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# Social group disparities in the incidence and prognosis of oesophageal cancer

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## Abstract

There are substantial disparities in the incidence and prognosis of oesophageal cancer across social population groups, including sex, race/ethnicity, geographical location and socio-economic status. Both squamous cell carcinoma and adenocarcinoma of the oesophagus are more common in men than in women, but the male predominance in adenocarcinoma is stronger and less well understood. The varying incidence and prognosis of oesophageal cancer across racial/ethnic groups show distinct patterns by histological type. Individuals residing in rural areas have a higher incidence and worse prognosis than those in urban areas in developing regions. Lower socio-economic status is associated with an increased incidence and reduced survival in oesophageal cancer. Sustained research identifying novel preventive and therapeutic strategies are needed to reduce the risk of oesophageal cancer and improve the prognosis in all social groups.

## Keywords

Oesophageal neoplasm, inequalities, gender, race/ethnicity, socioeconomic status

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## Introduction

Oesophageal cancer is the sixth leading cause of cancer-related deaths globally, causing over 400,000 deaths in 2015.[1] The prognosis of oesophageal cancer remains poor with the overall five-year survival rate below 20% in most developed countries.[2] The incidence varies remarkably between countries, which is mainly attributable to differences in the prevalence of environmental risk factors and distribution of oesophageal tumour histology across populations. Oesophageal squamous cell carcinoma (OSCC) and adenocarcinoma (OAC) are the two main histological subtypes of oesophageal cancer. OSCC accounts for over 80% of all oesophageal cancer cases globally and its incidence is highest in South-Eastern and Central Asia.[3,4] Many Western populations in Europe, Northern America and Oceania have witnessed a rapidly increasing incidence of OAC during the past four decades, while the incidence of OSCC has decreased in these populations during the same period.[5,6] Tobacco smoking and alcohol use are the main established risk factors for OSCC in Western populations, but cannot explain the high incidence in other regions where dietary factors may play a greater role.[4] Gastro-oesophageal reflux disease and obesity are the two main risk factors for OAC, whereas tobacco smoking is a moderately strong risk factor for this cancer type.[5,7] Gastric colonisation with *Helicobacter pylori* (*H. pylori*), on the other hand, is associated with a decreased risk of OAC.[5,7]

In addition to the distinct incidence patterns between countries, oesophageal cancer is also characterised by notable disparities in incidence and prognosis across social groups within populations, i.e. sex, race and ethnicity, geographic location and socio-economic status.[4,5] In this review, we evaluate and summarise the available literature examining how social group disparities influence the incidence and prognosis in oesophageal cancer.

## Sex differences

OAC has a striking male predominance in incidence (Figure 1). The male-to-female incidence ratio of

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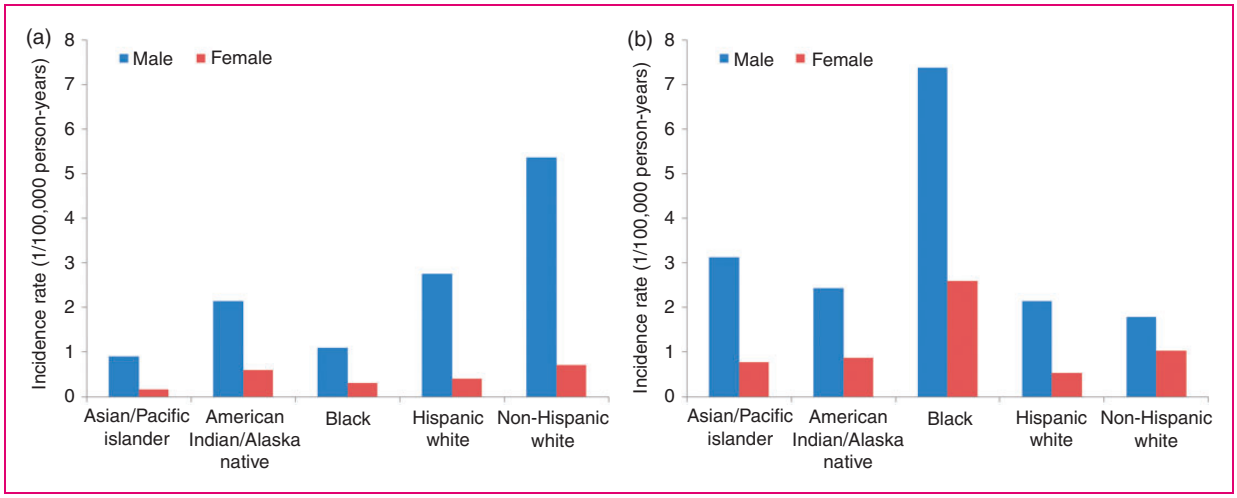


**Figure 1.** Age-standardised incidence rates of oesophageal adenocarcinoma (a) and oesophageal squamous cell carcinoma (b) by sex and racial/ethnic group in the USA, 1992–2014, using the US standard population in 2000 as the reference (data source: the Surveillance, Epidemiology and End Results Program 13 registries).

OAC is as high as eight-to-one in North America, six-to-one in European and Oceanian countries, and four-to-one in Asia and Latin America and the Caribbean.[3,8] The male-to-female ratio has remained fairly stable over time in most populations.[8] Barrett's oesophagus, the premalignant condition of OAC, is also characterised by substantial male predominance, suggesting that the sex disparity may begin early on in the disease pathway.[9] The strong male predominance in OAC is not explained by the relatively equal population prevalence of main risk factors or their similarly sized associations with OAC across the sexes.[7,10] It has been hypothesised that sex hormones may play a role, i.e. either female sex hormones protecting against OAC and/or male hormones increasing the risk, but existing evidence remains inconsistent and far from conclusive.[5,10] Interestingly, a pooled analysis of three population-based case-control studies has revealed a 40% decreased risk of OAC associated with breastfeeding (odds ratio 0.58, 95% confidence interval (CI) 0.37–0.92), and the association was stronger for longer duration of breastfeeding.[11] Women who breastfed for over one year had a 60% decreased risk (odds ratio 0.42, 95% CI 0.23–0.77).[11] The seemingly protective effect of breastfeeding may be related to long-lasting changes in female sex hormone levels or expression of sex hormone receptors caused by lactation.

OSCC is also more common in men than in women, though the male predominance is weaker compared with that for OAC (Figure 1). The global average of the male-to-female incidence ratio of OSCC is 2.7-to-one, but it varies greatly from 1.2-to-one in Northern Africa and Western Asia to 7.8-to-one in Eastern Europe.[3,4] The higher incidence of OSCC in men is at least partly explained by the differential prevalence of heavy alcohol use and tobacco smoking between the sexes.[4,10] Evidence regarding the role of sex hormones in OSCC is limited.[10]

Sex may also influence the prognosis of oesophageal cancer. Female patients have a lower disease-specific mortality compared with males, but this survival advantage seems to be restricted to patients with OSCC and not those with OAC.[12,13] The reasons for this potential sex difference are unknown, but differences in heavy alcohol use and smoking among men and women might potentially influence also the prognosis. The reasons for any influence of sex itself on the survival of OAC and the underlying mechanisms are currently unknown.

## Racial and ethnic disparities

Oesophageal cancer is characterised by notable disparities across racial/ethnic groups in incidence, with distinctly different patterns by histological type (Figure 1). In the USA, the incidence of OSCC in blacks, despite a steady decrease in recent years, is clearly higher than in other ethnic groups, whereas the incidence in whites is lowest.[5,14,15] The incidence of OAC has increased dramatically in whites, particularly in non-Hispanic whites, since the 1970s in the USA. However, the increase seems to have slowed down from the year 2000 onwards.[5,15] A recent analysis with multiple disparity measures of the racial and ethnic disparities in the USA in 1992–2013 showed decreased disparities in OSCC incidence over time and seemingly increasing absolute differences of OAC incidence across racial/ethnic groups.[15] Some of the disparities by race may be explained by differences in the prevalence of exposure to major risk factors.[15] In the UK, the incidence of

OAC is also substantially higher in whites compared with black and Asian populations, while the incidence of OSCC is highest in blacks.[16]

An analysis of cancer risks among immigrants in Sweden showed higher risk of OSCC in Finnish immigrants (standardised incidence ratio (SIR) 1.32, 95% CI 1.06–1.64, for men and 1.90, 95% CI 1.50–2.38 for women) and Iranian women (SIR 3.80, 95% CI 1.23–8.87), compared to the native population in Sweden.[17] The increased risk might be attributable to the higher prevalence of risk factors for OSCC, e.g. smoking, alcohol use and a diet low in fruit and vegetables, in these populations.[17–20] Compared with native Swedes, increased risks of OAC have been observed in male immigrants from Denmark to Sweden (SIR 1.66, 95% CI 1.08–2.45), which might be due to a higher mean percentage of body fat in Danish men, whereas the risk of OAC was lower in male immigrants from Finland, former Yugoslavia, and Asia, possibly due to lower body mass index.[17,21]

Earlier studies have suggested a worse prognosis in black patients with oesophageal cancer compared with patients of other ethnic groups.[22,23] However, some recent studies have suggested that this difference does not remain after adjustment for socio-economic status.[24,25] An earlier study in California in the USA has shown that black patients with oesophageal cancer were less likely to undergo oesophagectomy surgery than whites, and that Asian and Hispanic patients were less likely to undergo such surgery at high-volume hospitals.[26] A study of 2946 white patients and 367 black patients aged 65 years or older in the USA found that black patients had lower rates of seeing a surgeon and undergoing resectional surgery.[27] The overall two-year survival rate was lower in black patients than in white patients (18% versus 25%), but the difference did not remain after adjustment for treatment characteristics.[27] Thus, the ethnic survival disparity is likely to be attributable to differences in healthcare access in black patients compared to patients of other ethnic groups.

## Urban–rural disparities

Except for geographical variations across continents and countries, the incidence of oesophageal cancer also shows disparities within countries, particularly when comparing rural and urban areas. An analysis of data from 177 cancer registries across China in 2011 showed at least two-fold increased incidence rates of oesophageal cancer (almost only OSCC) in rural areas compared to urban areas.[28] A prospective cohort study of 0.5 m participants from five urban and five rural areas in China reported a substantially higher incidence of oesophageal cancer in rural areas than in urban areas (87 versus 25 per 100,000 person-years in men; 35 versus four in women).[29] The higher incidence of oesophageal cancer in rural areas in China suggests a role of risk factors linked with lower socio-economic status, such as higher prevalence of tobacco smoking and heavy alcohol use, and low intake of fruit and vegetables in rural residents of China.[29,30] Higher incidence of OSCC in rural areas than in urban areas was also reported in Northern Iran, and patients in rural areas also had shorter median survival time compared with their urban counterparts.[31] These disparities might also be related to the exposure to established risk factors.[32] In the USA, lower incidence of OSCC was observed in whites residing in rural areas compared with those in metropolitan areas (rate ratio 0.76, 95% CI 0.64–0.88), whereas the incidence was instead higher in blacks in rural areas than those in metropolitan areas (rate ratio 1.60, 95% CI 1.24–2.04).[33] Such observations might be explained by a lower prevalence of alcohol use in blacks and a higher prevalence in whites in rural areas.[34] On the other hand, the incidence of OAC was slightly higher in rural areas (rate ratio 1.15, 95% CI 1.05–1.25), which might be due to the higher prevalence of obesity in rural areas.[35] A nationwide Swedish case-control study found an increased risk of OSCC associated with residing in rural areas during childhood, whereas no such association was found for OAC.[36]

The mortality rates of oesophageal cancer in rural areas were clearly higher than in urban areas in China.[28] However, an analysis of 12,482 patients with oesophageal cancer (mainly OSCC) in Taiwan found similar survival in patients who lived in areas with different urbanisation levels.[37] No difference was observed in the prognosis between OAC patients in metropolitan and rural areas in the USA.[33]

Overall, the urban–rural disparity in oesophageal cancer in the developed world seems lower than in less developed regions, which might be partially due to differences in the distribution of the exposure to environmental risk factors.

## Socio-economic disparities

Lower socio-economic status has been consistently reported to increase the risk of OSCC in studies from different parts of the world, including China and other Asian countries,[30,38–40] the USA,[41] and Europe.[16,36,42,43] However, most studies using area-based indicators of socio-economic status did not find any association with the risk of OAC.[16,44,45] A cohort study of one million Israeli men suggested no association between socio-economic status determined by the area of residence and OAC risk, whereas higher education level decreased the risk of this cancer.[45] An earlier

population-based case-control study from the USA found a lower risk of OAC in individuals with higher education or income.[41] Another population-based case-control study in Sweden also revealed an increased risk of OAC associated with lower socio-economic status as indicated by occupational histories; the risk in unskilled workers was 3.7 (95% CI 1.7–7.7) times higher compared with age- and sex-matched professionals.[36] A recent nationwide study in Sweden found that lower education attainment and lower income were associated with an increased risk of OAC.[43] Overall, the risk of OAC seems to be dependent on individuals' socio-economic status levels, whereas no such association has been established when only the area of residence is used to assess socio-economic status.

The influence of socio-economic status on survival after oesophageal cancer varies across populations. Lower socio-economic status, when defined by the neighbourhood, has been associated with higher 30-day (odds ratio 1.37, 95% CI 1.03–1.85) and 90-day (1.30, 95% CI 1.04–1.63) mortality in patients who had undergone oesophagectomy in the UK.[46] However, a few other studies in Western populations found no association between socio-economic status measured by the area of residence and mortality after diagnosis of oesophageal cancer or oesophagectomy.[47,48] An analysis of 12,482 patients with oesophageal cancer diagnosed from 1998–2007 in Taiwan suggested higher mortality rates in patients with lower income.[37] A recent study in 4097 patients younger than 50 years in the same population (Taiwan) showed that higher individual socio-economic status, as indicated by occupational category, was associated with a decreased five-year mortality (odds ratio 0.61, 95% CI 0.47–0.77, highest versus lowest categories).[49] As tumour stage at diagnosis is the strongest prognostic factor for oesophageal cancer, the observed survival disadvantages in patients with low socio-economic status may be due to delayed diagnosis and treatment and less access to curative treatment.[50] The lack of association between socio-economic status and survival in some previous studies may be explained by less marked socio-economic disparities in healthcare access in the study population, adopted socio-economic status indicators (neighbourhood rather than individual socio-economic status), socio-economic gradient, or chance. It is also possible that the prognosis in oesophageal cancer is similar in patients with various socio-economic status levels as long as they actually receive equal treatment and have the same opportunities for early detection to improve prognosis.

## Summary

This review highlights the substantial social disparities in the incidence and prognosis in oesophageal cancer. Oesophageal cancer is characterised by a male predominance in incidence, which is especially strong for OAC, and the prognosis in OSCC might be better in women than men. The incidence and prognosis in oesophageal cancer vary across racial/ethnic groups, and the variations are partly dependent on the histological type of oesophageal cancer. Higher incidence and worse prognosis has been noted in rural areas compared with urban areas in developing regions with high incidence of OSCC. Lower socio-economic status is associated with an increased risk of both OSCC and OAC. The association between socio-economic status and prognosis in oesophageal cancer varies across populations.

Eliminating health disparities is a major overarching goal in public health. It is critical to consider the great social disparities in oesophageal cancer in order to optimise prevention and treatment. First, a continuous monitoring of the social disparities in oesophageal cancer is needed. Second, as the social disparities in the incidence of oesophageal cancer are not fully explained by known risk factors, more aetiological studies examining such disparities are needed. Third, more attention should be paid to disadvantaged social groups in terms of the risk of oesophageal cancer when planning for targeted screening programs. Fourth, more in-depth research is needed to verify how socio-economic disparities influence the prognosis of oesophageal cancer in different populations and to uncover the underlying reasons for these disparities. All individuals, independent of social groups, should have the same opportunities for timely detection of oesophageal cancer because it determines the prognosis, and all patients should have equal access to high-quality medical care and support. Thus, sustained research, prevention, and treatment efforts are needed to enable a reduction in the risk of oesophageal cancer and an improvement in the prognosis in all social groups.

### Declaration of conflicting interests

None declared.

### Ethics approval

Not applicable.

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### Informed consent

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