

REVIEW

Occupation and gastric cancer

A Raj, J F Mayberry, T Podas

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Gastric cancer is a cause of significant morbidity and mortality. There are several risk factors, with occupation emerging as one of these. There is considerable evidence that occupations in coal and tin mining, metal processing, particularly steel and iron, and rubber manufacturing industries lead to an increased risk of gastric cancer. Other "dusty" occupations—for example, wood processing, or work in high temperature environments have also been implicated but the evidence is not strong. The mechanism of pathogenesis of gastric cancer is unclear and the identification of causative agents can be difficult. Dust is thought to be a contributor to the pathological process, but well known carcinogens such as N-nitroso compounds have been detected in some environments. Further research on responsible agents is necessary and screening for detection of precursor gastric cancer lesions at the workplace merits consideration.

Cancer incidence and mortality rose during the 20th century to become a leading cause of death. Until 1985,^{1,2} gastric cancer was the most common cancer worldwide with an annual incidence of nearly 700 000 cases.³ More recently this has declined and has been surpassed by lung cancer.³

Much research has been conducted on external risk factors with several studies looking at occupation. Most available data on occupational exposure and cancer concern lung cancer. Only recently has gastric cancer been considered an occupational hazard. Here we have highlighted some of this research and critically assessed the results as well as identifying high risk occupations.

EPIDEMIOLOGICAL CONSIDERATIONS

The pathogenesis of gastric cancer appears multifactorial. Geography⁴ and diet play a part⁵; smoking is not only an important risk factor, but the type of tobacco might also influence the site of carcinoma development.⁶ Social class and socioeconomic parameters⁴ are significant risk factors and may influence survival.⁹ Religion has been associated with a reduced risk, possibly through dietary restrictions.¹⁰ A greater incidence has been reported in males,¹¹ and researchers have also reported genetic links with ethnicity¹²⁻¹⁵ and blood group A,¹⁴⁻¹⁵ which confers up to 16% higher risk. The possibility of family clustering was investigated by several studies.¹⁶⁻¹⁷ Despite limitations,

including incomplete data collection, an early review pointed towards aggregation of gastric cancer in some families.¹⁸

There is considerable regional variation within high risk areas.¹⁹⁻²⁰ Migration from high to low risk regions reduces the risk in second or third generations, providing the dietary habits of the host country are adopted.³ This lends weight to the hypothesis that environmental factors operate early in life.²¹ The discovery of *Helicobacter pylori* has given further impetus to the search for a cause of gastric cancer.²²⁻²³

Prevalence of gastric cancer obeys social stratification patterns. Occupations often have a definable social class, and this is frequently used to explain positive associations between cancer and occupation.

In view of the long latency of the carcinogenic process and the difficulties it imposes on research, interest has focused on early markers and risk factors. Such markers include atrophic gastritis and intestinal metaplasia.²⁴⁻²⁶ Others can be seen at a histochemical level. A significant risk predictor is the anomalous expression of blood group antigens in mucin, especially those of the Lewis group.²⁷ Other markers such as pepsinogens are currently under investigation and may help further risk identification.

SOME HISTOLOGICAL CONSIDERATIONS

The majority of gastric neoplasms are adenocarcinomas, which can be subdivided with each subtype exhibiting different behaviour. The most widely used histological classification was proposed by Lauren.²⁸ He defined two main types: The intestinal or "epidemic" form and a diffuse variety. The former is more prevalent in the elderly and men. It has a better prognosis and is more frequent in high risk areas.²⁹⁻³¹ The diffuse adenocarcinoma has a more uniform incidence.³⁰ It is poorly differentiated with a worse prognosis and its incidence, unlike the intestinal variety, has shown no tendency to decline.

Histological type is not usually recorded on death certificates which make collection and evaluation of data more difficult. As a result, few studies have investigated gastric cancer histology in relation to occupation. In studies that analysed histological type, the intestinal variety was most common.³² Further progress in our understanding of the carcinogenic process is being directed towards histological precursors, such as intestinal metaplasia and atrophic gastritis. There are

See end of article for authors' affiliations

Correspondence to:
Dr Anita Raj,
Gastrointestinal Research
Unit, Leicester General
Hospital, Gwendolen
Road, Leicester LE2 4TF,
UK; anitaaraj@aol.com

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Abbreviations: BRMA, British Rubber Manufacturer's Association; IARC, International Agency for Research on Cancer

Risk of gastric cancer and occupation**High**

- Carpenters.
- Steelworkers.
- Tin miners.

Increased

- Chemical industry workers.
- Coal miners.
- Coke plant workers.
- Oil refinery workers.
- Rubber manufacturing.

Possible

- Agricultural workers.
- Goldminers.
- Lorry and coach drivers.
- Jewellery workers.
- Metal (and components) manufacturers.

hardly any data linking occupational exposures with these conditions.

PATHOGENESIS

Few theories about the pathogenesis of gastric cancer have developed over the years.

Polyunsaturated fats have been suggested as possible initiators or modulators.¹¹ They may contribute to the formation of lipid peroxides in the stomach, which in turn could damage the gastric mucosa. Increased tissue levels of arachidonic acid can be produced through consumption of polyunsaturated fats. During this process "active" oxygen is generated and this may have a role in carcinogenesis, by damaging DNA.

Correa's *N-nitrosoamine* unifying theory has been developed over several years.¹²⁻¹⁴ It postulates that gastric carcinoma is the end result of a series of mutations and cell transformations that begin in the first decade of life. Mutagens responsible are thought to be nitroso compounds formed in the upper gastrointestinal tract. This process can be accelerated by the lack of micronutrients such as ascorbic acid or carotenoids, an excessively salty diet, or infections, for example, *H. pylori*.¹⁴ All these factors appear to act on a common pathogenic pathway. For example, a reduction in acid production results in increased formation of *N-nitroso* compounds by bacteria in the upper gastrointestinal tract. It is of note that these compounds can also be found in some occupational environments.¹⁵

Nitroso compounds can be formed in the stomach of humans by interaction of nitrite or nitrogen oxides and nitrosatable amines, such as citrulline, arginine, methylguanidine, etc. Intragastric *N-nitroso* compound formation has been suspected in carcinogenesis.¹⁶⁻¹⁷ The development of a nitrosamine-sensitive detector in 1975 demonstrated a complex pattern of human exposure, occurring via different routes.¹⁸

Endogenous exposure occurs through the uptake of amine precursors and formation of carcinogenic compounds in the saliva and gastric juice.¹⁹ Nitrite is abundant in the food chain, and is used both as a colouring agent and preservative. It has also been found in the saliva of people eating certain vegetables.⁴⁰ Nitrates in fertilisers can be found in agricultural products and are converted to nitrite at body temperature. Intragastric formation of nitrosamines is blocked up to 80% by ascorbic acid or up to 50% by tocopherols.¹⁹

Exogenous exposure can be related to lifestyle (tobacco, food, cosmetics, drugs, etc) or occupation. This latter category is the largest known exogenous source.¹⁵ Occupations with high levels of *N-nitrosamines* in the work environment include:

- Rubber industry.
- Metal industry: *N-nitrosodiethanolamine* has been found in cutting fluids which contain diethanolamine and nitrite as anticorrosives. Cutting oil mist can be inhaled, penetrate the skin, or contaminate other products.
- Leather tanning industry: *N-nitrosodimethylamine* formation has been attributed to chemicals used in the depilation process.
- Environmental exposure to preformed nitrosamines: Contact with cosmetics, drugs, agricultural chemicals, rubber products, and packaging materials can result in low level exposure to *N-nitrosamines*.

At a cellular level, the mechanisms responsible for cancer are unclear. Current views suggest that increased mitogenesis promotes mutagenesis.⁴¹ Yet, not all such substances are directly mutagenic and so carcinogenesis may follow more than one path.⁴²⁻⁴³

STUDY METHODOLOGY AND CLASSIFICATION OF OCCUPATIONS

Good epidemiological studies are not easy. The majority of surveys have been based on death certificates, which are susceptible to diagnostic errors or miscertification,⁴⁴⁻⁴⁶ or cancer registry information. Both are affected by discrepancies that exist between clinical and histologically confirmed diagnoses. Few studies provide histopathological data and consequently a proportion of deaths may have been wrongly attributed.

The search for an association between occupation and gastric cancer has been based on either general population studies or cohort and case-control studies of specific occupations in industries.

Classification of occupations is rather vague and descriptive in early studies. As knowledge about risks accumulates, it has become more structured and linked to working practices and exposure to specific agents. Use of internationally accepted classification of occupations has remedied some problems, although new techniques and agents in industrial processes will continue to frustrate accurate assessment of risk.

Early occupational surveys took little account of confounding elements such as diet, smoking, etc. Therefore, estimates of risks can differ widely between similar studies. As a result of these weaknesses occupational risks of gastric cancer remain the subject of debate.

METAL AND MINING INDUSTRY**Steel foundry workers**

The International Agency for Research on Cancer (IARC) concluded that occupational exposure to iron in steel and iron foundries is probably carcinogenic.⁴⁷ Analysis of a UK cohort of 10 438 workers from 10 different foundries concluded there was a significant excess of gastric cancer.⁴⁷⁻⁴⁹ Risk was highest for those working in the foundry area and more specifically in "furnace" related occupations.

Nickel and copper workers

In a thorough review the IARC concluded that nickel is carcinogenic,⁵⁰ with specific processes, such as nickel refining, carrying higher carcinogenic risk.⁵¹ Water insoluble nickel salts are retained in mucous membranes longer than water soluble salts. Consequently workers exposed during smelting have a higher exposure than those working in electrolysis.

In 1990, an international committee examined the evidence for the risk of gastric cancer in 10 cohort studies in the USA, UK, Canada, Norway, Finland, and New Caledonia.⁵² None supported an increased risk. However, data from four USSR refineries, not included in the committee's analysis, suggested an increased risk of gastric cancer. Karjalainen *et al* found a

slightly increased risk of gastric cancer among a cohort of workers at a copper/nickel smelter and nickel refinery in Finland.⁵⁵

Lead exposure

A high incidence of gastric cancer among 4500 workers of a battery plant has been associated with lead exposure.⁵⁴ Studies in other industries on smaller lead-exposed populations, have failed to confirm this link.^{55, 56}

Metal component manufacturing

Several studies have reported a link between metal component manufacture and gastric cancer.^{57, 58} This seems to be associated with use of cutting oils or the mist generated during manufacture.⁵⁹ These contain polycyclic aromatic hydrocarbons some of which are carcinogens. This link has not been supported in all studies,^{60, 61} some of which failed to provide information on levels of exposure or used small samples of employees. It is clear that further detailed research is necessary.

Tin miners

Tin mines in the UK are known to have the highest concentrations of radon in Britain.⁶² A study of 1333 miners in Cornish tin mines reported an increased risk of death from gastric cancer (standard mortality rate = 141), especially among underground workers.⁶³ The study attributed the risk to physical activity and exposure to dust.⁶⁴ A later study analysed mortality in a cohort of 3082 UK tin miners from 1941–86 and found the incidence of gastric cancer was increased by 40%.⁶⁵ There was no relation to time spent underground. Cancer of the stomach was, however, associated with exposure to arsenic, an important byproduct of some tin mines.

Other miners

Studies on Ontario goldminers by Kusiak *et al* demonstrated an excess mortality from gastric cancer⁶⁶; this was possibly due to exposure to mineral dust and chromium. There was some evidence that place of birth could be a further risk for certain age groups. A cohort study of miners from Kalgoorlie in Australia and other studies on gold miners in South Africa⁶⁶ and France,⁶⁷ however, have not shown a significant association with gastric cancer.

COAL INDUSTRY WORKERS

Coal contains a number of carcinogens including polyaromatic hydrocarbons, cadmium, chromium, etc.⁶⁸

In 1961, Stocks analysed data from the Registrar General's Decennial Supplements of Occupational Mortality.⁶⁹ Gastric cancer was one of the six commonest causes of mortality in coal workers. Enterline reported similar findings in the USA⁷⁰ and Rockette concluded that it is one of the three commonest causes of death in coal miners.⁷¹

Other studies have supported this view^{72–75} but others have failed to confirm these findings.^{76–79} Most studies are retrospective and have to deal with a number of confounding factors. Another possible reason may be inaccuracies in recording systems, including variation between a deceased person's occupation as determined by other sources of employment information and data from death certificates.

The risk of gastric cancer in coal mining is real but remains to be quantified. Conflicting results may be explained by the variability of other confounding factors such as diet, smoking, lifestyle, etc. A recent study investigated the value of screening for gastric cancer in a group of more than 2000 coal miners in Nottinghamshire.⁸⁰ They had a high incidence of gastrointestinal symptoms, acute and chronic gastritis, and intestinal metaplasia. The results suggested they would be a suitable

group for screening for malignant and premalignant lesions—that is, intestinal metaplasia, dysplasia, and chronic gastritis.

CHEMICAL INDUSTRY WORKERS

Oil refinery workers

Workers in oil refineries are in regular contact with known carcinogens, such as polyaromatic hydrocarbons. This has led to several studies over the last two decades.^{81–83}

Rushton and Alderson studied a cohort of over 34 000 employees in eight UK refineries for the years 1950–75.⁸² Cancer mortality, compared with the average British male mortality with adjustment for regional variations, was lower due to reduced lung cancer deaths. This was attributed to smoking restrictions at work, although smoking habits were not investigated. Gastric cancer risk was raised in four of the refineries affecting mostly labourers with long service. During a 15 year follow up Rushton noted that the “all cancer” deficit persisted due to a reduced incidence of lung cancer.⁸⁴ Gastric malignant neoplasms were again raised in number, mainly in operators and labourers.

Two studies from Canada found a significant incidence of gastric cancer,^{85, 86} as did a survey from 39 USA petroleum counties.⁸⁶ It was suggested that petroleum and its byproducts might pose an increased risk to employees as well as to the surrounding communities but further research is needed.

Other chemical workers

A population survey of 17 000 patients admitted to Roswell Park Memorial Hospital, New York suggested an increased risk among chemical industry operatives.⁸⁷ The risk was highest among the young (relative risk = 11), particularly for those with at least five years of exposure. Data on the levels of exposure were not available. There are also reports which suggest there may be an increased risk in the azo dye industry.⁸⁸

RUBBER AND LEATHER PRODUCT INDUSTRY WORKERS

Rubber industry workers

Rubber manufacturing involves many agents that are well recognised carcinogens and during manufacture there is considerable exposure to nitrosamines.⁸⁹

In 1982 the IARC accepted there was a risk of stomach cancer in the rubber industry.⁸⁹ This was supported by data from the British Rubber Manufacturer's Association (BRMA) study⁹⁰ and the USA,^{91, 92} particularly in jobs related to the early stages in processing. Some reports from Italy and Sweden did not support this view.⁹³ However, a follow up of the BRMA cohort by Sorahan *et al*⁹⁴ and a study by Coggon *et al*⁹⁵ reaffirmed the risk.

Leather and shoe industry workers

Workers in this industry are exposed to several carcinogens, such as chromium and chlorophenols. Studies from the UK in the 1950s reported an increased risk. A later British study found no excess of gastric cancer mortality among tanners,⁹⁶ although in Sweden there was a slightly increased incidence in 600 tannery employees.⁹⁷ The IARC accepts that there is some evidence of increased risk among boot and shoemakers.⁹⁸

WOOD PRODUCT INDUSTRY WORKERS

Population studies such as the Washington State survey based on 430 000 death certificates, found a significant risk for carpenters, loggers, plywood workers, and cabinet makers.⁹⁹ Other studies have produced similar results.¹⁰⁰

While carpenters have been shown to have a high risk of gastric cancer,^{99, 101} data on other wood related occupations including pulp and paper mill workers,^{102, 103} furnishers, cabinet makers, foresters, loggers, wood model makers, etc are less consistent. A large Danish study examined 65 000 cancer

cases and found a twofold increase in the risk of gastric cancer related to occupations in basic wood processing.¹⁰⁴ This was attributed to social factors, because there was no correlation with sinonasal cancer rates.

However, lack of details on social history, diet, and other habits that act as confounding factors make it difficult to arrive at clear conclusions.

WORKERS IN THE UTILITIES

Coking plant workers

A study of over 4900 workers in a gas-producing coke plant demonstrated a high risk of gastric cancer and the trend was confirmed by a similar Dutch study.^{105 106}

AGRICULTURE AND LAND WORKERS

Farmers may have an increased risk of gastric cancer because of their contact with fertilisers. However, studies on the mortality of nitrate fertiliser workers do not support this hypothesis,¹⁰⁷⁻¹⁰⁹ despite high concentrations of nitrate in their saliva. An occupational study of over 52 000 patients from Japan detected a significant cancer risk for agricultural workers.¹¹⁰ Some studies have linked gastric cancer with specific groups such as grain farmers in China,¹¹¹ and farm labourers in Italy,¹¹² but these results have not been confirmed.¹¹³

FOOD INDUSTRY WORKERS

Fishermen

A study from Sweden detected a significantly increased risk of gastric cancer among Baltic Sea fishermen.¹¹⁴ Dietary factors (high smoked food and low vegetable intake) were thought responsible for this excess risk. A similar high incidence of gastric cancer was also found among diver-fishermen in Singapore.¹¹⁵

TRANSPORT WORKERS

Drivers

Particles emitted from petroleum and diesel engines contain numerous polycyclic aromatic hydrocarbons which are mutagenic and carcinogenic in several animal species.

Stomach and other gastrointestinal tract cancers are commoner among Geneva's professional drivers.¹¹⁶ Risk was related to exposure to exhaust gas and fumes but there was no relation to the time of first exposure, although the numbers were small.

Similar findings have been reported from a longitudinal study of London drivers.¹¹⁷ Those affected mostly were lorry and coach drivers.

MISCELLANEOUS OCCUPATIONS

Jewellery workers

A death certificate based study of 931 men from Massachusetts, USA who died from 1957-75 suggested an excess of gastric cancer.¹¹⁸ Although it is known that some of the abrasives used in the trade are carcinogens, the sample size was rather small and further studies are needed.

OCCUPATIONAL POPULATION STUDIES

Population studies provide a broad picture but difficulties can arise in interpretation because of multiple comparisons and lack of exposure data.

Olsen and Jensen in a Danish cancer registry study analysed approximately 93 000 cancer cases.¹¹⁹ There was a high incidence of gastric cancer among workers in utilities (electricity, gas, and water), employees of the wood trade, and those in fishing, agriculture, and forestry occupations.

A cancer registry based case-control study from New Zealand examined 22 occupational groups and found an

increased risk of gastric cancer in forestry workers, field crop workers, grain millers and related workers, brewers, and beverage makers.¹²⁰

Kneller *et al* examined data on over 13 000 cases of gastric cancer from Shanghai, China and found an increased risk in "dusty industries" which included foundry workers, cement workers, coal miners, textile machine operators, wood workers and grain farmers.¹²¹ In addition, there was a "high temperature" group which included employees working near open fossil fuel combustion sources. This group included metal smelting/refining furnacemen, blacksmiths, railway engine drivers, boilermen, and firemen. Most have been reported at increased risk in earlier studies.

A Spanish study found increased risks for wood and furniture workers, construction workers, and glass and ceramic workers.⁷²

DISCUSSION

The search for links between occupation and gastric cancer has been intensive and wide ranging. The IARC recently considered that there is evidence, although not definitive, of an association between gastric cancer and coal, rubber, and leather industries and asphalt workings.⁹⁸

Early studies suffered some weaknesses but have generated hypotheses and outlined directions of research. Some of the reasons preventing definite conclusions are:

- Most studies are based on job titles. This has obvious flaws not least because the job content of a particular title may vary.
- Dose-response relationship has not been established in most studies. Occupations known to have a high risk of cancer do not have agreed minimum safe doses. When "safe dose" exposure exists, it is often arbitrary.
- Individual occupational history data are limited in most studies.
- Changes in work practice and therefore levels and type of exposure are almost impossible to establish. There is also a degree of mobility in the labour force within some industries which could lead to significant changes in levels of exposure.

Despite their methodological weaknesses, many studies have led to improved safety standards and exposure to suspect agents has been reduced. Effects of low level exposure are more difficult to identify. The situation becomes more complex if environmental exposure is also taken into account. For example, the use of talc in the preparation of rice and sugar confectionery has been partially incriminated in the development of gastric cancer in Japan.

Despite the absence of clearly defined associations between gastric cancer and some occupations, there is an undeniable trend in certain groups—for example, dusty occupations and work in high temperature environment.

The relation of gastric cancer to dusty occupations has been the focus of significant research. A cancer registry survey from California showed that exposure to occupational dust, particularly mineral and organic dusts, was an independent risk factor for gastric carcinoma.¹²¹ Wright *et al* suggested that dust particles have an abrasive effect on the gastric mucosa.¹²¹ Alternative ways by which occupational dust could promote gastric cancer is through absorption and delivery of carcinogens such as N-nitrosamines to the stomach.

Findings from another study in Stoke-on-Trent, UK did not support the general "dust" hypothesis.⁹⁵ This study concentrated on the rubber, steel and iron industries, coalmining, and ceramics. The results suggested an association with rubber manufacture but only a weak association with other industries.

Inhaled noxious dust is expelled from the airways by an intact respiratory epithelium and then swallowed. Meyer suggested that non-smokers in dusty industries may be at a

higher risk of gastric cancer,¹²² because their respiratory epithelium is more efficient at clearing airways, resulting in a higher load in the stomach. In smokers, this mechanism is impaired, hence a lower risk of gastric cancer despite a higher risk of lung cancer. In contrast Ames and Gamble suggested an alternative hypothesis.^{123, 124} They identified a higher risk among smokers and felt that prolonged exposure to coal dust and smoking overwhelms some unspecified defence mechanism, which then allows gastric carcinogenesis to proceed. Smoking and coal dust may have a synergistic effect, interacting locally to promote gastric carcinogenesis by enhancing nitrosation, although each is not sufficient alone to cause cancer.^{74, 122}

Stukonis and Doll found the amount of physical activity at work correlated strongly with gastric cancer mortality.⁶⁴ This only applied to social class III individuals. The trend was less clear among other social classes and cancers at other sites. One explanation is that people who work physically hard need to eat more often and in larger quantities, exposing themselves to more carcinogens in their food.

Dose-response relationships remain undefined for most suspected carcinogens. Mechanisms of action are unknown and may be related to mutagenic potential. A possible mechanism proposed by Cairns is that a high rate of mitoses leads eventually to survival of aberrant cells by overwhelming regulatory mechanisms.^{47, 125}

There is little doubt that chance associations with gastric cancer have resulted from the complexity of confounding factors operating in many occupational environments. It would be difficult to judge with confidence whether some people are more at risk as a result of their occupation or their social class, when some occupations attract workers from certain classes and indeed occupations define social classes. On the other hand, although there is an accepted link between social class and gastric cancer, the role of social class may have been over-emphasised, particularly as many studies do not provide data on social confounders.

Occupation and therefore socioeconomic status may also be an important determinant of extent and survival in cancer.⁹ This may be a reflection of early or late detection, nutritional intake, and quality of care.

Establishing gastric cancer as an occupational hazard could have a substantial impact. Asbestos related lung cancer is an example that has had significant social, financial, and legal consequences. Regardless of how weak the link with occupation is, it may not prevent claims being pursued.¹²⁶

Does occupational screening for gastric cancer have a place at work? Japan has a long established and rewarding experience of mass population gastric surveys since 1953, using primarily barium studies and endoscopy.^{127, 128} Efforts to assess the benefit in occupational groups such as miners through identification of precursor lesions in "dyspepsia" clinics may provide a model for screening. If serological methods of screening are also developed, occupational screening could come a step closer.

Authors' affiliations

A Raj, J F Mayberry, Gastrointestinal Research Unit, Leicester General Hospital
T Podas, Thessalonika, Greece

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