and gastric cardia adenocarcinoma may have led to underestimation of esophageal adenocarcinoma incidence.

An increased trend of adenocarcinoma of the esophago–gastric junction was observed among patients who had underwent surgery for advanced gastric adenocarcinoma in the National Cancer Center Hospital in Tokyo, from 2.3% in 1962–1965 to 10.0% in 2001–2005, however, the proportion of Siewert Type I (defined as adenocarcinoma of the distal esophagus) had remained very rare (approximately 1% among adenocarcinoma of the esophago–gastric junction) [3]. Since this finding was confined to operative cases with advanced gastric adenocarcinoma, the proportion of Siewert's type I tumors may have been underestimated.

1.2 Risk Factors

Established risk and protective factors for esophageal cancer are listed according to the level of certainty (Table 1.1). Tobacco smoking and alcohol consumption are convincing risk factors for esophageal cancer, especially squamous cell carcinoma [4–6]. Acetaldehyde associated with the consumption of alcoholic beverages has also been judged as a convincing risk factor for esophageal squamous cell carcinoma [7]. Very hot beverages including, but not limited to, mate, a traditional herbal beverage consumed in parts of South America, has been identified as a probable cause of esophageal squamous cell carcinoma [8]. Physical activity and vegetables may prevent both types of esophageal cancer [6].

Table 1.1 Established risk and protective factors for esophageal cancer

Evidence	Risk factors	Protective factors
Convincing	Tobacco smoking[a] Alcohol consumption[bc](squamous cell carcinoma) Acetaldehyde associated with consumption of alcoholic beverages[d] Body fatness [c](adenocarcinoma)	–
Probable	Mate[c] (squamous cell carcinoma) Very hot beverages including, but not limited to, mate[e](squamous cell carcinoma)	–
Limited suggestive	Processed meat[c] (squamous cell carcinoma)	Physical activity[c] Vegetables[c] Fruit[c] (squamous cell carcinoma)

[a]IARC monograph on the Evaluation of Carcinogenic Risks to Humans, Volume 83 (2003) [4]
[b]IARC monograph on the Evaluation of Carcinogenic Risks to Humans, Volume 96 (2007) [5]
[c]World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018.
Diet, nutrition, physical activity, and esophageal cancer [6]. Available at dietandcancerreport.org
[d]IARC monograph on the Evaluation of Carcinogenic Risks to Humans, Volume 100E (2012) [7]
[e]IARC monograph on the Evaluation of Carcinogenic Risks to Humans, Volume 116 (2018) [8]

1.2.1 Tobacco Smoking and Alcohol Consumption

The main risk factors for esophageal squamous cell carcinoma (ESCC) are tobacco smoking and alcohol consumption, which in individual studies have been found to account for 75–90% of cases [9]. The risk of esophageal cancer increases rapidly with the amount of both tobacco smoking and alcohol consumption, with no evidence of any threshold effect for either.

In Japan, four cohort studies and 11 case-control studies tested the association between tobacco smoking and esophageal cancer risk [10]. With the exception of three case-control studies, all cohort studies and eight case-control studies showed strong positive associations and dose–response relationships. Meta-analysis of 12 studies indicated that the summary estimate for current and former smokers relative to lifetime nonsmokers was 3.73 (95% confidence interval (CI), 2.16–6.43) and 2.21 (95% CI, 1.60–3.06), respectively. Similarly, four cohort studies and nine case-control studies tested the association between alcohol consumption and esophageal cancer [11]. With the exception of three case-control studies, all cohort studies and six case-control studies showed strong positive associations and dose–response relationships. Meta-analysis of 12 studies indicated that the summary estimate for ever drinkers relative to never drinkers, was 3.30 (95% CI, 2.30–4.74) and 3.36 (95% CI, 1.66–6.78) across the four studies adjusted for smoking.

We examined the effect of tobacco smoking and alcohol consumption on ESCC in a large-scale population-based cohort study [12] (Fig. 1.6). Forty-four thousand nine hundred seventy middle-aged and older Japanese men were followed up for up to 14 years, and a total of 215 cases of ESCC were newly diagnosed among participants during this time. Regular alcohol consumers of 150–299 and ≥300 g ethanol

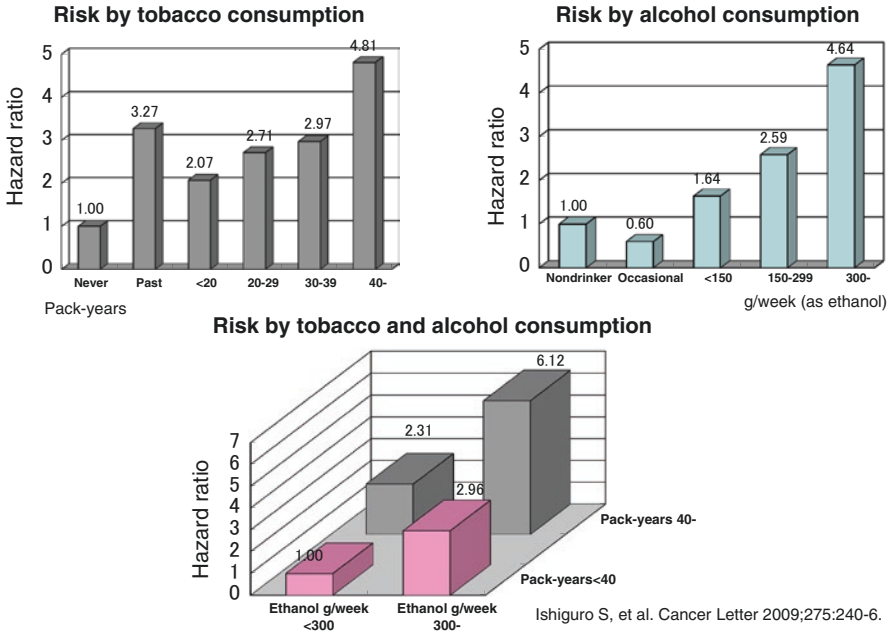


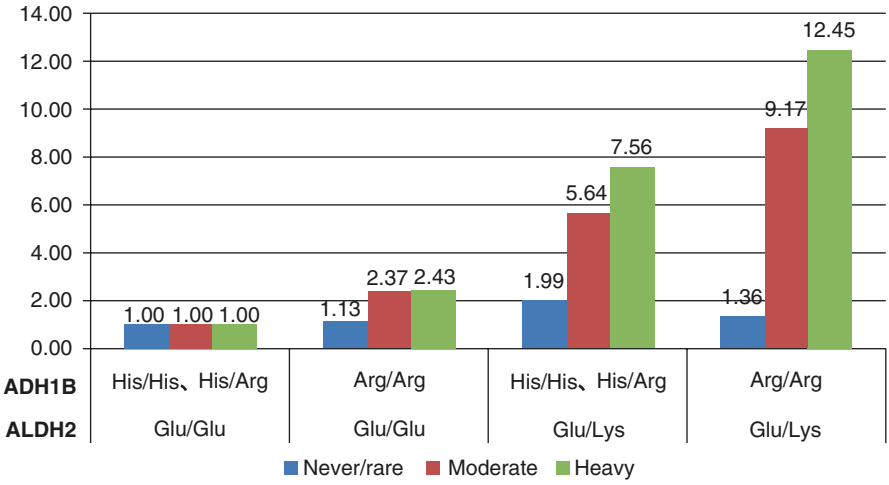
Fig. 1.6 Smoking of tobacco, alcohol consumption, and subsequent risk of esophageal squamous cell carcinoma in men—JPHC Study—[12]

per week had a 2.59—(95% CI, 1.57–4.29) and 4.64-fold (95% CI, 2.88–7.48) higher risk of ESCC than nondrinkers, respectively (p for trend = 0.001). Past smokers, as well as current smokers, had a higher risk than never smokers. Among current smokers, pack-year and cigarettes per day were also associated with the incidence of ESCC, with risk increasing in a dose-dependent manner (p for trend = 0.001). With regard to the interaction of tobacco smoking (pack-years: <40 vs. ≥40) and alcohol consumption (ethanol g/weeks: <300 vs. ≥300), no statistically significant results were identified (p for interaction = 0.70).

1.2.2 Genetic Susceptibility to Tobacco Smoking and Alcohol Drinking

Regarding genetic susceptibility, esophageal cancer does not exhibit any strong familial aggregation and genetic studies of esophageal cancer have instead focused on genes such as cytochrome P 450 (CYP), glutathione-S-transferase (GST), alcohol dehydrogenase (ADH), and acetaldehyde dehydrogenase (ALDH), which metabolize suspected tobacco- and alcohol-derived carcinogens. No consistent findings have emerged for tobacco-derived pathways, although the majority of studies have been limited in sample size.

Conversely, strongly significant effect modifications have been observed with ADH1B and ALDH2 genotype. Among those with ADH1B who have the His allele,



Yang SJ et al. World Journal of Gastroenterology 2010;16:4210-4220.

Fig. 1.7 Risk of esophageal cancer associated with combinations of alcohol dehydrogenase (ADH)-1B and aldehyde dehydrogenase (ALDH)-2 genotypes [13]

approximately 95% of Japanese and 10–20% of Caucasians show a rapid increase of blood acetaldehyde due to the high alcohol metabolizing activity of the ADH1B enzyme, compared with those who have the Arg allele. Among those with ALDH2 Lys allele, approximately 50% of Japanese and <10% of Caucasians, show a higher concentration of blood acetaldehyde after alcohol consumption compared to those who have the ALDH Glu allele, due to the low catalytic activity of ALDH2 enzyme.

A meta-analysis of 19 case-control studies was conducted to evaluate the effect of alcohol consumption modification by ADH1B and ALDH2 polymorphism, to the risk of esophageal cancer [13]. The majority of the studies focused on ESCC and were conducted in Asian populations. A meta-analysis of 13 case-control studies on ADH1B showed that ADH1B∗1/∗1 (Arg/Arg) increased the risk of esophageal cancer among never/rare [odds ratio (OR) = 1.56 (95% CI, 0.93–2.61)], moderate [2.71 (95% CI, 1.37–5.35)], and heavy alcohol consumers [3.22 (95% CI, 2.27–4.57)], compared with ADH1B∗2/∗2 (His/His). Similarly, a meta-analysis of 18 case-control studies on ALDH2 showed that ALDH2∗1/∗2 (Glu/Lys) increased the risk among never/rare [1.28 (95% CI, 0.91–1.80)], moderate [3.12 (95% CI, 1.95–5.01)], and heavy [7.12 (95% CI, 4.67–10.86)] alcohol consumers, compared with ALDH2∗1∗1 (Glu/Glu). The analysis of combined effects of ADH1B and ALDH2 genotypes showed that ADH1B∗1/∗1 plus ALDH2∗1/∗2 was associated with the highest risk of esophageal cancer among heavy drinkers [12.45 (2.9–53.46)] (Fig. 1.7), but no significant increase in risk was seen among never/rare drinkers. Recent large-scale genome-wide gene–alcohol consumption interaction analysis of ESCC in China also showed that drinkers with both of the ADH1B and ALDH2 risk alleles experienced a fourfold increase in risk compared to drinkers without the aforementioned risk alleles, while no increased risk was observed among nondrinkers [14].

Numerous experimental studies have also reported that acetaldehyde has a cytotoxic, genotoxic, mutagenic, and clastogenic potential. In fact, acetaldehyde can cause DNA–protein crosslinks, DNA strand breaks, DNA adducts, sister chromatid exchanges, chromosomal aberrations, and micronuclei in eukaryotic cells in vitro. In addition, acetaldehyde can induce DNA–protein crosslinks, sister chromatid exchanges, and chromosomal aberrations in rodents in vivo [5].

Based on sufficient evidence both in humans and in experimental animals for the carcinogenicity of acetaldehyde, the International Agency for Research on Cancer (IARC) Working Group on the Evaluation of Carcinogenic Risks to Humans has concluded that acetaldehyde associated with the consumption of alcoholic beverages is carcinogenic to humans and causes cancers of the esophagus [7].

1.2.3 Fruit and Vegetable Intake

Although the tobacco smoking and alcohol consumption are the primary lifestyle risk factors for esophageal cancer, dietary factors are also likely to be important [6]. Intake of fruits and vegetables appears to have a protective effect. Although the relationship for particular types of fruits and vegetables is unclear, citrus fruits, and green leafy vegetables appear to possess greater effects than other families of fruits and vegetables.

The Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan evaluated that fruit and vegetable intake probably prevent esophageal cancer based on a systematic review of epidemiologic evidence among the Japanese population (unpublished data, available at http://epi.ncc.go.jp/can_prev/). Seven studies, two cohort and five case-control studies, tested the association of esophageal cancer prevention with fruit intake and all studies showed a significant protective effect. Eight studies, three cohort and five case-control studies, tested the association with vegetable intake as a whole, and green-yellow or cruciferous vegetables. The majority of studies showed a significant relationship between the intake of such vegetables and esophageal cancer prevention. However, residual confounding by tobacco smoking and alcohol consumption cannot be ruled out even after adjusting for and stratified by these variables. Both of the variables are strong risk factors for esophageal cancer as well as correlate with the amount of fruit and vegetable intake. The casual association between such lifestyle behaviors and esophageal cancer should be investigated further.

We examined the effect of fruit and vegetable intake on ESCC in a large-scale population-based cohort study [15] (Fig. 1.8). An increase in consumption of total fruits and vegetables by 100 grams per day (g/day) was associated with an 11% decrease in the incidence of ESCC (95% CI, 1–21%). In particular, a higher intake of cruciferous vegetables was associated with a significant decrease in risk (hazard ratio per 100 g/day: 0.44; 95% CI, 0.23–0.82). Stratified analyses revealed that the beneficial effect of fruits and vegetables was observed regardless of smoking of tobacco and alcohol use; however, it did not completely offset the harmful effects of smoking of tobacco and alcohol consumption.

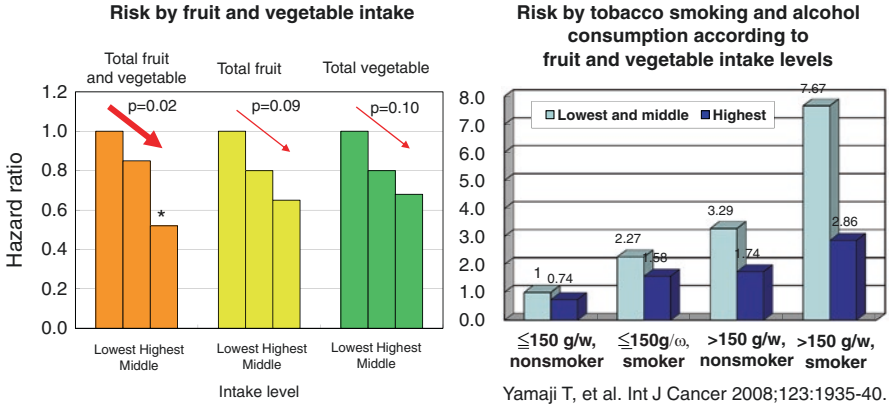


Fig. 1.8 Fruit, vegetable intake, and subsequent risk of esophageal squamous cell carcinoma—JPHC Study—[15]

1.2.4 Mate and Hot Beverages

Regarding the consumption of hot mate, a traditional herbal beverage consumed in parts of Southern Brazil, Argentina, and Uruguay, there appears to be a strong association with consumption of the beverage and development of esophageal squamous cell carcinoma. Meta-analysis of five case-control studies, all adjusted for smoking, showed a summary estimate of 1.16 (95%CI, 1.07–1.25) per cup/day. Mate is typically consumed very hot through a metal straw. This can cause burns in the esophagus and repeated damage of this nature can lead to cancer, although some have proposed that this may also be a result of chemical carcinogenesis from the composition of mate.

In addition to hot mate, there are several studies that show high-temperature drinks and foods are associated with the increased risk of esophageal squamous cell carcinoma, although some studies have not adequately adjusted for tobacco smoking and alcohol consumption. A recent systematic review has reported an overall OR of 2.28 (95% CI, 1.62–3.22) for the association between the consumption of hot beverages (other than mate) or food and risk of squamous cell carcinoma [16]. When the analysis was repeated in 11 studies with adjustment for smoking and alcohol drinking, the OR for all hot beverages (including mate) and food was 2.39 (95% CI, 1.71–3.22). Of interest, there was no statistically significant association with esophageal adenocarcinoma according to the meta-analysis of four studies (OR, 0.78; 95% CI, 0.45–1.35). Based on limited but suggestive evidence not only in humans for the carcinogenicity of drinking very hot beverages but also in experimental animals for the carcinogenicity of very hot water at 65 °C or above, the IARC Working Group on the Evaluation of Carcinogenic Risks to Humans has concluded that drinking very hot beverages at temperatures above 65 °C is probably carcinogenic to humans and may lead to squamous cell carcinoma of the esophagus [8].

The Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan evaluated that intake of hot tea and food is likely to have increased the risk of esophageal cancer based on the systematic review of epidemiologic evidence (two cohort and three case-control studies) among the Japanese population (unpublished data, available at http://epi.ncc.go.jp/can_prev/). A cohort study showed an increased risk of 1.6 fold (95% CI, 1.2–2.0) for the consumption of hot tea (drinking green tea at high temperatures) in comparison with not-hot tea (drinking green tea at moderate temperatures) [17], while another cohort showed that green tea consumption was significantly associated with an increased risk of esophageal cancer [18].

1.2.5 Causes of Esophageal Cancer in Japan

We estimated the population attributable fractions (PAFs) of esophageal cancer attributable to known risk factors from relative risks derived primarily from Japanese pooled analyses (e.g., tobacco smoking), the JPHC study (e.g., alcohol consumption, fruits, and vegetables), and the prevalence of exposure in the period around 1990 [19]. PAFs of tobacco smoking, alcohol consumption, insufficient intake of vegetables and fruit were estimated to be 58.9%, 53.8%, 10.4%, and 10.9% in men and 14.7%, 28.9%, 10.4%, and 10.9% in women. Thus, 88% of esophageal cancer in men was estimated to be avoidable by lifestyle improvement such as quitting smoking, refraining from too much alcohol consumption, and sufficient intake of fruits and vegetables, after considering combined effect of risk factors. The corresponding statistic for women was estimated at 52%. Therefore, esophageal cancer can be regarded as a lifestyle-related disease.

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