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Aspects of the etiology of gastric adenocarcinoma

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Optimus parentibus

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Abstract

Gastric adenocarcinoma is the fourth most common malignancy and the second leading cause of cancer death in the world. Tremendous effort has been made to look into the causation of gastric cancer. Etiological research plays a key role in identifying possible preventive and interventional measures. This thesis is based on four large prospective, population-based cohort studies, focusing on environmental risk factors for gastric cancer other than infection with *Helicobacter pylori*.

In the first study, the relations of tobacco smoking and alcohol to gastric cancer were investigated in a public health survey of the adult population of the Nord-Trondelag County in Norway (HUNT-1). During follow-up, we identified 251 new cases of gastric cancer. The risk of non-cardia gastric cancer was almost twice as high in daily smokers as in non-smokers. Earlier age at initiation of daily smoking was associated with an increased risk of non-cardia gastric cancer, independently of adjustment for duration of smoking, suggesting a dose-response relation with earlier onset of smoking. Excessive smoking combined with high alcohol intake was associated with a nearly 5-fold increase in risk of non-cardia gastric cancer, compared to non-users.

In the second study, we hypothesized that specific airborne exposures, which often occur in the male-dominated construction industry, such as dust, fumes, and solvents, could be inhaled and swallowed and have a direct harmful effect on the gastric mucosa. To elucidate the relation between such exposures and risk of gastric cancer in a male-dominated industry, we used prospectively collected data from the Swedish Construction Workers Cohort. In total, 948 incident cases of gastric cancer were identified. There were seemingly dose-response positive associations between exposure to cement dust, quartz dust, and diesel exhaust and risk of gastric cancer. Increased risk of this tumor was found among workers exposed to cement dust (IRR 1.5 [95% CI 1.1-2.1]), quartz dust (IRR 1.3 [95% CI 1.0-1.7]), and diesel exhaust (IRR 1.4 [95% CI 1.1-1.9]).

In the third study, we prospectively investigated the influence of body mass index (BMI) and recreational physical activity on risk of gastric cancer in the HUNT-1 cohort. No statistically significant association was found between different levels of BMI and risk of gastric cancer. A statistically significant 40-50% decrease in the risk of gastric cancer was seen among persons who had at least a moderate level of recreational physical activity, and a dose-response relation was indicated.

In the fourth study, we assessed the effect of dietary salt intake on the risk of gastric cancer in a low-incidence Western region, again based on the HUNT-1 cohort. There was no statistically significant association between level of intake of salted foods and risk of gastric adenocarcinoma. This result highlights the question as to whether cofactors more prevalent in high-incidence populations, such as other dietary factors and *Helicobacter pylori* infection, interact with salt in producing a potentially carcinogenic effect on the gastric mucosa, or whether previously reported positive associations might have been an artifact of residual confounding by such factors.

Krister Sjödahl

List of Publications

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals (I-IV)

I. Sjödahl K, Lu Y, Nilsen TI, Ye W, Hveem K, Vatten L, Lagergren J.
Smoking and alcohol drinking in relation to risk of gastric cancer: a population-based, prospective cohort study.
Int J Cancer. 2007 Jan 1;120(1):128-32.

II. Sjödahl K, Jansson C, Bergdahl IA, Adami J, Boffetta P, Lagergren J.
Airborne exposures and risk of gastric cancer: a prospective cohort study.
Int J Cancer. 2007 May ;120(9):2013-8.

III. Sjödahl K, Jia C, Vatten L, Nilsen T, Hveem K, Lagergren J.
Body mass and physical activity and risk of gastric cancer in a population-based cohort study in Norway.
Cancer Epidemiol Biomarkers Prev. 2008 Jan;17(1):135-40. Epub 2008 Jan 9.

IV. Sjödahl K, Jia C, Vatten L, Nilsen T, Hveem K, Lagergren J.
Salt and gastric adenocarcinoma: a population-based cohort study in Norway.
Cancer Epidemiol Biomarkers Prev. In press.

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Contents

List of Abbreviations

BMI	Body mass index
CI	Confidence interval
HR	Hazard ratio
IRR	Incidence rate ratio
H. pylori	*Helicobacter pylori*
HUNT-1	Helseundersokelsen i Nord-Tröndelag 1 (The Nord-Tröndelag Health Survey 1)
CagA	Cytotoxin-associated gene A
PPI	Proton pump inhibitors
PET	Positron emission tomography
NSAID	Nonsteroidal anti-inflammatory drugs
SIR	Standardized incidence ratio

Foreword

This thesis is based on four studies in which I, together with colleagues, have investigated the causal role of a few selected environmental and lifestyle factors that may be involved in the risk of gastric cancer. In recent years, etiological research concerning gastric cancer has been dominated by *Helicobacter pylori* (*H. pylori*). It is becoming increasingly clear, however, that other environmental factors are probably of critical importance in the causal chain leading to gastric cancer. About half of the world's population is infected with *H. pylori* and it is a reasonable assumption that other factors are involved in gastric cancer causation, both through interaction with this bacterium and by affecting the risk independently. So in a sense, this thesis, based on large prospective studies and focusing on risk factors other than *H. pylori*, could be viewed as a very conscious choice of going "back to the basics" of gastric cancer etiology. First follows an introduction which contains my own thoughts and reflections on different topics related to epidemiological research in general. It is hoped that it may help some of my readers to put the work presented in this thesis into a broader perspective. This introduction does not claim to be complete or comprehensive, or even fully objective. It is a selection, and every selection is by nature and necessity subjective. As a background to the present investigation, selected parts of the literature concerning gastric adenocarcinoma in general and the etiology of this malignancy in particular, are reviewed. Thereafter, the scientific approach to the current studies is considered, and the results are then summarized and finally discussed.

Introduction

Cancer epidemiology

> *"Disagreement and confusion about basic ideas in epidemiology do not necessarily attest to the thick-headedness of epidemiologists; a more charitable interpretation would be that the basic ideas fundamental to the new science have not displayed traditional thinking."*
>
> Kenneth Rothman

Science allows us to improve our understanding of the world and how it works. We identify causal links and these indicate ways in which the world can be acted upon and modified. In the field of epidemiology occurrence of diseases and its relation to different factors are studied. It is often considered to be the core science of public health. The factors studied can be environmental or characteristics of the individual. Aims of cancer epidemiology are to detect patterns of occurrence of different forms of cancer and identify determinants of disease (and health), to study survival and new treatment regimens, and to investigate the health-related quality of life of affected patients.

A central concept within the field of epidemiology is the *population thinking*, and the understanding that, given certain premises, we can make reasonable predictions concerning occurrence of disease. This is in contrast to clinical medicine, with its need for a strictly individual approach. It is sometimes a major conceptual leap to realize that there is something to learn concerning the individual from studies on populations. For most of us, it takes a shift in perspective to understand that a population does not behave as if it was consisted of unique and unpredictable individuals, but rather has its own individuality. Another key principle in cancer epidemiology (indeed in every area of epidemiology) is the concept of *group comparisons*.

The most groundbreaking discovery in the history of cancer epidemiology is probably the carcinogenic effect of tobacco, and some consider that the most important discoveries of the two past decades in cancer epidemiology relate to the carcinogenic effects of infectious pathogens that had not been characterized twenty years ago.[1] Research on disease etiology has to rely either on animal models, with sometimes overenthusiastic assumptions about inter-species analogies and exposure or exposure dose extrapolations, or on epidemiological studies. The latter have generated much of what is currently known about the etiology about human cancer. Animal studies have been criticized as having results that are to a large extent false positive, for the reason that high doses of test compounds have been used on particularly susceptible strains of animals. There are many authorities in cancer research who believe that in order to draw confident conclusions about normal or pathological processes in humans, humans must be studied.[2, 3] This is why, for example,

the International Agency on Research on Cancer (IARC) grades epidemiological evidence highest when compiling the scientific "burden of proof" regarding a specific exposure or process.

Several biological factors have been found to be carcinogenic to humans, the quantitatively most important being hepatitis viruses, human papilloma viruses, and *H. pylori*.[4] Reproductive and intrauterine factors have shown documented effects on several types of cancer. However, occupational and lifestyle factors are the most important in human carcinogenesis.[5, 6] Major genes are unlikely to be responsible for a large fraction of human cancers, because of selection processes,[7] while gene-environment interactions might potentially make more substantial contributions.[8] But if many genes contribute to the large genetic effects that seem to underlie many common cancers, these genes may be discoverable only through advances in our understanding of carcinogenic mechanisms. Traditional epidemiological studies, as well as laboratory studies, could help us on this road to better understanding.

Epidemiology is a recently defined scientific discipline. Epidemiological concepts were, however, applied long ago. Nowadays, the methodology is evolving constantly and rapidly, making whispers of previously unconceivable applications. Integration of laboratory methods into etiological research will, for example, allow further development of genetic epidemiology, uniting immunological virology and bacteriology with epidemiology, and make markers of pre-carcinogenic morphological changes available. It is interesting that computer security experts have been described as "a new breed of epidemiologists who vigilantly monitor the health of our online universe".[9]

Etiological research is of central importance in setting preventive and interventional objectives. It has been found that a small risk applied to a large number of people can generate many cases, implying that to be effective, a preventive strategy should consider targeting the mass of the population and not only the minority that is at high risk of developing the disease.[10] However, epidemiological studies with etiological objectives have the disadvantage of being feasible only when a potentially carcinogenic factor has already been introduced into the population. Epidemiology sometimes fails to constitute an early warning system, as the increase in cancer incidence caused by exposure to a carcinogen might not be detectable for several decades.

Clinical researchers in Scandinavia have better potentialities for epidemiological research than those in most other places in the world. Large and comprehensive databases are often available and the society has, I believe, a comparatively strong faith in science, making it less susceptible to paranoid misconceptions regarding the ability of researchers to handle collected information in an ethically appropriate manner, not only with regard to the question of confidentiality, but also concerning our research objectives. We should feel obliged to make use of this source of register information in the best way possible and to combat paralyzing interpretations of medical secrecy.

Causality in epidemiological research

> *"I cannot give any scientist of any age better advice than this: the intensity of the conviction that a hypothesis is true has no bearing on whether it is true or not."*
>
> Peter Medawar

Causality is the essence of epidemiology. This is an indisputable fact and my strong personal conviction. Yet, many people are doubtful regarding the ability of this research discipline to provide us with valid results regarding causal effects between exposures and diseases. When lay people one day read in the newspaper that a particular aspect of their everyday life is dangerous to health, and the next day learn, from the same source, that the very same exposure is of exceptional value for their vigor, this naturally creates problems of faith in medical science in general, and epidemiology in particular. Ever since I began my research training, I have even come across physicians, with academic training in research, who are absolutely ignorant when it comes to interpreting epidemiological data, discarding the results of generations of brilliant epidemiologists with reference to the "epidemiological nature" of the studies. Some of these scientists seem to think that there is some state of opposition between, for example, molecular-biological research and the type of investigations conducted within the field of epidemiology. I do not believe that this is true. On the contrary, researchers from different fields should collaborate even more, and not allow prejudice and ignorance to affect their intellectual exchange. Some of these research-educated skeptics claim that epidemiological studies can never be anything else than "hypothesis-generating". I strongly oppose this opinion. People generate hypotheses. Not studies. This being said, I also believe that new ideas and hypotheses can be spawned from coincidental findings in epidemiological studies. This is in perfect analogy with every other field of research, the accidental discovery of penicillin being a good example of this phenomenon. However, I believe that it is of utmost importance to have a clearly stated hypothesis when conducting an epidemiological investigation, in order to avoid the error of interpreting chance findings as something meaningful. Some epidemiologists have a different view, and consider that epidemiology is most useful when it ventures into territories unconstrained by biological knowledge, since it is in this terrain that it may stumble upon novel findings of public health importance.[11] When, for example, we are able to identify a new and unexpected confounder in an epidemiological study, it might in itself be more interesting than the original hypothesis, leading us to pursue deeper biological explanations.

I have become interested in causality in general, and in causality within epidemiology in particular. Studies in this field have strengthened my conviction that we can achieve new, important, and valid knowledge from epidemiological studies, including those that I am conducting. I humbly admit that I might not fully understand all conceptual models and arguments, but even my attempts to understand them have been an educational and enjoyable experience.

During childhood we have all struggled to understand the concept of cause and effect, and it is sometimes a challenge to discard these naïve and rudimentary ideas in favor of more complicated and contra-intuitive theoretical models, for example, that any given disease, classical monogenic diseases included, can be viewed upon as being caused 100% by hereditary factors and as being caused 100% by environmental factors.[12] Causation involves a relation between at least two entities, an agent and a disease. The work of Pasteur and Koch led to an era in which an agent of a

disease was conceived as a single necessary cause. It was truly a microbiological revolution, a shift in scientific paradigm.[13] Many infectious and occupational diseases are themselves partly defined on the basis of their cause. The term INUS (insufficient non-redundant component of unnecessary sufficient complex), conceived by the British philosopher John Mackie, led to the concept of "causal web theory" in epidemiology.[14] Kenneth Rothman from the US made a substantial contribution to epidemiological causation philosophy in developing this concept further. Rothman states: "A cause is an act or event or a state of nature which initiates or permits, alone or in conjunction with other causes, a sequence of events resulting in an effect".[15] Furthermore, he considers that a theoretical complete causal mechanism of a given disease should be called a *sufficient cause*. In every patient who develops a certain disease, this will occur because of a single mechanism of sufficient cause, or causal complex. However, a given causal mechanism, leading to a sufficient cause, may contain different *component causes*. If we consider causality at the individual level, in cancer epidemiology there are only causal mechanisms without single necessary component causes. It is impossible to identify the necessary cause that explains the occurrence of a single case of cancer. This is a fact worth remembering both by clinicians and by self-blaming cancer patients. It is possible, however, to infer that a specific individual's illness more likely than not was caused by a specified exposure – something which frequently occupies American lawyers specialized in suing for damages concerning health. However, at the population level the INUS model is valid for diseases of long duration such as cancer.[16] It could be argued that the monocausal viewpoint has been promoted in medicine because of practical interest in therapy, but from a scientific perspective monocausality must be opposed.

Another peculiar aspect of causation in epidemiology is the definition of a "strong" cause. This is a component cause which plays a causal role in a large proportion of cases in a population. Thus, the strength of a risk factor depends on the prevalence of the complementary risk factors needed to create a sufficient cause. The same exposure can be strong in one population if its complement causes are common, and weak in another if its complement causes are rare.[12] Another central concept is that of biological interaction, which can be defined as two component causes acting in the same sufficient cause. The degree of observable interaction between two specific component causes depends on how many different sufficient causes produce disease and the proportion of cases that occur through sufficient causes in which the two component causes both play a role. The extent or apparent strength of biological interaction between two factors is therefore dependent on the prevalence of other factors.

Criteria for inferring causation from epidemiological investigations have been proposed, and the most widely known principles are probably those formulated by Hill[17, 18]: (1) strength, (2) consistency, (3) specificity, (4) temporality, (5) biological gradient, (6) plausibility, (7) coherence, (8) experimental evidence, and (9) analogy. Each of these (except for temporality) has been, and should be, questioned. Nevertheless, they serve as useful concepts.

The concept of *induction time* is very often misunderstood. Cancer has been said to be a disease with a long induction time. This is wrong. Every component cause has a specific induction time, i.e. the time from causal action to initiation of the disease. It is not correct to characterize a disease itself as having a long or short induction time. The time between disease initiation and detection is called the *latent period*.[19] In carcinogenesis, the terms *initiator* and *promoter* are used to refer to component causes of cancer that act early and late, respectively, in the causal mechanism. A promoter will have a short induction time. For the last acting causal component in a causal process

the induction time will be zero. Cancer risks in old age may depend as much on lifestyle factors in early life as on current habits.

In order to claim the existence of a causal relation at all, much epidemiological evidence is required. And by that I do not necessarily mean a large number of studies on a particular subject, since one methodologically strong study can provide more evidence than ten methodologically weak ones. Sometimes there is a tendency, even among epidemiologists, to be over-eager when discussing causality based on epidemiological results. It is dangerous when, for example, the Hill criteria are used as a "checklist" for causality, and not as a general guide, when discussing the degree of truth regarding some observed association. Very often a large body of evidence needs to be created before a causal relation can be considered established. If a hypothesis cannot be refuted, it can be accepted preliminary, and if the results are repeated, the evidence will grow stronger until enough consistent evidence has been accumulated.[20] Both individual researchers and national and international agencies are working on compilation of evidence in this way. For example, the aforementioned IARC is doing this in a manner worthy of imitation. However, some regulatory agencies and policy makers may recommend standards and set limits even when the scientific evidence is inconclusive. These procedures serve public health objectives by introducing a very wide safety margin, but they are in a way arbitrary and should not be confused with the establishment of causation.

In epidemiology sophisticated theoretical models have been developed for bias and confounding, but a belief that differences between people can be summed up in measures of a few "potential confounders" and adequately adjusted for in statistical analyses fails to recognize the complexity of reasons why humans differ with regard to particular and general aspects of their lives.[21] Indeed, most variables are proxies for other things, as for example the commonly used variable of "socioeconomic status", which is best understood as a surrogate confounder. But to be dealt with, a confounder must be identified or at least suspected. Furthermore, it (or a surrogate) must be accurately measured. Claiming the existence of causality requires a lot of knowledge, wisdom, humbleness, and courage.

As mentioned earlier, unwarranted public concern about exposures in daily life is a problem. Sometimes, the sources of this problem are conflicting epidemiological data or prematurely drawn conclusions about causality. But, more frequently, I feel, the blame should be put on less particular and unlearned journalists who are looking for an easy way to sell single copies of tabloid newspapers, exploiting people's concern about their health. However, I must emphasize that I believe it is of utmost importance that the scientific community informs the public of new findings of meaningful links between exposure and disease, but it is equally important to try to make sure that the information is conveyed correctly to a public of laymen who cannot be expected to have the knowledge to appreciate and interpret it to its full extent. If the information is not given correctly, alarming reports could lead to devastating and widespread nihilism regarding epidemiological findings. Another type of public anxiety concerns risks that are feared to an extent far out of proportion to their likelihood of occurrence. This could also be largely avoided by proper and balanced information. Together, researchers and journalists should make an effort to inform and educate the public as correctly and in as well-balanced a manner as possible, since this is their moral duty. Furthermore, I believe that scientists have no right to tell people what to do. This would declare us as agents of social control, and I feel that the general population would justifiably lose some of its confidence in researchers if we did.

Wishful thinking...
And shouldn 't all the tax revenue that goes to research finally give us a little bonus?

"Well, look at this – a study that shows that fat food and a good red wine together with a fine Havana prolongs life by ten years!"

"Cheers for science!"

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Cancer

> *"One day, we imagine that cancer biology and treatment – at present a patchwork quilt of cell biology, genetics, histopathology, biochemistry, immunology, and pharmacology – will become a science with a conceptual structure and logical coherence that rivals that of chemistry or physics."*
>
> Douglas Hanahan and Robert A. Weinberg

The term cancer comprises hundreds of disparate diseases that differ in their genetic basis, etiology, progression, and final outcome to sufficient degrees to be classified as separate entities. Genetic alterations are at the very center of tumor genesis so that, at a cellular level, cancer can be designated an acquired genetic disease. During the last decades we have witnessed remarkable progress in the understanding of the pathogenesis of cancer. As mentioned earlier, much of what is currently known about the etiology of human cancer has been derived from epidemiological research.[1] However, this knowledge has not yet had an overall major impact on the treatment and

survival of affected individuals. The clinical manifestation of any cancer depends on the tissue type affected and the location, but usually involves an expanding tumor mass, which causes symptoms through local invasion, local expansion, distant metastases or the production of biologically active molecular products such as hormones or cytokines.

Virtually all mammalian cells carry similar molecular machinery regulating their proliferation, differentiation, and death. Many types of cancers are diagnosed in the human population with an age-dependent incidence, implicating four to seven rate-limiting genotoxic "hits", leading to defects in regulatory circuits that govern normal cell proliferation and homeostasis.[22] Oncogenes are mutated genes that in their normal ("wild") form exert crucial functions in the metabolism of the cell, and are highly conserved on the evolutionary scale. Simply expressed, these genes impel the cell to proliferate. In contrast, tumor-suppressor genes have a general growth-constraining effect. Loss of function of these latter genes is also an important element in homeostatic disruption leading to malignant growth. A wide range of processes have evolved which are designated to repair DNA that alters its coding capacity, i.e. becomes mutated, e.g., when chemical carcinogens or ultraviolet light cause chemical reactions at DNA bases. Hanahan and Weinberg have suggested that cancer cells manifest six basic and critical characteristics that are essential alterations in cell physiology, which together dictate malignant growth: 1) self-sufficiency in growth signals, 2) insensitivity to growth-inhibitory signals, 3) evasion of apoptosis, 4) limitless replicative potential, 5) sustained angiogenesis, and 6) tissue invasion and metastasis.[22] The available evidence suggests that most of these traits are acquired through accumulation of changes in the genomes, and the cells are able to do so because of acquired genetic instability, e.g. loss of p53 function.

Pathological analyses of a number of organ sites have revealed lesions that appear to represent intermediate steps in a process through which cells evolve progressively from normalcy via a series of pre-malignant states into invasive cancers.[23] Observations of human cancers and animal models suggest that tumor development undergoes a process analogous to Darwinian evolution. A succession of genetic changes, each conferring one or another type of growth advantage, leads to a progressive conversion of normal human cells into cancer cells.[23, 24] Fundamentally, cancer represents a form of dedifferentiation, or at least a disturbance of the normally differentiated state that is associated with loss of growth control.

Therapeutic immunosuppression causes a marked increase in the occurrence of some cancers,[25-27] suggesting that unidentified viruses may be important in the etiology of various malignancies. There are still a number of types of human tumors with a possible infectious etiology, including lymphomas and leukemias, as well as some epithelial tumors. Several human tumor viruses are ubiquitous and only a low proportion of infected individuals develop the respective form of cancer. It is thought that such malignant conversion occurs either as a consequence of additional genetic modifications in the latently infected cells, or under conditions of severe immunosuppression.[4] Ubiquitous virus infections which may rarely lead to malignant tumors would be difficult to trace epidemiologically.[4] The alternative is the theory, for which there is considerable evidence, claiming that many non-viral cancers are kept in check by immunosurveillance.[28] Suppression of the immune system could lead to an impaired elimination of tumor cells.

The overall burden of cancer in the world is immense. In the year 2002 it was estimated that there were 10.9 million new cases, 6.7 million deaths, and 24.6 million persons alive with cancer (within three years of diagnosis).[29] Most of the marked international variation is due to exposure

to known or suspected risk factors related to lifestyle or environment.[1, 5, 6] Indeed, it has been estimated that 30% of all cancer cases would not occur if tobacco smoking was entirely abandoned.[1] Among non-smokers overweight, oncogenic infections and excess exposure to ultraviolet radiation are the most important preventable risk exposures. The proportion of all deaths from cancer attributable to overweight and obesity in US adults may be as high as 14% in men and 20% in women.[30] It has been estimated that biological agents (viruses, bacteria, parasites) explain 5% of cancer mortality in developed countries.[31] About 18% of cancers worldwide are caused by known infectious agents.[32] It should be acknowledged that some preventive measures will proportionally be more important in developing countries, e.g., vaccination against hepatitis B virus, which causes hepatocellular cancer.

Background

"After my death I wish you to do an autopsy. Do not let any English physician other than Dr. Arnott touch my body. Preserve my heart in alcohol and deliver it to Marie Louise in Parma. Give her all the details of my death. Examine well my stomach, and make a detailed report to my son. Indicate to him what remedies or mode of life he can pursue which will prevent his suffering from a similar disease…"

Napoleon Bonaparte

Historical remarks and perspective

According to legend, Hippocrates, Master of the Greek medical school, in the second century AD, was the first to use the words "cancer" and "carcinoma". He was convinced that this disease attacked the body from the outside, penetrating through the skin, infiltrating tissues and organs. In the Egyptian, Greek, and Roman civilizations human cadavers could not be utilized for medical anatomical studies and therefore knowledge concerning internal tumors was not easily obtained. Avicenna was a Persian, living in the eleventh century, who became renowned as a physician and philosopher. He described what might have been a gastric cancer. However, as early as in 1600 BC, some possible cases of gastric cancer had been reported in the *Ebers papyrus*, which is considered to be among the most important medical papyri of ancient Egypt. Despite the prohibition concerning necropsy of human corpses, there is a description of a patient with dysphagia in whom the stomach had the appearance of a shriveled fetal face. With the Renaissance, medieval knowledge rapidly changed. In 1774 a thesis entitled "Dissertatio Accademica de Cancro" was published by Dr. Peyrile and this has been considered to be the starting-point of a new oncological era. However, during the 18th century gastric cancers were formally unknown, as benign and malignant gastric ulcers were only described in 1835 by J Cruveilhier, a highly influential French anatomist of his time. A treatise in 1839 by Robert Bayle clearly described the detailed pathology of gastric cancer. The lack of knowledge about this cancer might partly explain the medical mystery surrounding the death of Napoleon Bonaparte.

After his defeat at Waterloo, Napoleon Bonaparte, leader of the French revolution and self-crowned emperor, was exiled to the island of St. Helena. He enjoyed reasonable good health until two years before his death. In 1819 he began to suffer from recurrent episodes of fever, abdominal pain, persistent hiccupping, and vomiting. The symptoms worsened, and on April 27th, 1821, he vomited coffee-ground material and had severe hiccupping and tachycardia.[33] He made a request to his friend Dr. Antonmarchi, "After my death I wish you to do an autopsy. Do not let any English physician other than Dr. Arnott touch my body. Preserve my heart in alcohol and deliver it to

Marie Louise in Parma. Give her all the details of my death. Examine well my stomach, and make a detailed report to my son. Indicate to him what remedies or mode of life he can pursue which will prevent his suffering from a similar disease…"[34] Several members of the Bonaparte family had died after suffering from abdominal pathology, justifying Napoleon's concern for his son. On May 2nd the vomiting returned and he was treated with a massive dose of calomel, an anti-emetic of the time. This substance is not well absorbed and would have caused diarrhea in the already probably hypokalemic emperor.[35] These events have prompted historians to speculate whether the immediate cause of his death was *torsade de pointes*, predisposed by arsenical effects on the cardiac conduction system and hypokalemia.[35] Since hair samples collected in 1961 clearly showed that he had been exposed to excessive concentrations of arsenic, it is unclear if Napoleon died *with*, or *of* arsenic poisoning. As already mentioned, it is of course not possible to determine the exact cause of a single event in an individual, and intellectual experiments like these can serve to illustrate this. However, for those with a historical interest it can be quite amusing. Shortly after these events, the emperor had a massive bowel movement with tarry stools followed by circulatory collapse. He died two days later. Autopsy findings clearly showed that Napoleon had an extensive scirrhous carcinoma of the stomach, probably complicated by partial obstruction.[36] Other historical persons who have succumbed to gastric cancer are the Irish author James Joyce, Pope John XXIII, and King Charles the 11th of Sweden.[33]

Surgical resection of a gastric cancer was first attempted by Jules Pean in 1879 and one year later by Ludwig von Rydiger.[37] However, the first successful resection of a gastric antral carcinoma was performed by Theodor Billroth on January 29, 1881. He had Swedish and French ancestry and graduated from the University of Berlin, and became chairman of the famous Second Surgical Clinic at the *Allgemeine Krankenhaus* in Vienna, a position he kept until his death. The patient, a 43-year old mother of eight children, lived for four months after the surgical procedure. She was anesthetized by Dr. Barbieri with a mixture of chloroform, alcohol, and ether. Billroth closed the greater curvature side of the stomach and anastomosed the lesser curvature to the duodenum, an operation that became known as the Billroth I. In 1885, Billroth and von Hacker, with the aim of achieving more radical resection of an extensive tumor, performed a gastric resection with closure of the gastric and duodenal stump and anastomosis between the remaining stomach and an antecolic jejunal loop. This operation became known as the Billroth II, and was further modified by various surgeons. The principles of these reconstructions are still applied in gastric surgery today, and are labeled with the names Billroth I and II.

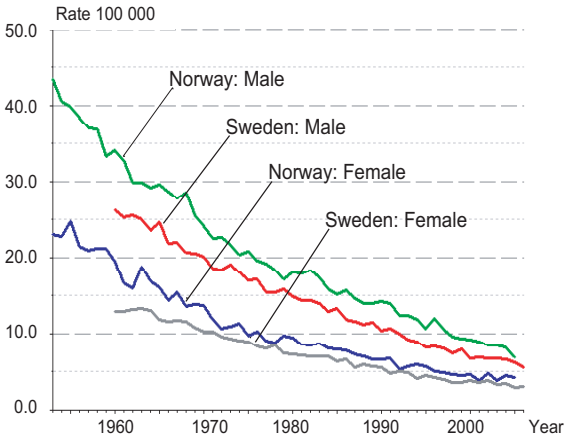
Gastric cancer occurrence

Gastric adenocarcinoma is the fourth most common malignancy in the world and the second leading cause of cancer death.[29] Only cancer of the lung, breast, and colon are more common. It has been estimated that 934,000 new cases of stomach cancer occur every year worldwide, and that 700,000 people die annually from this disease,[29] representing more than 10% of all cancer deaths. There has been a marked fall in incidence in developed countries during the last decades. This decline has occurred in most populations since the 1930s, and has been described as one of the greatest medical triumphs of the last century. However, as a consequence of the aging and growing global population, it is predicted that the absolute number of gastric cancer cases will increase up to the year 2050.[38] [39] Gastric cancer is closely associated with age, the peak incidence being

between the 5th and 7th decades of life. There is an overall male predominance, with 2-3 males per every female affected. The decline has occurred in both sexes, and reflects a change in incidence rather than earlier diagnosis, better treatment, or changes in definition.[38] Two thirds of the patients live in developing countries. Increased attention has been directed to what seems to be an opposite (increasing) trend in incidence in the proximal stomach, the gastric cardia. Classification of tumors of the gastroesophageal junction is potentially difficult, and in Sweden and Norway it is typically made by clinicians, who might use different definitions when reporting to the national cancer registries. A widely used system of classification was proposed by Siewert in 1998.[40] The acceleration in the incidence of cardia cancer seems, however, to be real, although the apparent increase is probably partly an effect of better reporting to various cancer registries. In Sweden, where cancer incidence reporting has been virtually complete since the 1960s, an increasing trend of cardia cancer has been noted, even though considerable misclassification of the site within the proximal stomach has been demonstrated.[41, 42] For cardia cancer, there is an even more pronounced male to female ratio, around 6:1, and this cancer is more common among whites and in Western countries.[43-45] These striking epidemiological changes are still only partly explained. Elucidation of the causes of these trends could potentially lead to an acceleration of the decline in the incidence of non-cardia gastric cancer, as well as a reverse of the opposite incidence trend regarding cardia cancer. Moreover, it could increase the understanding of other malignancies and contribute to future preventive work.

Globally, there is a 10-fold variation in reported national incidence rates of gastric cancer. The histologically intestinal subtype is relatively more common in areas with a high incidence of the disease. However, underestimation of new cases from less developed parts of the world where health care availability, diagnostic methods and cancer reporting practices all exhibit major shortcomings, could be a problem when making comparisons. High incidences of gastric cancer have been noted in Japan, South Korea, Central and South America, and Eastern Europe. Low incidence rates have been reported from parts of East Asia, Scandinavia, Western Europe, North America, Australia, and regions in Africa. In 2002, the worldwide average estimates of age-adjusted incidence were 22.0 per 100,000 person-years in men and 10.3 per 100,000 person-years in women.[29] In 2006, the Swedish gastric cancer incidence in men was 11.7 per 100,000 person-years, and in women the corresponding incidence was 7.6. The total number of gastric cancer cases diagnosed in Sweden in 2006 was 875, of which 527 (60%) occurred in men and 348 in women. Cardia cancer was reported in 198 cases, with 149 (75%) occurring in men and 49 in women.[46] In Sweden, as in many other countries, the decline in incidence of gastric cancer has followed a birth-cohort phenomenon.[47] In 2006, the Norwegian gastric cancer incidence in men was 7.0 per 100,000 person-years, and in women the corresponding incidence was 3.8. The total number of gastric cancer cases diagnosed in Norway in 2006 was 500, of which 298 (60%) occurred in men and 202 in women.[48]

Incidence of gastric adenocarcinoma in Sweden and Norway



Incidence trends of gastric adenocarcinoma in Sweden and Norway during the last decades. Age-standardized incidence rate (World Standard Population) per 100,000.

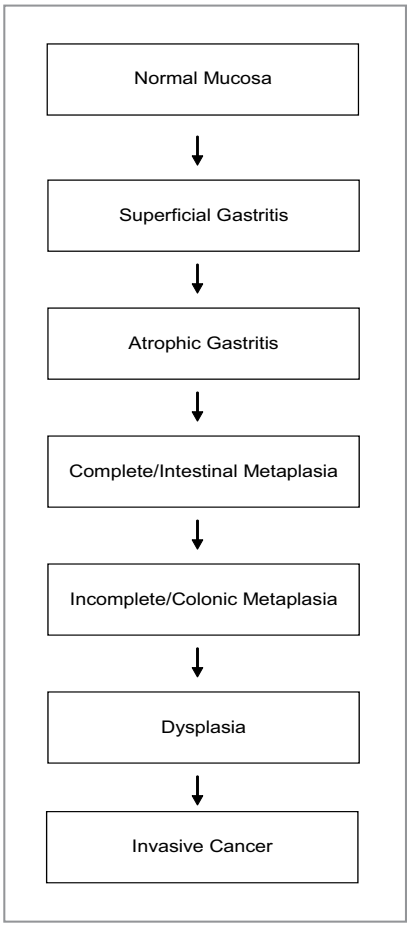
Adapted from: Gerda Engholm, Hans H. Storm, Jacques Ferlay, Niels Christensen, Freddie Bray, Elínborg Ólafsdóttir, Eero Pukkala and Åsa Klint (2008). NORDCAN: Cancer Incidence, Mortality and Prevalence in the Nordic Countries, Version 3.1. Association of Nordic Cancer Registries. Danish Cancer Society. (http://www.ancr.nu).

Gastric carcinogenesis and biology

Lauren suggested that gastric adenocarcinoma cases should be divided into two histologically distinct groups: gastric cancer of the intestinal type, with glandular epithelium composed of absorptive cells and goblet cells, and gastric cancer of the diffuse type, with poorly differentiated small cells in a dissociated noncohesive growth pattern. In addition, mixed tumors occur, representing a combination of the intestinal and diffuse types.[49, 50] As mentioned above, the intestinal histological type is relatively more common compared to the diffuse histological type in areas with a high incidence of the disease. Adenocarcinomas represent more than 95% of gastric neoplasms. Other types include stroma cell tumors (GIST), lymphomas, lipomas, carcinoids, adenomas, and metastases.

There are marked clinical and genetic differences regarding the two histological types of gastric adenocarcinoma, and much evidence supports the possibility of separate disease etiologies.[38, 51] However, no clear-cut differences in the pattern of risk factors have been revealed in a number of studies where the two histological types of gastric cancer have been analyzed separately.[52-54] A wide range of genetic and epigenetic abnormalities, including point mutation, loss of heterozygosity, microsatellite instability, and hypermethylation, are described in the intestinal type and its precursor lesions.[55] The diffuse type is characterized by absence of such pre-neoplastic lesions, and mutation or epigenetic silencing of the E-cadherin gene seems to be the most important carcinogenic event.[55, 56] Furthermore, it is more frequent in younger individuals and has a more equal male-to-female ratio.[50] Much of the decline in the incidence of gastric cancer seems to be

the result of a falling rate of new cases of the intestinal type. A classical hypothesis regarding the pathogenesis defining this subtype was presented in 1975 by Correa et al.[57] According to this suggestion, which has been slightly changed during the years, the development of gastric cancer follows the sequence (Correa's cascade): *H. pylori – superficial gastritis –atrophic gastritis – intestinal/complete metaplasia – colonic/incomplete metaplasia – dysplasia – carcinoma*.[57, 58] The progression of these lesions follows a pattern of steady state, with episodes of progression to more advanced lesions and episodes of regression to less advanced lesions. Gastric atrophy leads to loss of parietal cells and hyposecretion of gastric acid, in turn leading to an increased pH of the gastric juice, facilitating proliferation of anaerobic bacteria which reduce nitrate to nitrite, abundant in many foods. From nitrite, carcinogenic N-nitrosamines can be generated. Reducing agents such as ascorbic acid prevents the formation of nitrosated and nitrated compounds.[59] Intramucosal production of carcinogens has also been suggested.[60] There are some concerns that widespread treatment with proton pump inhibitors (PPI) could lead to an increase in gastric cancer,[61] since PPI therapy causes corpus-dominant gastritis in patients with *H. pylori* infection which is associated with hyposecretion.[62] However, the evidence is not strong that it really affects cancer development in the gastric mucosa.[63]



Two main histological variants of gastric cancer have been identified: intestinal and diffuse subtypes. The picture shows the multistep model of the gastric precancerous process in the intestinal subtype. The diffuse subtype lacks well-recognized precursor changes.

It is quite possible that the intestinal type of cancer arises in a gastric mucosa that has undergone a sequence of mutations and histopathological changes that may have started in the first decades of life. Although the exact mechanisms leading to neoplastic transformation remain largely unknown, focus has been directed to the possibility that "oxidative stress" might be crucial in the carcinogenic process.[64, 65] This implicitly suggests that counteractive "antioxidant" measures could be active in protecting the DNA of the mucosal cells from a continuous barrage of genotoxic agents. Recently, intriguing evidence that bonemarrow-derived stem cells are crucial in gastric cancer development has become available. Experimental data suggest that chronic inflammation leads to tissue injury, and ultimately to failure of peripheral tissue stem cells in the gastric mucosa. This in turn leads to the recruitment and permanent engraftment of bonemarrow-derived stem cells into the tissue stem cell niche. With ongoing inflammation and injury these cells are exposed to an abnormal tissue environment characterized by elevated cytokine and growth factor levels which are likely to initiate differentiation, but fail to regulate growth programs appropriately and instead progress through stages of metaplasia and dysplasia.[66, 67]

The intestinal type of gastric cancer is in gross appearance commonly sessile, ulcerating or penetrating.[68] It can sometimes resemble a benign ulcer. Occasionally it grows in a polypoid fungating manner with a nodular polypoid surface with superficial ulceration. Superficially spreading carcinoma is more unusual, corresponding more to the histologically diffuse type, and is diffusively infiltrative over a wide area. A further subgroup of these tumors is the *linitis plastica* (leather bottle) carcinoma, characterized by extensive infiltration of the submucosa and the muscular layers.

Etiology of gastric cancer

Environmental factors are of greater importance than genetic factors in gastric cancer etiology. Familial clustering of cases does occur, suggesting a prominent genetic causal role in some cases, but exposures other than hereditary generally play a more decisive role. Supporting these findings is the observation that first generation migrants sustain the risk of their country of origin but that the incidence rate in subsequent generations tends to fall.[69] This pattern is also seen, for example, for colon cancer, but in the case of gastric cancer this adaptation seems to be slower. These observations strengthen the hypothesis that factors acting early in life could have a very important role in gastric carcinogenesis.

Older age is linked with increased risk. In this context it is a proxy for degenerative changes and accumulated DNA damage, but it is certainly an important marker of risk. In addition, cancer of the stomach occurs predominantly in lower socioeconomic groups. This inverse relation with socioeconomic status is observed in almost every population, but there is no exact correlation to the national level of economic development.

Differences according to anatomic localisation of gastric cancer

	Cardia	Non-cardia
Incidence	↑	↓
Geographic location		
Western countries	+	-
East Asia	-	+
Developing countries	-	+
Age	++	++
Male gender	++	+
Low socioeconomic status	0	+
***H. pylori* infection**	?	++
Diet		
Fruit/vegetables	-	-
Salt	+?	+?
Obesity	+	?
Tobacco smoking	+?	+?

++ strong positive association; + positive association; - negative association;
? ambiguous results; 0 absence of association

Helicobacter pylori

The Nobel Prize in Physiology or Medicine in 2005 was awarded to the Australian physicians Barry J. Marshall and J. Robin Warren "for their discovery of the bacterium *Helicobacter pylori* and its role in gastritis and peptic ulcer disease".[70] This remarkable discovery was made in 1983, and since then it has become increasingly clear that this bacterium also plays a prominent causative role in the etiology of gastric cancer. In 1994, IARC classified *H. pylori* as a definite class 1 carcinogen.[71] As conflicting results accumulated, some scientists came to believe that this decision was made somewhat prematurely, but added together, the results obtained over the last 20 years strongly indicate that *H. pylori* plays a causal role in gastric cancer etiology.[72-74] The average strength of the relationship as determined by meta-analyses produces an effect size of 2.00, i.e. an approximately doubled risk.[75-77] However, some recent studies that restricted the outcome to non-cardia gastric cancer and considered the frequent occurrence of "false-negative" tests for *H. pylori* antibodies resulting from the tendency of disappearance of infection from the cancerous or pre-cancerous stomach, reported a stronger association. *H. pylori* infection has been found in human stomachs all over the world. It is thought that most infections are acquired in childhood, typically lasting for many decades or for lifetime.[78] The mode of transmission is not completely understood, but the fecal-oral bacterial transmission route is probably the most important.[79] Approximately half of the global population is infected, and the occurrence is strongly correlated with low socio-economic status.[80] In some low-income countries, 70-90% of the population are infected, whereas in high-income countries, the prevalence is 25-50%. *H. pylori* infection is associated with an inflammation of the gastric mucosa. The exact mechanisms by which this bacterium causes gastric cancer are still under investigation and remain to be elucidated,[81] but the clinical outcome of this infection is determined by an interplay between *H. pylori*, host derived factors, and environmental factors.[67] In some areas of the world a very high prevalence of *H. pylori* infection runs parallel with low gastric cancer rates.[82] Many bacterial virulence factors that are thought to play a role in *H. pylori* related disease outcomes have been identified. Cytotoxin associated gene A (CagA) positive strains are, for example, associated with an increased risk of gastric adenocarcinoma.[81]

In the Western countries, around 60% of *H. pylori* isolates possess CagA, compared to virtually all isolates in Japan.[83] As a result of polymorphisms coding for this virulence factor, populations infected with East Asian CagA-positive strains may be at greater risk for gastric cancer.[84] However, antibodies against CagA seem to persist longer in serum than conventionally used antibodies utilized for bacterial detection. This could partly explain the stronger association between CagA positive strains and gastric cancer; i.e., it could be due to a reduction in the assumed differential exposure misclassification originating from the loss of infection from the increasingly inhospitable precancerous intragastric environment.[85, 86] A strong, but ineffective, immune response is typically associated with *H. pylori* infection. Genetic polymorphisms influence interindividual variation in the extent and pattern of cytokine response, and thus seem to contribute to the clinical outcome of the individual.[87] It has been proposed that environmental factors and host related factors may be more important than bacterial virulence factors in producing gastric cancer.[88] In line with this suggestion is the observation of a rapid change in the worldwide incidence of this malignancy. This could potentially be explained by a similar decrease in the prevalence of a particular bacterial virulence factor. However, studies have shown that this is not the case.[89] *H. pylori* can be diagnosed by a variety of tests and is readily treated with antibiotics. There are still no preventive vaccinations.[90] Before recommendations of preventive strategies are suggested, it is important to evaluate possible negative effects of such attempts. There are strong indications of an inverse relation between *H. pylori* infection and risk of esophageal adenocarcinoma, a cancer with a rapidly increasing incidence, which is one reason to maintain a prudent attitude toward grand-scale vaccination programs.[86, 91, 92] The relation of *H. pylori* to cardia gastric cancer is less clear than that to non-cardia gastric cancer, but there is also evidence of an inverse risk between cardia cancer and *H. pylori* infection.[93] Furthermore, the issue of antibiotic resistance must be considered.[94] Better sanitation and improved public health has probably led to a spontaneous decline in the prevalence of *H. pylori* infection in the industrialized world. *H. pylori* could be viewed as one of the causative agents underlying the popular statement "poverty is a carcinogen."

Fruit and vegetables

There is reliable evidence that a diet rich in fruit and vegetables is protective against gastric cancer.[95, 96] Prospective studies have repeatedly shown significant reductions in the risk of gastric cancer in association with high consumption of fruit and vegetables.[97-99] Findings in numerous case-control studies have also supported this relationship.[54, 100, 101] However, as mentioned above, carcinogenic N-nitrosamines can be generated from nitrite. This anion is formed from reduction of nitrate, abundant in many foods. For people who consume a typical Western diet, vegetables account for 60-80% of the daily intake of nitrate.[102] The highest concentrations of nitrate are present in leafy green vegetables such as salad and spinach, although the nitrate levels in vegetables can vary considerably depending, for example, on the use of nitrogen fertilizers.[103] Small amounts of nitrite also come from food, such as processed meat.[102]

Tobacco smoking

The relation between tobacco smoking and cancer of the stomach has been the focus of many studies over the years, and taken together these studies seem to indicate that smoking is a moderate risk factor for gastric cancer.[104] However, given the rapid increase in the lung cancer incidences and the progressive fall in gastric cancer incidences worldwide since the 1930s, tobacco use is unlikely to be a very strong risk factor in stomach cancer. Moreover, there is a sparsity of prospective studies, and it is reasonable to believe that recall bias could be an especially serious source of bias when using retrospectively collected data in investigations of smoking in relation to cancer.

Smoking is a risk factor typically acquired rather early in life. In a meta-analysis of the relation between gastric cancer and smoking, the excess risk associated with smoking was estimated to be 50-60%.[105] The relative risk was higher in men (1.59) than in women (1.11). If this association is true, the high prevalence of tobacco smoking in the world suggests that a substantial number of gastric cancer cases (80,000) could be due to smoking.[105] A recent systematic review and meta-analysis only considering cohort studies showed that the risk of gastric cancer is increased by 60% in male smokers and by 20% in female smokers, compared to never smokers, and that the associations are weaker in former smokers.[106] A difference in risk depending on the anatomical location of the tumor within the stomach is a possibility. Some prospective studies have indicated that non-cardia gastric cancer is associated with a stronger risk,[107] whereas others, e.g., a large prospective European study,[108] have shown the opposite. Interaction between *H. pylori* infection and smoking in relation to risk of gastric cancer has also been studied, and there is some evidence of a strongly increased risk among people with CagA-positive strains who smoke.[109]

Alcohol

On the basis of previous research, alcohol consumption has been considered to be an unlikely cause of gastric cancer.[53, 96, 110-112] But previous results are partly contradictory and alcohol use may possibly increase the risk of cardia cancer.[112, 113]

Obesity

The number of studies addressing the influence of body mass index (BMI) on the risk of developing gastric cancer is sparse. Although BMI is linked with an overall increase in the risk of cancer in general, results from case-control studies addressing the risk of gastric cancer have rather indicated an association between low BMI and gastric cancer,[114-117] while prospective studies have yielded contradictory results.[110, 118-125] In a Swedish case-control study the highest BMI quartile was associated with an increased risk of gastric cancer. However, this association was confined to BMI at age 20.[126] Obesity is, on the other hand, one of the major risk factors for gastric cardia adenocarcinoma.[110, 118, 127]

Physical activity

Only in a few studies has physical activity been investigated in relation to risk of gastric cancer. One prospective study has shown an increased risk of stomach cancer associated with several measures of increased activity,[128] while others have failed to show any association.[129, 130] A biological mechanism clearly linking physical activity to gastric cancer risk is lacking, but physical activity affects the body in many different ways and multiple pathways are plausible. Potential mechanisms include a genetic predisposition of habitually active persons, possibly influencing interest in exercise and susceptibility to cancer.[131] Moreover, an improved immune function has been proposed, including increases both in levels of circulating tumor-inhibiting natural killer cells and in their cancer inhibitory abilities.[132] Physical exertion up-regulates the activity of free scavenger systems and oxidant levels.[133, 134] Decreased levels of insulin and insulin-like growth factors are also plausible mechanisms by which a protective effect could be mediated. These potent mitogens do not only stimulate cell proliferation and inhibit apoptosis, but they also interact with other molecules involved in cancer initiation and progression.[135] The association between endogenous reproductive hormones and physical activity is probably of relevance in decreasing the risk for certain cancers.

Salt intake

The hypothesis that high dietary salt intake could increase the risk of gastric adenocarcinoma was spawned in the 1960s, and evidence has gained support from ecological, case-control and cohort studies, mainly from high-incidence Asian countries, over the past decades.[95, 96, 136, 137] The falling incidence of this malignancy has coincided with the spread of refrigeration, which should be inversely associated with salting and other salt-based methods of food preservation.[96] Salt is thought to increase the risk of gastric adenocarcinoma through induction of chronic inflammation of the gastric mucosa. A high salt concentration in the gastric mucosa leads to diffuse erosion, and the induced proliferation in the inflamed environment could promote the effect of carcinogens derived from food.[58] However, few prospective studies have assessed the association of salt intake with the risk of gastric adenocarcinoma, particularly in Western societies, and the results from these studies have been inconsistent.[136]

Occupational exposures

Many studies with gastric cancer as the outcome have been conducted within occupational settings. Most of these investigations, however, have used job titles as a proxy for exposure of specific carcinogenic exposures.[138] Moreover, there has often been a lack of information regarding potential confounding factors. There is considerable evidence that occupations in coal and tin mining, metal processing, particularly of steel and iron, and rubber manufacturing industries lead to an increased risk of gastric cancer.[138] Other "dusty" occupations have also been implicated, but the evidence is not strong.[139-141]

Gastroesophageal reflux

Cancer of the gastric cardia is positively associated with gastroesophageal reflux, obesity and tobacco smoking.[142] Obesity and reflux are associated with each other, but gastroesophageal reflux is also an independent risk factor of cardia cancer.[143]

Genetic causes

Some 10% of patients with gastric cancer have a family history of this disease, and there is a slightly greater disease correlation between identical rather than fraternal twins.[144] A positive family history of gastric cancer is especially serious when positive for genetic syndromes such as Li-Fraumeni syndrome and hereditary non-polyposis colon cancer.[145-147] Nevertheless, many genes that underlie inherited cancer syndromes have a more widespread role in sporadic cancers, as a result of somatic mutations that arise during tumor initiation or progression.[56] The discovery of germ line mutation at the E-cadherin gene, coding for a cell-adhesion protein, in familial gastric cancers of the diffuse histological subtype is an example of progressing understanding of gastric cancer genetics. It has also been shown that expression of E-cadherin decreases along Correa's cascade,[148] and that *H. pylori* infection is associated with downregulation of E-cadherin.[149, 150] Other studies have shown intriguing associations between polymorphisms in genes coding for pro-inflammatory cytokines and risk of gastric cancer. Mutations in the Interleukin-1B gene have been considered to be possibly among the most crucial, although a recent meta-analysis did not provide any support for such an association.[151]

Socioeconomic status

Socioeconomic status has consistently been shown to be associated with gastric cancer.[38, 126] It has been found that the increase in the incidence of cardia cancer has occurred predominantly in professional classes, but subsequent studies in other populations have yielded conflicting re-

sults,[152] indicating that a low socioeconomic status is linked with an increased risk of gastric cardia cancer.[124, 153] Socioeconomic status is a potential proxy for a number of factors. It is associated with lifestyle patterns, dietary habits, BMI, *H. pylori* infection and smoking habits,[154] but some researchers also stress the potential influence on disease risk of commercial marketing activities, relative social status, levels of income and education (often used as proxy measures for socioeconomic status), access to the health care system, and the strength or absence of social networks.[155]

Female sex hormones
The yet unexplained 2-3:1 male predominance has prompted the hypothesis that premenopausal women are protected from developing gastric adenocarcinoma by virtue of their high endogenous estrogen exposure before the menopause. The global finding that women develop the intestinal type of gastric adenocarcinoma on average 10-15 years later than men,[156] and that the incidence of this type of cancer increases after the menopause, has sparked an interest in further investigations. One prospective study indicated that hormone replacement therapy with estrogens is associated with a risk reduction of gastric cancer, particularly of the non-cardia site.[157] Other studies have shown further indications favoring such an association.[158]

Previous gastric surgery
Prior gastric surgery for benign conditions has been shown to be associated with gastric cancer.[159, 160] Twenty years after gastric resection for a benign disease the relative risk has been found to be increased, and this risk was further elevated if the original procedure was a Billroth II. The risk of cancer in the gastric remnant ("stump" cancer) can relate to the production of nitrosamines by bacteria in the relatively hypoacidic stomach remnant or as a result of long-term bile damage to the gastric mucosa. However, since peptic ulcer disease is also related to gastric cancer, the relation between gastric surgery for this benign condition and gastric cancer is difficult to establish.[161]

Pernicious anemia
There is an excess risk of developing gastric adenocarcinoma in persons with pernicious anemia. This appears to be an autoimmune disease leading to chronic atrophic gastritis Type A (Type B is represented by gastritis related to *H. pylori*) located mainly in the corpus of the stomach.[162]

Epstein-Barr virus
Epstein-Barr virus may play an etiological role in a subset of gastric adenocarcinomas.[163, 164] This virus is ubiquitous in all human populations, and it has been estimated that about 10% of gastric cancers throughout the world show monoclonal proliferation of Epstein-Barr virus-infected cells.[165] In contrast to Burkitt lymphoma and nasopharyngeal carcinoma, which are endemic in Africa and Southeast Asia, Epstein-Barr-positive gastric cancers are non-endemic and distributed throughout the world.[165] Some authors consider that lymphoepithelioma-like gastric carcinoma seems to be the main, if not the only, gastric cancer positive for Epstein-Barr cancer.[166]

Atrophic gastritis
Atrophic gastritis is a stage in Correa's model of gastric carcinogenesis and should be regarded as a premalignant state if found in a patient, even in the absence of *H. pylori* infection.

Blood group A
The relative risk of gastric cancer among people with blood group A, compared to those with blood group 0, is 1.2. This was reported as early as in 1953 by Aird.[167] This difference has been

attributed to the nature of mucopolysaccharide secretion in the stomach of blood group A individuals, and to a greater susceptibility to ingested carcinogens.

Radiation
Follow-up of atomic bomb survivors has revealed an increased risk of gastric cancer, as of cancer at many other sites.[121, 168]

Hypogammaglobulinemia
Patients with primary immunodeficiency are at increased risk of developing hematological malignancies, and sometimes also carcinoma. The risk of developing chronic atrophic gastritis, metaplasia, and non-cardia gastric cancer seems to be especially pronounced.[169]

Diagnosis, treatment and survival

Almost two thirds of all cases of stomach cancer occur in the developing world. A diagnosis of stomach cancer in Western countries may bring a feeling of dread, but dread brightened with hope. That is often not remotely the case elsewhere. In developing countries the diagnosis of this cancer is almost without exception terminal. Opportunities for surgery rarely exist, and drugs such as chemotherapy are not on the menu of pharmaceutical options.

However, the prognosis in the Western hemisphere is also disappointing, and the relative 5-year survival (i.e., survival adjusted for expected normal life expectancy) varied between 10% and 20% among patients diagnosed during the 1980s in the USA and Europe. But there has been a slight improvement during the past 20-30 years, despite a lack of major therapeutic discoveries.[170] In Japan, screening is carried out for gastric cancer, resulting in detection of up to 40% of these cancers at an early stage.[171] In Europe, this proportion is less than 15%.[171] In general, nations with a higher incidence of gastric cancer show better survival rates,[172] a result possibly related to the distribution of the tumor location within the stomach.[83]

The symptoms from gastric adenocarcinoma are often vague and non-specific. The most common symptoms are vague indigestion or upper abdominal pain, followed by weight loss, nausea and vomiting, hematemesis and melena, profound anorexia, early satiety, and flatulence.[68] By the time the diagnosis has been made, the tumor is often in an incurable stage. Tumor stage is the dominating prognostic factor. Gastric tumors may spread by direct extension and invasion of adjacent structures, including the liver, pancreas, and spleen. Metastatic spread to the liver, lung, ovaries, bones, and cervical and supraclavicular lymph-nodes is also frequent in advanced cases. Any distant spread implies virtually no chance of cure. Involvement of regional lymph nodes is common, and greatly worsens the prognosis. The degree of local tumor growth, mainly the depth of invasion of the cancer through the gastric wall, also has a marked influence on the prognosis. If the muscularis propria and then the serosa are breached, the prognosis following treatment becomes considerably worse. The tumor stage thus determines the treatment options, and decides whether the intent of the therapy is cure or palliation. As mentioned earlier, tumors in the proximal stomach seem to be increasingly common. There is some evidence that tumors located in the fundus (upper part) are more aggressive, with a greater tendency toward submucosal invasion, irrespective of the histological type. This might possibly be due to the thinner muscularis propria. In general, proximally located tumors appear to be more advanced at clinical presentation and have a worse prognosis than those sited more distally.[68]

Routine hematological tests may reveal anemia, but there are no biochemical markers specific for gastric carcinoma in clinical use. In Japan, double-contrast radiography is used for mass screening. In Western countries, including Sweden, endoscopy with biopsy is usual first choice when investigating the gastric mucosa. Computed tomography, ultrasonography (sometimes also performed endoscopically), and positron emission tomography (PET) are most helpful in the diagnosis of metastatic disease. Laparoscopy can be valuable as initial operative assessment to exclude widespread disease, particularly spread to the peritoneum.

Because of differences in tumor growth, lymphatic spread and prognosis, patients with tumors in the vicinity of the gastroesophageal junction are recommended different treatments according to the precise location of the tumor, i.e., distal esophagus, cardia, or subcardial region, as classified by Siewert.[40] Type I tumors, located in the distal esophagus, are typically treated by a subtotal resection of the esophagus and the proximal stomach, *en bloc* with the celiac axis lymph nodes. Type II tumors, located in the anatomical cardia, are usually treated with total gastrectomy and resection of the esophagus. Type III, located in the subcardial region, as well as other proximal gastric tumors and large tumors (>5 cm in diameter), are typically treated with total gastrectomy including the distal esophagus.[173] Distally located delimited cancers of the stomach can be treated with a subtotal gastrectomy, leaving the gastric fundus and cardia. Gastric cancers that are diffuse, large, multifocal, or have a short distance between the upper tumor margin and the esophagus (<5 cm) are usually treated with total gastrectomy.[174] The current consensus is that removal of adjacent organs, mainly the spleen or the pancreatic tail, is justified only when necessary to ensure complete visible tumor removal.[174] The optimal extent of lymphadenectomy, and the question of possible differences in beneficial effects between D1 and D2 lymphadenectomy, are controversial and still under debate.[175] The evidence from randomized clinical trials does not, however, support a more extensive nodal dissection than D2.[176, 177]

According to a recent randomized trial addressing the issue of adjuvant treatment in patients with operable gastric cancer, a perioperative regimen of epirubicin, cisplatin, and infused fluorocil decreased the tumor size and stage and significantly improved progression-free and overall survival.[178] This regimen is now the standard of care in many hospitals. Radiotherapy has not been proven successful and is not part of any standard care for gastric cancer, although it can be useful in selected cases.

Perspectives of gastric cancer prevention

The great end of life is not knowledge but action. Prevention of cancer may generally be accomplished through primary prevention, secondary prevention, or a combination of these approaches. Primary prevention refers to efforts that aim to prohibit effective contact with the carcinogen in question. Secondary prevention refers to presymptomatic detection of disease at an early, treatable stage, before symptoms or signs occur. Screening reflects such an intention to reduce mortality and/or morbidity from a disease, but is difficult undertakings and the evaluation of their effectiveness is complex and very important. In order to make population screening of a disease justifiable, the disease must be curable, the tests used reliable (of a high predictive value), and the effort must be reasonably cost-effective. There is always the potential of suffering and anguish related to being informed about having a malignant or even premalignant condition. Hence, primary cancer prevention can be considered to be superior, even though its benefits are sometimes difficult to

quantify, and thus to appreciate. A crude approximation of the potential of cancer preventability can be made by identification of the lower rates for any particular type of cancer in any large population in the world with reliable cancer registration data. However, estimates of this kind could potentially be seriously biased, since many populations share a number of risk factors. It is also important to recognize that the effectiveness of any kind of preventive strategy will never be 100%, taking into account that a fraction of all populations will remain poorly educated, inadequately informed, or unable to access adequate health services. It is also reasonable to believe that some people will be careless, or otherwise refractory to the principles of good preventive practices. Such is human nature.

Chemoprevention trials of gastric cancer have been attempted with varying success. In a trial conducted in China, a statistically significant reduction in gastric cancer mortality and incidence was found after five years in a group that received daily supplementation with beta-carotene, vitamin E, and selenium.[179] Another study in a low-risk population of male physicians showed no statistically significant effect of beta-carotene after an average of 12 years of follow-up.[180] Gastric precancerous lesions have been used as an end-point, and several studies have shown prevention of the progression of preneoplastic mucosal changes after *H. pylori* eradication and antioxidant supplementation.[181-183] In a recent clinical trial conducted in a high-risk area in Venezuela, supplementation with antioxidant vitamins was not found useful in prevention of gastric precancerous lesions.[184] A trial in a high-incidence area in Colombia studied various interventions on precancerous lesions at baseline. The treatment arms included triple anti *H. pylori* therapy, ascorbic acid supplements, beta-carotene supplements, and all possible combinations of these three interventions. All of these interventions resulted in significant regression of existing premalignant lesions in a pattern not clearly indicating the relative effectiveness of the individual agents.[185]

The role of conventional nonsteroidal anti-inflammatory drugs (NSAIDs), Cyclooxygenase 2 inhibitors (COX-2), and aspirin as chemopreventive agents remains controversial.[186] In observational studies investigating the relation between these drugs and gastric cancer, confounding by indication is often a serious source of bias. However, NSAIDs seem to exert preventive effects against gastric cancer.[187] Unfortunately, no randomized trials with gastric cancer as outcome have yet been completed.

Screening for gastric cancer has been reported to be effective in some populations, but this is not universally accepted.[188] There is currently no biomedical marker of progression of the precancerous process which can reliably be used in screening programs. Screening with pepsinogen serum levels has been suggested as a complement to *H. pylori* antibody titers for high-risk patients.[189, 190]

Recent advances related to human cytokine polymorphisms should, in the near future, allow the design and implementation of more targeted, large-scale screening programs aimed at identifying persons at the highest risk of gastric cancer. Interventions may become more specific if genetic polymorphisms are identified with the potential to affect cancer risk in combination with environmental exposures. These are more likely to concern premalignant lesions than invasive cancer.

Some authors consider that a reduction in dietary salt intake, an increase in the consumption of fruit and vegetables, and avoidance of tobacco smoking are likely means to reduce the incidence of gastric cancer.[191] The unplanned prevention that has taken place in the West is probably a result

of a better overall socioeconomic standard, leading to a reduced prevalence of *H. pylori*, and of widespread use of refrigeration, less consumption of salted foods, and increased intake of fresh fruit and vegetables. By elucidating the factors explaining the decline in incidence, this process could potentially be accelerated, making it more effective, e.g., by acting against exposures that counteract this trend. A healthy and active attitude of cancer-epidemiological vigilance should be maintained in respect to gastric cancer in order to ensure maintenance of the falling incidence trends. Moreover, if the developed world can work to globalize wealth, it should be similarly able to globalize the opportunities for health.

Aims of the Studies

"Whenever a theory appears to you as the only possible one, take this as a sign that you have neither understood the theory nor the problem which it was intended to solve."

Karl Popper

Study I (Paper I): To provide valid evidence of the role of smoking and alcohol drinking in relation to gastric adenocarcinoma, and to assess the extent to which preventive measures could reduce the incidence of this disease.

Study II (Paper II): To establish whether specific airborne exposures, which often occur in the construction industry, such as dust, fumes, and solvents, increase the risk of gastric adenocarcinoma.

Study III (Paper III): To clarify the influence of BMI and recreational physical activity on the risk of gastric cancer.

Study IV (Paper IV): To uncover the effect of dietary salt intake on the risk of gastric adenocarcinoma in a low-incidence Western region.

Materials and Methods

"Although in most cases all our discussions have yielded only negative result with regard to the etiology of cancer, it is nevertheless believed that this will not be completely worthless for future cancer research. It may be the privilege of a later generation to avoid these rocks and to throw some light on the apparently impenetrable secret of cancer."

Jacob Wolff (written in 1906)

Studies I, III, and IV

Design

These were population-based, prospective cohort studies based on the HUNT-1 (Helseundersökningen i Nord-Trondelags fylke 1) public health survey.

The HUNT-1 public health survey

Nord-Trondelag is one of 19 counties in Norway, and it is divided into 24 municipalities. Its population was about 127,000 in 1984 and 127,500 in 1995. With regard to ethnicity it is very uniform and has a geographical, demographical structure that is fairly representative of Norway as a whole.[192-194] There is, however, no large city in Nord-Trondelag and the average income is slightly lower than the national average.

Between 1984 and 1986, all 85,100 adult inhabitants of in the county of Nord-Trondelag, aged 20 years or more on 31 December 1983, were invited to participate in the HUNT study. The 75,058 (88%) who agreed to participate filled out a questionnaire that was included with the invitation, and attended a limited clinical examination at their local health center. At the examination, the participants received a second questionnaire to be completed at home and returned in a pre-stamped envelope. Information was collected in this way, at baseline, on a range of lifestyle and health-related factors, including measures of physical activity, use of smoking, alcohol consumption, dietary salt intake, occupation and education, behavioral habits, use of medications, and aspects of psychosocial well-being. Body height and weight were measured objectively by trained study personnel as part of the clinical examination. Participation was voluntary and each participant signed a written consent form.

The Norwegian Cancer Register

Reporting to the Norwegian Cancer Register is mandatory, and since 1953 all new cancers diagnosed in Norway have been registered with information on the affected organ, subsite within the organ, and histological type.[48] In the current study we included patients diagnosed with gastric adenocarcinoma. Virtually all gastric cancers (>98%) are histologically confirmed, and the few cases without adenocarcinoma were not included in these studies. The classification of gastroesophageal junction cases was made by the physicians and pathologists who reported the case to the Cancer Register. The unique 11-digit identity number of Norwegian citizens was used to link individuals from the HUNT study to information on cancer incidence in the Cancer Register,[195, 196] where stomach cancer was registered according to the International Classification of Diseases 7th edition (ICD-7), codes 151.0, 151.8, and 151.9.

Register linkages

For accurate censoring, we also performed register linkages with the Norwegian Central Person Register, which provided information on vital status and emigration.

Statistical analyses

In **study I** hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated by a Cox proportional hazards regression model, using attained age as the underlying timescale. Each cohort member contributed person-time from the date of the health survey examination to the date of a cancer diagnosis (all sites), or to the date of death, emigration, or end of follow-up (December 31, 2002), whichever occurred first. Cohort members who were followed up for less than three years were excluded. Proportional hazards assumption was tested by Schoenfelds's method[197] for all potential risk factors and confounders, and we found that the gender variable did not conform to the assumption of proportionality. Thus gender-stratified Cox regression models were used. For the analyses of gastric cancer incidence in **studies III** and **IV**, each participant contributed person-time in the same way as in study I, i.e., from the date three years after the health survey examination to the date of a cancer diagnosis (all sites), or to the date of death, emigration, or end of follow-up. To avoid selection bias caused by influence of a yet undetected cancer on the exposure prevalence, we excluded 3,163 members of the study cohort whose follow-up time after participation in the health survey was less than three years. Hazard ratios and 95% confidence intervals of gastric cancer between categories of BMI, physical activity, and salt intake were estimated by a Cox proportional hazards regression model. In multivariable models, adjustments were made for attained age, BMI, physical activity, smoking status, alcohol use, salt intake, and occupation[198]. Since BMI did not influence the risk of gastric adenocarcinoma in our analyses, this variable was excluded from our final model in study IV. Trend tests for the different exposures were made in study III by introducing the categories as ordinal variables into the Cox model. For BMI, the trend test was based on the median value in each category. Interaction terms were constructed to determine whether multiplicative interaction modified the associations of BMI and physical activity with risk of gastric cancer. We also performed the analyses stratified for gender in studies III and IV. Furthermore, in study III the analysis of the risk of overall gastric cancer was stratified for

BMI (<25 and ≥25). Since the proportional hazards assumptions were violated in some regression models, mainly by the age variable, stratified analysis by age group was also performed. Non-responders to the questions regarding salt intake were analyzed as a separate group in study IV. Trend tests for the different exposures were made by entering categorical data as ordinal variables into the Cox regression model.

Study II

Design

This was a prospective, population-based cohort study based on the Swedish Construction Workers Cohort.

The Swedish Construction Workers Cohort

The Swedish Construction Workers Cohort consists of almost 400,000 employees in the Swedish construction industry who between 1971 and 1993 were regularly invited to attend health examinations by a nationwide occupational health service organization with almost complete coverage of the construction industry.[199] This organization was established jointly by the trade unions and the employers' association in the Swedish construction industry in the late 1960s. The main purpose of this organization was to provide preventive health examinations to all employees within the construction industry. The participation rate among the invited persons was high (85-90%). The first visit (health examination) was used to define entry into the cohort. Information on job titles and other variables, notably tobacco smoking and anthropometric measures, was obtained prospectively through self-administered questionnaires and forms completed by specially trained nurses within the health service organization. A vast majority (95%) of the cohort members were men.

The exposure assessment was based on job titles as described in previous reports.[199-202] The job title at each worker's first health examination was used. Between 1971 and 1976 industrial hygienists assessed the exposure patterns within more than 200 occupations specific for the Swedish construction industry. Each of these occupations was studied at visits to approximately five different sites in different geographical regions in Sweden. The job-exposure matrix regarding airborne exposures included 12 agents: asbestos, asphalt fumes, cement dust, concrete dust, diesel exhaust, epoxy resins, isocyanates, mineral fibers, metal fumes, organic solvents, quartz dust, and wood dust. The level of exposure to of each of these agents was graded on an ordinal scale from 0 to 5, where level 3 corresponded to the Swedish threshold limit value at the time of the study. When no such limits were applicable, level 3 corresponded to an exposure level considered to be "acceptable" at that time. No specific quantitative meaning was assigned to the other grades. The exposure level scales were categorized into no exposure (0), moderate exposure (0.5-1), and high exposure (2-5). We also examined exposure to "combined" dust (defined as exposure to any of the following: asbestos, cement dust, concrete dust, mineral fibers, quartz dust, or wood dust) and fumes (defined as diesel exhaust, asphalt fumes, or metal fumes).

The Swedish Cancer Register

The Swedish Cancer Register was founded in 1958. Both clinicians and pathologists are obliged to report every new case to their regional register, which in turn reports to the national Swedish Cancer Register.[46] Only persons who have their official residency in Sweden are included in the register. The National Registration Number, a unique personal identifier assigned to all Swedish residents, was used to identify each cohort member and to link each member to the Swedish Cancer Register. By this means, all incident cases of gastric cancer occurring during follow-up of the cohort, in the period 1971 through 2002, were identified. The Swedish Cancer Register codes gastric cancer (ICD-7: 151.0, 151.8, and 151.9) with an overall completeness of 98% according to validation studies.[41, 203]

Register linkages

For complete follow-up and for correct censoring of persons in whom death or emigration precluded the risk of gastric cancer, each cohort member was also linked to the nationwide Swedish registers of Causes of Death and the Total Population.

Statistical analyses

Cox regression was used to estimate incidence rate ratios (IRR) and 95% confidence intervals, using time since entry into the cohort as the underlying timescale. In multivariable models, adjustments were made for attained age, calendar period at entry into the cohort, tobacco smoking status at entry, and BMI. Individuals with missing data for any of the covariates included in the models were excluded from the analyses. Because of the small number of women included in the cohort, we restricted our study to men. The overall effect of each covariate was assessed by a Wald test of homogeneity across all exposure strata.

Overview of the four studies described in this thesis

	Study I	Study II	Study III	Study IV
Data source	HUNT-1	Swedish Construction Workers cohort	HUNT-1	
Design	Prospective population-based cohort studies			
Participants	Inhabitants of Nord-Trondelags fylke aged 20-100 years of both sexes	Men employed in the Swedish construction industry	Inhabitants of Nord-Trondelags fylke aged 20-100 years of both sexes	
Study period	1984-2002	1971-2002	1984-2002	
Exposure	Smoking and alcohol drinking	Airborne occupational exposures	BMI and physical activity	Dietary salt intake
Outcome	Gastric adenocarcinoma			
Follow-up	Register linkages to the Norwegian Cancer Register and the Norwegian Central Person Register	Register linkages to the Swedish Cancer Register, Swedish Registers of Causes of Death and the Total Population	Register linkages to the Norwegian Cancer Register and the Norwegian Central Person Register	
Adjustment/ control	Age, sex, education, BMI (and smoking and alcohol drinking)	Age, sex, calendar period, smoking, and BMI	Age, BMI, tobacco, alcohol, salt, and occupation	Age, tobacco, alcohol, physical activity, and occupation
Statistical analyses	Cox proportional hazards regression			

Results

"It is one of the worst aspects of our present developmental stage in medicine that the historical knowledge of things diminishes with each generation of students. Even independent young research workers can normally be assumed to have a historical knowledge of no more than three to five years at a maximum. Anything published more than five years ago does not exist."

Rudolf Virchow (written in 1870)

Study I

Study participants

The 69,962 study cohort members were followed up for an average of 16 years, contributing a total of 1,117,648 person-years at risk. During this follow-up, we identified 251 new cases of gastric cancer, of which 224 (89%) were non-cardia gastric cancer. There was a male predominance among gastric cancer patients that was stronger among those with cardia adenocarcinoma (74%) than among those with non-cardia adenocarcinoma (55%). Almost 80% of the tumors occurred in persons older than 55 years. Compared with the cohort members at large, patients who developed gastric cancer had a shorter period of formal education.

Risk of gastric cancer

Tobacco smoking and risk of gastric cancer

The risk of non-cardia gastric cancer was increased almost 2-fold increased among daily smokers (adjusted HR 1.88 [95% CI 1.33-2.67]), compared to non-smokers. Based on the point estimates, the associations with smoking found for non-cardia and cardia cancers did not differ substantially (data not shown). Cigarette smoking and pipe smoking were associated with a similarly increased risk of gastric cancer, compared to non-smokers. With a combination of two or more types of tobacco smoking, further increases in HR were noted. Earlier age at initiation of daily smoking was associated with an increased risk of non-cardia gastric cancer, irrespective of adjustment for duration of smoking, suggesting a dose-response relation with earlier onset of smoking (p for trend = 0.02). There was also an increased risk of gastric cancer with increased duration of smoking ($p < 0.01$). A combination of early start of smoking (age < 20 years) and long duration of smoking (> 30 years) rendered an adjusted HR of 1.91 (95% CI 1.22-2.99). Increased number of smoked ciga-

rettes per day was similarly linked to risk of gastric cancer in a dose-response manner (p for trend < 0.01). Among persons who smoked more than 20 cigarettes daily, the adjusted HR of gastric cancer was 1.99 (95% CI 1.16-3.42), compared to non-smokers. Analyses of categorical and continuous models revealed that both duration and intensity of smoking contributed to the increased risk to a seemingly similar extent. After adjustment for smoking duration, no trend remained with smoking cessation. The unadjusted risk estimates regarding tobacco smoking were only slightly changed after adjustment for the potentially confounding variables listed in the methods section, including alcohol drinking. Thus, no strong confounding effects of these covariates were identified. In the non-smoking cohort, the standardized incidence ratio (SIR) was 22.9 (95% CI 17.9-27.8) / 100,000 person-years while among current smokers the corresponding SIR was 31.6 (95% CI 24.0-39.1) / 100,000 person- years, and thus the attributable risk of current smoking was 8.7 / 100,000 person-years. The corresponding population attributable risk was 18.4% (95% CI 12.1%-24.8%).

Smoking and hazard ratio (HR) of developing gastric cancer in 69,962 persons in the HUNT-1 cohort 1984-2002

	Subjects (n)	Non-cardia gastric adenocarcinoma	
		n	HR (95% CI)[1]
Smoking status			
Never smoking *	25,692	82	Reference
Current smoking daily	19,759	70	1.83 (1.27-2.64)
Former smoking	12,148		1.14 (0.75-1.73)
Former and current smoking	31,907		1.46 (1.05-2.04)
Age at start of daily smoking[2]			
< 15 years	1,687	6	2.99 (1.00-8.89)
15-19 years	17,986	52	2.04 (0.94-4.44)
20-24 years	7,076	29	1.92 (0.86-4.27)
25 years or more	3,970	21	1.71 (0.77-3.76)
P value for trend			0.04
Frequency of smoking			
< 10 cigarettes/day	8,667	28	1.36 (0.87-2.14)
10-19 cigarettes/day	14,258	42	1.55 (1.03-2.35)
20 or more cigarettes/day	4,640	17	1.93 (1.09-3.42)
P value for trend			0.01
Duration of smoking			
< 10 years	5,939	6	1.40 (0.59-3.33)
10-19 years	9,632	15	1.27 (0.71-2.29)
20-29 years	6,401	26	1.70 (1.05-2.73)
30 years or more	7,944	55	1.47 (0.99-2.19)
P value for trend			0.04

[1] Attained age as time scale. Adjusted for sex, education, BMI and alcohol drinking.
[2] Only ever, excluding some currently smoking pipes and others but smoking cigarettes only
[3] Including adjustment for duration of smoking
Subjects with missing data not presented in this table
* Reference category throughout the table

Alcohol drinking and risk of gastric cancer

The relative risk estimates regarding alcohol drinking and risk of gastric cancer were attenuated after adjustment for tobacco smoking status. Although the point estimates were increased (HR range 1.13-1.56), no statistically significant associations remained after adjustment for various degrees of exposure to alcohol and risk of gastric cancer or non-cardia gastric cancer.

Alcohol and hazard ratio (HR) of developing gastric cancer in 69,962 persons in the HUNT-1 cohort

	Subjects (n)	Non-cardia gastric adenocarcinoma	
		n	HR (95% CI)[1]
Frequency of alcohol drinking during the last 14 days			
Never drank alcohol *	6,325	26	reference
Drank alcohol occasionally	25,878	95	1.16 (0.74-1.82)
1-4 times	21,667	51	1.29 (0.76-2.18)
≥ 5 times	3,406	17	1.66 (0.87-3.20)
P value for trend			0.09
Feeling of intoxication when drinking			
No	20,691	65	1.12 (0.69-1.82)
Yes	10,172	23	1.50 (0.80-2.83)
Drinks excessively, or at least a little too much			
No	35,668	101	1.13 (0.71-1.79)
Possibly or maybe	6,419	26	1.49 (0.82-2.72)
Yes	5,086	15	1.30 (0.65-2.60)

[1]Attained age as time scale. Adjusted for sex, education, BMI and tobacco smoking
Subjects with missing data not presented in this table
* Reference category throughout the table

Combination of tobacco and alcohol and risk of gastric cancer

Smoking more than 20 cigarettes daily combined with alcohol consumption more than 5 times per 14 days was associated with a nearly 5-fold increase in the risk of non-cardia gastric cancer (HR 4.90 [95% CI 1.90-12.62]), compared to non-use. The interaction between tobacco smoking and alcohol drinking was not statistically significant regarding total gastric cancer (p=0.32) or non-cardia gastric cancer (p=0.44).

Study II

Study participants and incidence rates of gastric cancer

From the original cohort of 384,147 members, we excluded all women (n=19,224), and we also excluded men with a) a diagnosis of gastric cancer before inclusion in the cohort (n=31), b) incorrect death dates (n=28), or c) missing or insufficient information on job title, smoking status (mainly due to lack of recording of smoking status during 1975-1978), or BMI (n=108,507). Hence, 256,357 men constituted the final study cohort. Together, the participants contributed 5,378,012 person-years at risk of developing gastric cancer during the follow-up. In total, 948 incident cases of gastric cancer were identified. The total incidence rate of gastric cancer was 17.6 per 100,000 person-years. The incidence rate of gastric cancer was higher among participants who attended for their first health examination during the earliest years of inclusion in the cohort. The incidence rate was increased among previous or current smokers, and among those who had a BMI above 25 at entry into the cohort.

Airborne occupational exposures and risk of gastric cancer

There were positive and seemingly dose-response associations between exposure to cement dust, quartz dust, and diesel exhaust and risk of gastric cancer. Statistically significantly increased risks of gastric cancer were found among workers highly exposed to cement dust (IRR 1.5 [95% CI 1.1-2.1]), quartz dust (IRR 1.3 [95% CI 1.0-1.7]), and diesel exhaust (IRR 1.4 [95% CI 1.1-1.9]), and among workers exposed to "combined" fumes (IRR 1.2 [95% CI 1.1-1.4]). An inverse association was observed between exposure to organic solvents and risk of gastric cancer (IRR 0.6 [95% CI 0.5-0.9]). No consistent associations were found between exposure to any of the other studied specific agents or "combined" dust exposure and risk of gastric cancer.

Incidence rate ratios (IRR) for non-cardia gastric cancer associated with occupational exposures among Swedish construction workers

Occupational exposure	Subjects n (%)	Gastric cancer All cases	IRR[1] (95% CI)	P value[2]
Asbestos				
No exposure	245,872 (96)	920	1.0 (reference)	
Moderate exposure	6,971 (3)	21	0.8 (0.5-1.2)	
High exposure	3,514 (1)	7	0.7 (0.3-1.4)	0.33
Asphalt fumes				
No exposure	251,626 (98)	934	1.0 (reference)	
Moderate exposure	- (-)			
High exposure	4,731 (2)	14	0.9 (0.5-1.5)	0.64
Cement dust				
No exposure	234,419 (91)	812	1.0 (reference)	
Moderate exposure	18,550 (7)	99	1.1 (0.9-1.4)	
High exposure	3,388 (1)	37	1.5 (1.1-2.1)	0.03
Concrete dust				
No exposure	159,661 (62)	586	1.0 (reference)	
Moderate exposure	48,065 (19)	154	1.0 (0.8-1.1)	
High exposure	48,631 (19)	208	0.9 (0.8-1.1)	0.74

Incidence rate ratios (IRR) for non-cardia gastric cancer associated with occupational exposures among Swedish construction workers

Occupational exposure	Subjects n (%)	Gastric cancer All cases	IRR[1] (95% CI)	P value[2]
Diesel exhaust				
No exposure	222,720 (87)	758	1.0 (reference)	
Moderate exposure	27,889 (11)	146	1.3 (1.1-1.6)	
High exposure	5,748 (2)	44	1.4 (1.1-1.9)	<0.01
Epoxy resins				
No exposure	254,000 (99)	939	1.0 (reference)	
Moderate exposure	2,357 (1)	9	0.7 (0.4-1.4)	0.30
High exposure	-			
Isocyanates				
No exposure	240,068 (94)	903	1.0 (reference)	
Moderate exposure	15,431 (6)	41	1.2 (0.8-1.6)	
High exposure	858 (<1)	4	1.6 (0.6-4.2)	0.46
Metal fumes				
No exposure	232,107 (91)	867	1.0 (reference)	
Moderate exposure	1,092 (<1)	3	0.7 (0.2-2.2)	
High exposure	23,158 (9)	78	1.0 (0.8-1.3)	0.83
Mineral fibers				
No exposure	237,113 (92)	887	1.0 (reference)	
Moderate exposure	12,122 (5)	50	1.1 (0.9-1.5)	
High exposure	7,122 (3)	11	0.6 (0.3-1.0)	0.12
Quartz dust				
No exposure	205,286 (80)	690	1.0 (reference)	
Moderate exposure	42,165 (16)	200	1.2 (1.0-1.4)	
High exposure	8,906 (3)	58	1.3 (1.0-1.7)	0.03
Organic solvents				
No exposure	228,915 (89)	885	1.0 (reference)	
Moderate exposure	7,014 (3)	18	0.7 (0.4-1.1)	
High exposure	20,428 (8)	45	0.6 (0.5-0.9)	<0.01
Wood dust				
No exposure	239,004 (93)	892	1.0 (reference)	
Moderate exposure	16,796 (7)	53	0.9 (0.7-1.2)	
High exposure	557 (<1)	3	1.2 (0.4-3.6)	0.65
Dust[3]				
Unexposed	114,226 (45)	367	1.0 (reference)	
Exposed	142,131(55)	581	1.0 (0.9-1.3)	0.59
Fumes[4]				
Unexposed	199,250 (78)	686	1.0 (reference)	
Exposed	57,107 (22)	262	1.2 (1.1-1.4)	<0.01
Total[5]	256,357	948		

[1] In the multivariable Cox regression models adjustments were made for attained age (in 5-year age-groups), calendar period at entry into cohort (in 3 categories; 1971-75, 1976-80, 1981-93), tobacco smoking at entry into cohort (in 3 categories; never, previous, and current), and BMI at entry into cohort (in 3 categories: ≤21.9 underweight, 22.0-24.9 normal, 25.0-29.9 overweight and ≥30.0 obese).

[2] Wald test of overall effect across all occupational exposure strata.

[3] Combined dust exposure, defined as exposure to: asbestos, cement dust, concrete dust, mineral fibers, quartz dust, or wood dust.

[4] "Combined exposure" to fumes defined as exposure to asphalt fumes, diesel exhaust or metal fumes.

[5] Observations with missing data for any covariate included in the models were excluded from the analyses. Total number of person-years analyzed was 5,378,012

Study III

Study participants

The 73,133 study cohort members were followed up for an average of 15.4 years, contributing a total of 1,122,765 person-years at risk. During this follow-up, we identified 313 new cases of gastric cancer, of which 264 (84%) were non-cardia gastric cancer. There was a male predominance among the gastric cancer patients (60%). At baseline the mean age of the cohort members was 49 years, and that of the gastric cancer patients was 65 years. Approximately 10% of the study cohort members were obese (BMI >30 kg/m^2), and the mean BMI was 25.2 kg/m^2, which was similar to that of the gastric cancer cases. Current smoking was reported by 27% of the cohort participants and by the same proportion of the gastric cancer cases, while formal education was lower among the patients with gastric cancer. The mean physical activity scores of the cohort members and gastric cancer were 1.85 and 1.72, respectively.

Risk of gastric cancer

BMI and risk of gastric cancer

No statistically significant associations were found between different levels of BMI and risk of gastric cancer. The point estimates were close to unity and did not change materially in the fully adjusted model. Persons with obesity (BMI > 30 kg/m^2) had an adjusted hazard ratio of 1.1 (95% CI 0.7-1.8) for gastric cancer compared to those classified as having normal weight (BMI 18.5-24.9 kg/m$^{2)}$, and no indications of any dose-response effects were revealed (p for trend = 0.74). The hazard ratios for non-cardia gastric cancer were similar to those for the risk of overall gastric cancer. On stratification for gender, no gender-specific effects were seen. The proportion of missing values for BMI among the study participants was <1%.

Body mass index (BMI) and hazard ratios (HR) of incident non-cardia gastric cancer, among 73,133 Norwegians during 15.4 years of follow-up. Both sexes combined.

		Non-cardia gastric adenocarcinoma	
BMI	Person-years	n	HR[1] (95% CI)
<18.5	11,834	2	0.9 (0.1-6.7)
18.5-24.9 *	497,872	84	1.0
25.0-29.9	309,368	92	1.1 (0.7-1.6)
≥30.0	86,318	29	1.2 (0.7-2.1)
P for trend			0.42

[1] Adjusted for age, recreational physical activity level (physical activity score calculated from a weighted sum of frequency, intensity and duration among participants who reported a physical activity frequency of once a week or more), smoking, alcohol drinking, salt intake, and occupation.
* Reference category

Physical activity and risk of gastric cancer

A statistically significant 40-50% decrease in the risk of gastric cancer was found among persons who had at least a moderate level of recreational physical activity, as based on the summary score, compared to persons who reported no activity (HR 0.5 [95% CI 0.3-0.9]), and a dose-response relation was indicated (p for trend = 0.01). A statistically significant 40% risk reduction was associated with exercising once a week (HR 0.6 [95% CI 0.4-0.9]). There was only one gender-specific effect: in the multivariable model we identified a 50-60% risk reduction for both overall and non-cardia gastric cancer only among men who reported exercising for at least 15 minutes on each exercise occasion. The age-adjusted risk estimates regarding physical activity were not materially altered after adjustment for the potentially confounding variables listed in the methods section, including BMI. Stratification for BMI did not indicate differences in effects of physical activity between heavier and leaner persons. Thus, no strong confounding effects of the listed covariates were identified. There was a considerable amount of missing information on the physical activity variables. No evidence of any interaction between BMI and different measures of physical activity was obtained.

Physical activity and hazard ratio (HR) of incident non-cardia gastric cancer, among 73,133 Norwegians during 15.4 years of follow-up. Both sexes combined.

	Non-cardia gastric adenocarcinoma		
Physical activity	Person-years	Number	HR[1] (95% CI)
Frequency per week			
<1*	300,381	83	1.0
1	192,094	34	0.6 (0.4-1.0)
>2	256,550	62	0.7 (0.5-1.0)
P for trend			0.06
Duration per episode of exercise (minutes)			
<15 *	50,978	22	1.0
15-30	170,573	37	0.7 (0.4-1.4)
31-60	214,697	32	0.6 (0.3-1.2)
>60	89,058	18	0.8 (0.4-1.6)
P for trend			0.43
Intensity			
Low *	279,330	90	1.0
Moderate	219,832	23	0.9 (0.5-1.6)
High	19,232	2	2.2 (0.5-9.4)
P for trend			0.83
Summary score[2]			
No activity *	87,523	42	1.0
Low	212,858	41	0.7 (0.4-1.1)
Moderate	202,688	50	0.5 (0.3-0.9)
High	226,352	36	0.5 (0.3-0.9)
P for trend			0.01

[1] Adjusted for age, body mass index, smoking, alcohol drinking, salt intake, and occupation.
[2] Physical activity score calculated from a weighted sum of frequency, intensity and duration, among participants who reported a physical activity frequency of once a week or more.
* Reference category

Study IV

Study participants

The same cohort members were followed up as in study III, and 313 gastric cancer cases were analyzed. The mean BMI and the frequency of current smoking were equal among all cohort participants and the cases, while formal education was lower among the cases.

Salt intake and risk of gastric adenocarcinoma

Different levels of intake of salted foods showed no statistically significant associations with the risk of gastric adenocarcinoma. The point estimates were generally close to unity and did not change materially after adjustment for potential confounders. Persons reporting having a high intake of salted foods (more than twice a week) had an adjusted HR of 1.1 (95% CI 0.6-1.8) for gastric adenocarcinoma, compared with cohort members who reported never, or almost never, consuming salted foods. No indication of a biological gradient was revealed (p for trend = 0.39). The habit of always or almost always sprinkling extra salt on hot food did not seem to increase the risk of gastric adenocarcinoma (HR 1.4 [95% CI 0.7-2.6]). There was no indication of any association between the highest salt intake category, compared to the lowest, according to the summary score variable, and the risk of gastric adenocarcinoma (HR 1.0 [95% CI 0.7-1.4]). The hazard ratios for non-cardia gastric adenocarcinoma were similar to those for overall gastric adenocarcinoma. No gender-specific effects were identified.

The proportion of missing values for both of the two primary salt variables among the study participants was around one out of six. When the group with missing information was analyzed as a separate group, no evidence of an increased risk for this group was revealed. To further identify potential characteristics of non-responders, we conducted univariate analyses of this group with every variable chosen as a potential confounder in the multivariable analyses. No clear pattern was observed.

Dietary salt intake and hazard ratios (HR) of incident non-cardia gastric adenocarcinoma, among 73,133 Norwegians during 15.4 years of follow-up. Both sexes combined.

	Non-cardia gastric adenocarcinoma		
Frequency intake of salted foods	Person-years	Number	HR[1] (95% CI)
Never or almost never *	129,664	32	1.0
1-2 times/month	232,492	45	0.9 (0.6-1.4)
Up to once /week	215,862	51	0.8 (0.5-1.3)
Up to twice/week	123,889	37	0.8 (0.5-1.3)
More than twice/week	54,223	17	0.8 (0.4-1.4)
P for trend †			0.81
Frequency of sprinkling extra salt on food			
Seldom *	358,065	110	1.0
Occasionally	278,082	48	0.7 (0.5-1.0)
Often	77,541	16	1.2 (0.7-2.1)
Always or almost always	44,415	9	1.3 (0.6-2.6)
p for trend †			0.56
Summary score of salt intake[2]			
Low *	362,156	77	1.0
Moderate	144,676	48	1.0 (0.7-1.4)
High	245,804	54	0.8 (0.6-1.1)
p for trend			0.87

[1] Adjusted for age, smoking, alcohol drinking, physical activity, and occupation.
[2] Salt intake summary score calculated from a weighted sum of frequency of salted foods intake, and frequency of sprinkling extra salt on hot food.
* Reference category.

Discussion

"As for Ludmila Afanasyevna herself, she inspired only confidence (...) by the confident way in which, right from the very first day, she had felt for the outline of his tumor and traced its circumference so precisely. The tumor itself proclaimed the accuracy of her touch, for it had felt something too. Only a patient can judge whether the doctor understands a tumor correctly with his fingers."

Oleg Filimonovich Kostoglotov, gastric cancer patient in Alexander Solsjenitzyn's "Cancer Ward"

Methodological considerations

There are several types of epidemiological studies, and the definitions of the different types are not always very clear-cut and generally accepted. However, the following distinctions are useful:

Observational studies can be either "analytical" or "descriptive". The following study designs represent observational studies: case-control studies, cohort studies, ecological studies, and cross-sectional studies. The different designs all have their inherent advantages and drawbacks and it is important to acknowledge that not all studies can serve etiological objectives, at least not directly. *Experimental studies*, in a clinical setting are most often represented by randomized clinical trials, which are considered by many to be the "gold standard" when striving for valid scientific results.[204] However, it has been found, for example, that observational studies of treatment effects do not systematically overemphasize the magnitude of treatment effects in clinical studies, as is often pointed out, and observational studies can be at least as valid as randomized trials.[205, 206] In etiological research, when investigating disease causation, observational studies are the most important since it is unethical to perform experiments on humans if the exposure is harmful or potentially harmful.

The terms "database study" and "data-mining" are sometimes used to describe research which utilizes large data-sets. However, these terms, which are occasionally used in a somewhat depreciatory sense, underestimate the complexity of the methods used to conduct such studies. Large databases can be powerful sources of information and research using such sources require an intelligent study design, expertise in analytical methods, and relevant research questions.

Cohort studies

The term "cohort study" was introduced by Frost in 1935 to describe a study that compared the disease experience of people born in different periods, in particular the sex- and age-specific incidence of tuberculosis, and the method was extended to the study of non-infectious disease by Kortweg, who used it 20 years later to analyze the epidemic of lung cancer in the Netherlands. However, he was preceded by a Norwegian named Andvord, who nine years earlier used and described a study of similar design.[207, 208]

A cohort study can be defined as a study in which a group of people with defined characteristics are followed up to determine the incidence of, or mortality from, some specific disease, all causes of death, or some other defined outcome. The risk of these outcomes can then either be compared with some outside standard, such as the incidence or mortality for all people of the same sex and age distribution over the same period nationally or locally, or it can be compared internally between different sections of the cohort defined as having different characteristics.[209] Cohort studies have the great advantage that they allow collection of exposure information before the outcome has occurred, and thus avoid some of the most important sources of bias that may affect case-control studies. A common problem, however, is that the incidence rates and/or mortality rates are often low, requiring observation of a large number of subjects over long periods of time to obtain statistically significant results. This makes cohort studies often complex to organize and expensive to carry out. Methodological modifications can be introduced, making cohort studies more fruitful and efficient; e.g., use of a nested case-control study design.

As stated above, cohort studies have the advantage over case-control studies that they avoid several important sources of bias that might be introduced by the people under study when they know that a specific disease has occurred, by the investigator when he or she knows whether a person is a case or a control, and unintentionally in the selection of controls, as the person's exposure to the factor of interest is recorded before the outcome is known. The possibility of diagnostic bias remains if those responsible for diagnosing the outcome know in which groups the affected individuals are placed. However, in the four cohort studies constituting this thesis this is not a problem, as the diagnoses were made in the ordinary course of medical practice, independently of the investigators. The HUNT-1 is a general population cohort, and furthermore it can be considered to be a *closed cohort* (in contrast to an *open cohort*), as it only lost members through death, emigration, or a diagnosis of cancer. The Swedish Workers Cohort can also be considered to have been a closed cohort, since no new members were added over time.

Prospective design

The term prospective is usually used to describe a study which is forward looking, with observations of occurrence of disease in the future, i.e., there is a prospective exposure assessment and covariate measurements in relation to the outcome.[209]

Retrospective cohort studies do occur. Sometimes the distinction between prospective and retrospective is used to refer to the timing of subject identification, rather than to assessment of exposure and covariates. Another, perhaps more appropriate denotation, of retrospective studies is *historical cohort studies*. The technique of a retrospective cohort study is well suited to study of long-term occupational hazards.

The information on relevant exposures was assessed prospectively in studies I, III, and IV. However, there is a retrospective component in these cohort studies in that the subjects are asked at baseline about previous exposure. This could theoretically lead to non-differential misclassification due to *inaccuracy of recall*. It could be argued that in study II the exposure assessment was not really prospective. The information on exposure was collected prospectively, but the exposure assessment involving occupational hygienists was done retrospectively. However, since the industrial hygienists were unaware of any diseases that might occur in the cohort, we still consider the exposure assessment to be as unbiased as it would have been if it had been entirely prospective in relation to the disease under study.

Population-based design

The term population-based is another epidemiological prestige term which refers to the situation of full (or high) coverage of the cases occurring in the population being studied. A population-based design minimizes concern about selection bias. The conditions in Norway and Sweden are favorable for population-based studies, since there is a tradition of keeping large and complete registers of their populations, and of filing information on different aspects of the citizens' lives.

All studies in this thesis can be said to be population-based. High participation rates among the study populations, 88% of the eligible people in studies I, III, and IV, and 85-90% in study II, render any major selection bias unlikely. Theoretically, the group of non-participants could, however, comprise persons more exposed to risk factors for gastric cancer. However, a recent Danish study examined the consequences of non-response in a follow-up survey concerning associations between early-life factors and lifestyle-related health outcomes in adulthood, and although the non-responders differed from the responders in terms of early-life exposures and incidence of the lifestyle-related outcomes, this was found to have no overt effects on the exposure-risk associations.[210]

Validity

Validity refers to a lack of systematic error and is usually divided into two categories: *internal validity*, meaning the validity of the inferences drawn as they apply to the members of the source population, and *external validity,* as they apply to people outside the source population.[209] These are closely linked, since internal validity is always a prerequisite for external validity, or *generalizability* of the conclusions to other populations. However, it may be said that the question of generalizability is far more philosophical than this.

There are two principal threats to the validity of a study, namely *bias* (a systematic error imposed by the investigator) and *confounding* (inherent associations between exposures in the study populations, a source of error "generated by nature").

Selection bias

Selection bias is a ubiquitous concept, which is applied to many different settings and under many different terms, including inappropriate selection of controls, Berkson's bias, incidence-prevalence bias, loss to follow-up, non-response bias, missing data bias, volunteer bias, self selection, "healthy worker effect", and others. Selection bias is characterized by a different association

between exposure and outcome among those selected or participating in the study compared with those who are eligible or non-participating. The "healthy worker effect" is most often described as a kind of selection bias and is often a problem in occupational study settings. However, one can argue that selection is based on unknown variables leading to confounding that cannot be controlled for. The healthy worker effect consists of an initial selection process whereby healthy people are more likely to seek and gain employment in a specific industry, and a continuing selection process implying that those who remain employed tend to be healthier than those who leave the employment.[211] It is reasonable to believe that a healthy worker effect varies in magnitude according to which disease and which job is concerned in a study. In study II, any "healthy worker effect" was avoided, since workers were internally compared.[209] This means that the exposed persons were compared with the unexposed persons in the same group with regard to socioeconomic factors. The methodological relevance of doing this is underlined by the fact that the cohort had a lower incidence of cancer (all sites) than the general Swedish population, where the standardized incidence ratio was 0.95 for cancer, according to a previous study.[199]

Generally, in cohort studies selection bias can occur when there is *loss to follow-up* or when the investigators do not adequately consider the effect of *competing risks*.[209] Owing to the virtually complete follow-up in the studies described in the current thesis (including death and emigration), no bias was introduced, on account of immortal person-time. Furthermore, the problem of competing risks was largely circumvented by this complete follow-up.

Information bias

Information bias can occur whenever there are errors in the measurement of study participants.[209] *Differential misclassification* takes place when an error of classification of exposure is dependent on the classification of disease (outcome), or vice versa. *Nondifferential misclassification* occurs when the proportion of study participants misclassified does not depend on the disease status or when the proportion of study subjects misclassified regarding disease does not depend on exposure. The latter usually leads to an underestimation of effect, but under certain circumstances it can also lead to bias away from the null.[209]

Some remarks need to be made about the information bias in these four studies. Regarding the variables assessing alcohol consumption in studies I, III, and IV, the data collection was limited to two weeks immediately prior to the time of the questionnaire. This was done because of the risk of considerable misclassification of recalled previous use of alcohol. The questions regarding physical activity were not limited to the past two weeks, but information was rated as average current activity during leisure time. Anthropometric measurements in all the current studies (used to calculate BMI) were made by the study personnel. This is a great advantage compared to self-reported height and weight, which is generally considered to be less accurate, potentially leading to differential misclassification.[212, 213] The amount of missing data regarding frequency of physical activity is not unusually large, but it raises the question of whether the non-responding group differed in any other substantial way. Nutritional epidemiology is a difficult area, with a high risk of substantial misclassification. We had information on different aspects of dietary salt intake, but no information on urinary salt excretion levels, a possibly more accurate measure of the intake of salt.

In study II no quantitative meaning was assigned to the different levels of airborne occupational exposures. The use of the job-title as a kind of dosage surrogate certainly guarantees some degree of misclassification. Uncertainty in the classification of exposures was handled by each individual

industrial hygienist, using his or her expert knowledge. The job-exposure matrix has been used successfully in several studies, but it has not been formally validated. The exposure assessment was based on a comprehensive survey carried out between 1971 and 1976 by the Construction Industry's Organization for Working Environment, Occupational Safety and Health, where the exposure pattern within each occupation was studied at visits to approximately five different work sites in different geographical regions in Sweden. We did not have data that allowed us to include a category representing "ever exposed"; we were only able to use the information obtained from the first visit of the cohort members. Given the very interesting dose-response patterns for some of the agents studied, it would have been vaulable to have some more details of the exposure duration, but unfortunately we did not have such information. However, in a previous study based on this cohort it was found that among construction workers examined before 1986 few persons had changed their work tasks, and that 96% had the same exposure level for both the previous and current job title.[214] This correlation between current and previous job indicates that the construction industry had a stable work force.

In studies I, III and IV the first three years of follow-up were excluded from the analyses, to avoid misclassification. This was done because of the presumedly long time between contact with the studied exposures and the occurrence of an invasive gastric cancer, and such exposures occurring late might not influence development of malignancy. Patients with pre-diagnostic weight loss may have biased estimates of weight, a methodological problem which is largely circumvented by using a prospective study design with exclusion of initial person-time. This also holds true for the prevalence of other study variables and potentially confounding factors. It is plausible, for example, that a person may stop smoking before a gastric cancer diagnosis is made, because of the symptoms of the yet undetected disease under study (*reverse causality*).[209]

Ideally, it would have been desirable to classify the experience of a single individual into different exposure categories at different times, since exposures can vary over time. No repeated assessments were made in any of studies I, III or IV. In study II some follow-up measurements were performed, but we were unable to use this information. This meant that quite extensive and simplifying assumptions were made regarding the representativeness of baseline information regarding the relevant aspects of exposure in relation to the disease in each individual. Cross-sectional information might be effectively longitudinal depending on what exposure is being studied (e.g., blood type, genetic setup) and what hypotheses are being made. A period during which the exposure accumulates to a sufficient extent to trigger a step in the causal process should ideally be conceptualized, with the induction period beginning only after this hypothetical threshold has been reached. The "chronic" exposures investigated in the present investigations probably have a considerable average induction period, and if "person-years" began to be counted before the minimum or maximum induction period we would risk underestimating the effect of the studied exposures.

Misclassification with respect to case status is probably not of major concern in these four studies. However, in a study with etiological objectives the incidence should refer to the onset of the disease (i.e., the first malignant cell conversion). But this was not feasible, and instead we therefore used the date of diagnosis, which of course is influenced by the *latency time*. More than 98% of the gastric cancer cases were histologically confirmed, and the few cases with tumors other than adenocarcinoma were not included in these studies. However, it is likely that some misclassification regarding the anatomical location in the stomach did occur, since the classification of gas-

troesophageal junction cases was made by the physicians and pathologists who reported the case to the Swedish and Norwegian Cancer Registries. Furthermore, we did not have data on intestinal and diffuse histological subtypes and therefore could not evaluate potential differences in risk factor profiles between these subtypes.

Confounding

The term confounding comes from the Latin *confundere*,[215] meaning to mix together, and is a source of error of central importance in observational epidemiological research. It characterizes situations where group comparisons cannot distinguish between the effects of multiple causes.[209] The measured association is therefore a mix of the effects of several causes. The mixed causes beyond the one being studied are the confounders or confounding variables. A true confounder has an association with the exposure under study and is at the same time a determinant of the disease. However, it cannot be an intermediary causal variable in between the exposure and the disease, since the intermediary variable is always linked somewhat more closely to the disease than an exposure that is more remote in the causal chain. No statistical model can discriminate between true confounders and variables that are intermediary in causal pathways. Instead, many potential confounders, effect modifiers (i.e., factors underlying the phenomenon of biological interaction), and mediators can be identified *a priori* from previous research, and the decisions on how to treat the variables must be made by the investigator. However, confounding should always be looked upon in the context of a particular study base. Controlling for confounding can be made in several ways: in the study design by restriction, matching, and randomization, and in the analyses of the data by stratification, and use of multivariable regression analyses. But it is important to keep in mind that as long as the measured confounder is not a perfect measure of the idealized confounder, residual confounding will remain in the data.

Multivariable regression can be a powerful tool for three important purposes[216]: *Prediction*; it can be used for multiple measured covariates, or predictors, to make useful predictions of future observations. *Isolating the effect of a single predictor*; sometimes multiple related predictors contribute to study outcomes and it is important to consider multiple predictors even when a single predictor is of particular interest. Randomized clinical trials represent a special case where the predictor of primary interest is the intervention; confounding is not usually an issue in this case, but covariates are sometimes included in the model for other reasons. *Understanding multiple predictors*; multivariable regression can be used when the aim is to identify multiple independent predictors of a study outcome, and to understand how predictors jointly influence the outcome.

When making selections as to which predictors to include in the regression models, we considered that it would make sense to include well-established or probable causal factors (on which we had information) without regard to the strength or statistical significance of their associations with the predictor of primary interest and outcome in the dataset used. Alternative ways are advocated by some researchers, e.g. exclusion of factors not having any material impact on the association under study, but we generally prefer a predefined model. However, we allowed slight modifications of the predefined models during some of the analyses. The goal was to obtain a minimally confounded estimate of the effect of the different study variables on the risk of developing gastric cancer.

Remarks on potential confounding in these studies are warranted. In studies I, III, and IV we had data that allowed adjustment for several potentially confounding factors, namely age, sex, smok-

ing, alcohol, salt intake, BMI, physical activity, and occupation. Infection with *H. pylori,* a strong and well known risk factor for gastric cancer,[71, 81] is the potentially most relevant confounding factor on which we had no information. Previous analyses in the HUNT study have shown that there is a small overrepresentation of *H. pylori* infection among male smokers (data not published). It is unlikely, however, that this weak association would have introduced major confounding of the results in study I. No increased alcohol consumption among the *H. pylori* positive persons has been identified in the HUNT-1 cohort. Moreover, no detailed information on nutritional factors was available, including intake of antioxidative vitamins, which may have a protective effect against gastric cancer.[95, 96] But again, no association between such dietary factors and the use of tobacco or alcohol has been found, and thus dietary factors should not have confounded our results. However, it is plausible that such dietary factors could be associated with weight and level of physical activity. More reassuring is in fact that no association between BMI or physical activity and the occurrence of *H. pylori* infection has been detected in this cohort, according to previous analyses.

In study II we again had data that allowed adjustment for several potentially confounding factors, namely age, smoking, calendar period, and BMI. Furthermore, potential effects of gender were eliminated by the restriction to men. More detailed and complete information on the participants' smoking habits would have been desirable, but this was not available. Residual confounding from smoking might therefore be a problem, even if this exposure is not linked to gastric cancer as strongly as, for example, to lung cancer. Any association between the studied exposures and *H. pylori* infection in this cohort is not likely to be strong enough to cause appreciable confounding. Moreover, the high socioeconomic homogeneity of the cohort reduces potential confounding associated with such infection or with lifestyle factors. Furthermore, we had no information on alcohol consumption, but alcohol does not seem to be a risk factor for gastric cancer, thus excluding this as a confounder.[96]

Precision

Precision in measurement and estimation corresponds to the reduction of random error or chance.[209] Precision can be improved by increasing the size of the study or by modifying the design of the study to increase the efficiency with which information is obtained from a given number of study subjects. A large sample size enables small differences in rare outcomes to be detected, but one should not confuse a large sample size with the number of outcomes of interest. The power of a cohort study, such as those constituting this thesis, is ultimately dependent on the number of outcomes (gastric cancer cases), and on having sufficient information on potential confounders. The prevalence of the exposures under study in the population is also of importance in determining the power of the study.

Statistically the precision is mirrored by the sizes of confidence intervals and p values. The point-estimate is the best estimate that the investigators can provide. P values measure the strength of the evidence of an effect, but not its magnitude. Furthermore, it is important to recognize that the level of confidence most often used in medical research (0.05) is arbitrary and that a "dichotomization" when interpreting these values could be misleading. A p value of 0.04 is not perhaps very

different from 0.06. Furthermore, when the p value is non-significant this does not imply that the null hypothesis is true, and vice versa. Some investigators have been very critical of significance testing:

> *"Statistical significance testing retards the growth of scientific knowledge; it never makes a positive contribution."*[217]

> *"Null-hypothesis significance testing is surely the most bone-headedly misguided procedure ever institutionalized in the rote training of science students… It is a sociology-of-science wonderment that this statistical practice has remained so unresponsive to criticism."*[218]

Opinions are also expressed in favor of statistical significance testing. Among these is the argument that in the real world decisions have to be made, and that tests provide a basis for decision-making. It is also tradition, and we have to say something about the data at hand.

The term *type I error* is sometimes used to denote an error that occurs when an association between exposure and disease appears to be statistically significant even though in fact no causal relation exists. This error often hampers studies that include many analyses, i.e., multiple testing. A *type II error* occurs when no statistical association is found although a causal relation does in fact exist. This is most commonly due to insufficient statistical power.

In study I, we initially studied the number of cardia cancer cases separately but the small number of cases resulted in limited statistical power for specific analyses of the cardia cancer site and consequently in very wide confidence intervals. We therefore decided not to study cardia cancer separately in the HUNT-1 cohort. The overall power of the studies described in this thesis must be considered to be high.

Findings and implications

Tobacco smoking and alcohol

Study I provided evidence in support of a moderately strong association between tobacco smoking and the risk of gastric cancer. Earlier initiation, a higher frequency, and a longer duration of smoking resulted in higher estimates of relative risk in a seemingly dose-dependent manner. Several of Hill's principles of causality[17, 18] could be invoked supporting a causal relation. It is well known that that smoking has harmful effects, but it is important to know what health effects a decrease or increase in smoking will lead to. If it is believed that the associations found are true, calculations of *attributable risk* are justified, but not otherwise. The attributable risk is a function of the exposure prevalence and the strength of the association, and is a measure that quantifies the proportion of the disease burden among exposed people that is caused by the exposure.[209] Our calculations indicated that 28% of gastric cancer cases among smokers are caused by this exposure. The finding that earlier initiation of smoking, regardless of duration, is associated with an increased risk of gastric cancer in a "dose-dependent" manner has not to our knowledge been reported before.

However, some investigators have studied the risk of early initiation, but only one study found an increased risk of early initiation (≤19 years compared to ≥20 years) and the effect of duration of smoking was not considered.[219] It might be biologically plausible that the anti-carcinogenic defenses more easily become overwhelmed in a younger organism. The same kind of association has been demonstrated regarding smoking and lung cancer.[220] These findings highlight the question of how to develop the most intelligent strategies for preventive measures. The risk estimates of non-cardia cancer decreased with time after cessation of smoking, which is encouraging.

No consistent associations between alcohol drinking and non-cardia gastric cancer were found. However, combined exposure to high levels of tobacco smoke and alcohol seemed to increase the risk synergistically. Previous results on alcohol and gastric cancer are partly contradictory, but the current findings add some evidence that excessive alcohol drinking is unhealthy and should be avoided.

Airborne occupational exposures

Studies on industrial workers have been important sources of innovations in methodology and in development of logical reasoning leading to acceptance of causal relationships of occupational exposures to respiratory diseases and cancer. This is a classical field of epidemiology and the co-operation of labor unions has often been an important factor in the collection of essential data.

The results of study II indicate positive, dose-dependent associations between exposure to cement dust, quartz dust and diesel exhaust and risk of gastric cancer. No such increased risk was detected among workers exposed to asbestos, asphalt fumes, concrete dust, epoxy resins, isocyanates, mineral fibers, organic solvents, or wood dust. "Dusty" occupations have previously been implicated in the etiology of gastric cancer. The finding that exposure to cement dust increases the risk of gastric cancer is supported by results of a study of Lithuanian cement masons,[221] and of a study of US cement-producing workers,[222] while no clear associations have been found in other studies of cement workers in Sweden or the US.[223, 224] The authors of a recent Swedish cohort study, based to a large extent on the same patients as in our investigation, concluded that cement dust appears to be a major occupational risk factor.[225] The positive association between quartz dust and risk of gastric cancer found in our study is in line with reports on workers exposed to silica dust in Canada,[226-228] Spain,[229] and Japan.[230] Diesel exhaust contains several carcinogenic chemicals, such as polycyclic aromatic hydrocarbons. Increased risks of gastric cancer have been found in studies of lorry drivers in London[231] and professional drivers in Geneva.[232] Our study adds some evidence of a true link between diesel exhaust and the risk of gastric cancer.

We hypothesized that a possible mechanism by which some airborne particles might increase the risk of gastric cancer is that inhaled dust and fume particles are swallowed and thereby act directly as carcinogens on the gastric mucosa. Particular agents such as cement dust and quartz dust could have an abrasive effect on the gastric mucosa, thus acting as irritants.[140, 233] An inflammatory milieu can promote mitogenesis and lead to increased mutagenesis.[138, 234] Excessive, persistent formation of reactive oxygen species from inflammatory cells is considered as the hallmark of secondary genotoxicity of non-fibrous and fibrous particles, and it is believed that these reactive molecules also play a major role in primary genotoxicity of particular agents.[235] Furthermore, occupational exposures most likely act together with numerous non-occupational risk factors at various steps of gastric cancer development. It is possible that dust may have a permissive or synergistic effect on

other carcinogens such as tobacco smoke. Dusts and fumes could potentially also act as carriers delivering other carcinogens to the stomach.

Environmental safety controls have successfully been developed and implemented in many industrial settings, on the basis of the principles of dust suppression. Workplace dust monitoring and medical surveillance programs have been instituted.

Physical activity and BMI

The results of study III indicate that at least a moderate level of recreational physical activity is protective against the development of gastric cancer, whereas BMI is not associated with risk of this malignancy. The literature is sparse regarding studies addressing these exposures in relation to gastric cancer risk, and prospective studies are lacking. No biological mechanism clearly linking physical activity to gastric cancer risk has been established, and our study provides no evidence of a link through obesity. However, increased BMI could potentially cause decreased exercise (part of the causal chain) as well as responding to it (confounding), a complexity difficult to sort out with use of observational data like ours.

When using BMI as a measure of overweight and obesity, it is important to appreciate that the underlying assumption is that most variation in weight in persons of the same height is due to variation in fat mass, and that owing to other differences in body proportions, BMI may not correspond to the same degree of fatness across different populations (or in different individuals). Increased body weight has been associated with increased death rates for all cancers combined and for multiple specific sites,[30] and obesity and overweight cause or exacerbate many other health problems. IARC has concluded that there is sufficient evidence to show that avoidance of weight gain has a preventive effect against cancers of the colon, breast (in postmenopausal women), endometrium, kidney, and esophagus (adenocarcinoma). The obesity epidemic[236-238] is preventable, since it has occurred during the past twenty years from a relatively constant genetic pool. A previous study in Nord-Trondelag has shown that during a period of approximately ten years, the body weight increased in all age groups below 70 years. Furthermore, the prevalence of overweight and obesity was approximately 20% higher at the second survey (1995-1997) than at the first (1984-1986).[239]

It could be argued that the finding of a lack of association between BMI and gastric non-cardia adenocarcinoma in study III might support the hypothesis that the mechanism by which a high BMI is related to cardia adenocarcinoma is through gastro-esophageal reflux. However, this speculation regarding causal pathways is indeed just speculation, and our study focused on non-cardia adenocarcinoma.

As mentioned above, there is no clear biological link between physical activity and gastric cancer. If our results are true, possible mechanisms could include improved immune function, since short-term stress can exert immuno-enhancing effects.[240, 241] Insulin-like growth factors (IGFs), one of the most important peptide hormones for growth and development, are associated with an increased risk of cancers of the breast, colon, and prostate.[242-244] Decreases in insulin and IGFs are also plausible ways by which a protective effect could be mediated. Moreover, it has been shown that well-trained athletes seem to have less oxidative damage after exercise, compared to less fit individuals after physical strain.[133, 134]

Dietary salt intake

The results of study IV provided no evidence of an association between dietary salt intake and the risk of gastric adenocarcinoma. Our study is one of the largest ever made addressing this relationship. Furthermore, there has been a a sparsity of prospective studies conducted in low-incidence populations such as in Norway. In a report in 2003 from the World Health Organization it is stated that high salt intake "probably" is a risk factor for gastric cancer.[245] However, it should be noted that salt has not been found to be a carcinogen per se. A high-salt diet in humans and experimental animals is associated with a higher risk of atrophic gastritis.[57] Salt could have an abrasive, and in relation to other carcinogens, permissive effect.

Our finding of a lack of association highlights the question as to whether cofactors more prevalent in high-incidence populations, such as *H. pylori* infection and other dietary factors, interact with salt in producing a potentially carcinogenic effect on the gastric mucosa, or whether previously reported positive associations could in fact have represented artifacts of residual confounding by such factors.

Conclusions

- Smoking seems to be a dose-dependent, moderately strong risk factor for gastric adenocarcinoma.
- Early initiation of smoking seems to be linked with gastric cancer in a dose-dependent manner.
- Alcohol consumption does not seem to be associated with an increased risk of gastric adenocarcinoma.
- A combination of a high level of tobacco smoking and alcohol consumption might be linked with a substantially increased relative risk of this cancer.
- Theoretically, successful tobacco preventive measures could reduce the number of gastric adenocarcinoma deaths considerably.
- BMI seems not to be associated with risk of gastric adenocarcinoma.
- Exercise is seemingly protective against gastric adenocarcinoma.
- The ongoing decline in the incidence of gastric adenocarcinoma might be counteracted by the sedentary lifestyle gaining ground in Western societies.
- High intake of dietary salt might not be associated with an increased risk of gastric adenocarcinoma, at least not in a low-incidence Western population.
- Quartz dust, cement dust, and diesel exhaust might be moderate risk factors for gastric adenocarcinoma; i.e., specific dust and particle exposures, in contrast to “dusty” environments in general.
- Exposure to quartz dust, cement dust, and diesel exhaust does not seem to have a substantial influence on the overall incidence rate or the sex distribution of gastric adenocarcinoma.
- Preventive measures such as reduction of airborne dust might reduce the mortality from gastric adenocarcinoma among workers in highly exposed occupations.

Future Perspectives

"Knowledge is not a couch whereon to rest a searching and restless spirit."

Francis Bacon

Tremendous effort has been made to shed light on the causation of gastric cancer. It will be interesting to see what long-term results will be provided by the ongoing randomized trials investigating dietary supplementary interventions and *H. pylori* eradication. Etiological research based on traditional observational studies will in the future probably play a limited role regarding the exposures addressed in this thesis. However, methodological improvements do still occur.

The field of genetic epidemiology is rapidly evolving and future research toward an understanding of the etiology of gastric cancer will certainly move in the direction of molecular epidemiology to a greater extent. A foreseeable consequence of these methodological advances in assessing gene-environment interactions in occupational settings, for example, is that workers might be labeled according to their cancer susceptibility. The availability of such information would raise ethical issues regarding the protection of workers from occupational hazards. This is also of course, a valid argument regarding lifestyle factors in other sections of a population when deciding to test for newly identified potentially critical genetic variants. It is conceivable that every person in a population is at much higher risk than other persons for a specific cancer type, and the question should always be discussed on an individual level before a decision is made to take the test or not. Knowledge can sometimes be a burden.

A second collection of information within the HUNT public health survey series has been carried out (HUNT-2), and a third is ongoing (HUNT-3). Blood samples have been obtained from study participants in HUNT-2 and in HUNT-3. The overall participation rates in these surveys were not as high as in the first one, but the information gathered is a virtual goldmine. Prospective, population-based studies addressing the relation between polymorphisms in genes coding for cytokines and *H. pylori* infection are an exciting possibility.

Svensk Populärvetenskaplig Sammanfattning (swedish summary)

”Han kände själv genast hur detta invärtes odjur, hans livsledsagare, låg någonstans djupt därinne och tryckte.”

Alexander Solsjenitsyn i”Cancerkliniken” om Oleg Filimonovich Kostoglotov, inneliggande patient med magsäckscancer

Allmän bakgrund

Adenocarcinom i magsäcken är den fjärde mest förekommande cancerformen i världen, även om graden av nyinsjuknande (incidens) har sjunkit påtagligt i västvärlden under flera decennier. En ökad förekomst av cancer i magsäckens övre del (cardia) har emellertid rapporterats från ett flertal västerländska länder. Orsakerna till den minskande incidensen av magsäckscancer nedanför cardia är inte säkerställd, men kostfaktorer anses ha stor betydelse. Ökat intag av frukt och grönsaker samt minskad saltkonsumtion och bättre förvaring av råvaror, bl.a. genom användning av kylskåp, har sannolikt bidragit till denna utveckling. Orsakerna till ökningen av cardiacancer är också ofullständigt kända.

Magsäckscancer har hög dödlighet och är efter lungcancer den näst vanligaste orsaken till död i cancer. Trots ny diagnostik och behandling har inte den generella prognosen för patienterna nämnvärt kunnat förbättras. Detta stärker betydelsen av forskning kring riskfaktorer, då preventiva åtgärder kan ha stor potential att leda till en minskad dödlighet.

De stora geografiska skillnaderna i förekomst av magsäckscancer kan inte förklaras av ärftliga faktorer, utan dessa skillnader orsakas rimligen av omgivningsfaktorer. Det är också omgivningsfaktorer som är den sannolika förklaringen till de stora förändringarna av incidensen under de senaste decennierna.

Infektion med bakterien *Helicobacter pylori* (”magsårsbakterien”, vars upptäckare fick Nobelpris 2005) har identifierats som en riskfaktor. Detta samband har dominerat forskningen kring riskfaktorer om magsäckscancer under senare år. Hälften av världens befolkning bedöms emellertid vara infekterad av *Helicobacter pylori* och det är därför ett rimligt antagande att andra omgivningsfaktorer både kan samverka med denna bakterie och påverka risken för cancerutveckling oberoende av infektion. Denna avhandling fokuserar på andra omgivningsfaktorer än *Helicobacter pylori*

som möjligen kan påverka risken för magsäckscancer. Undersökningarna den bygger på stora s.k. prospektiva kohortstudier, där tiotusentals människor har följts upp över en lång tid. Undersökning av samband mellan exponering och insjuknande genomförs genom att jämföra personer som vid studiens början uppgivit olika grader och typer av exponering avseende de faktorer man vill studera i relation till sjukdomen.

Delarbete 1

Sambandet mellan rökning och magsäckscancer har tidigare studerats i en rad undersökningar. I vissa studier har en stark association mellan rökning och denna cancerform påvisats, medan andra studier inte funnit något samband. Det råder brist på stora, kohortstudier. Även sambandet mellan alkoholintag och risk för magsäckscancer har undersökts i flera studier, men resultaten har varit motstridiga. Vi valde att använda information från Helseundersökelse i Nord-Tröndelag 1 (HUNT-1) för att genomföra en prospektiv kohortstudie av den relativa risken att utveckla cancer i magsäcken beroende på användning av tobak och alkohol. I Nord-Tröndelags fylke i Norge har det under åren 1984-86 genomförts en stor folkhälsoundersökning av nästan hela den vuxna befolkningen (HUNT-1) De 75 000 invånare i åldern 20-100 år som deltog i HUNT-1 motsvarade hela 88 % av länets vuxna invånare. Data om ett stort antal hälsoparametrar insamlades genom skriftliga frågeformulär. Genom länkning till det norska cancerregistret kunde vi identifiera nyinsjuknade fall av magsäckscancer i gruppen. Totalt 251 fall av magsäckscancer identifierades under observationstiden. En nära fördubblad risk fanns för personer som rökte dagligen, jämfört med icke-rökare. Dessutom noterades ett samband mellan tidig ålder för rökdebut och risk för magsäckscancer. Detta samband kvarstod trots efter att vi i analyserna tagit hänsyn till hur många år rökningen förekommit. Inga säkra samband påvisades avseende alkohol och risk för magsäckscancer. Däremot ökade risken påtagligt vid kombinerad och stor användning av tobak och alkohol. *Studien visar att rökning är en dosberoende, måttligt stark riskfaktor för magsäckscancer. Även om alkoholkonsumtion i sig inte medför en påvisbar ökad risk, så leder kombinerat högt intag av alkohol och stort antal rökta cigaretter per dag till en påtaglig riskökning för denna cancerform.*

Delarbete 2

Det råder en oförklarad mansdominans (2-3:1) hos patienter med magsäckscancer i många länder. Denna könsskillnad skulle delvis kunna förklaras av potentiella riskfaktorer i mansdominerad industri. I yrken som tidigare förknippats med ökad risk för magsäckscancer skulle exponering för luftburna partiklar kunna bidra till utvecklandet av sjukdomen. Det finns även tidigare resultat som stöder hypotesen att luftburna partiklar, t.ex. i form av damm som sväljs ned, kan öka risken. För att kartlägga sambandet mellan specifika luftburna yrkesexponeringar och magsäckscancer inom mansdominerad industri genomförde vi en prospektiv kohortstudie inom den s.k. svenska Bygghälsokohorten. Över 200 yrken inom kohorten är exponeringsklassificerade och data avseende exponering för 12 specifika luftburna partiklar i denna kohort analyserades (asbest, asfaltsångor, cementdamm, betongdamm, dieselavgaser, epoxylim, isocyanater, mineralfiber, metallångor, organiska lösningsmedel, kvartsdamm och trädamm). Via länkning av kohortmedlemmarna med

svenska cancerregistret fick vi uppgifter om nya fall av magsäckscancer. Bland 256 357 manliga kohortmedlemmar som följdes upp under många år fann vi att exponering för cementdamm, kvartsdamm och dieselavgaser ökade risken för magsäckscancer på ett dosberoende sätt, d.v.s. att risken ökade med stigande dos av exponeringen. Relativa riskökningar på 30-50 % noterades. Inga sådana samband identifierades för de andra studerade exponeringarna. Dessa resultat antyder att det är exponering för specifika typer av damm, snarare än dammiga miljöer i allmänhet, som ökar risken för denna magsäckscancer. *Denna studie stödjer hypotesen att specifika luftburna yrkesexponeringar, som cementdamm, kvartsdamm och dieselavgaser, är dosberoende och måttligt starka riskfaktorer för magsäckscancer. Emellertid bör inte dessa samband påverka den totala incidensen eller könsskillnaden påtagligt eftersom exponeringarna är ovanliga i befolkningen i sin helhet. Preventiva åtgärder skulle dock kunna minska dödligheten inom högexponerade yrken.*

Delarbete 3

Övervikt och låg fysisk aktivitet medför en ökad risk för en rad olika cancerformer och förekomsten av övervikt är ökande i västvärlden. Det finns ett nyligen etablerat samband mellan övervikt och cardiacancer, men sambandet mellan kroppsmassa (body mass index = BMI) och magsäckscancer nedanför cardia är ännu oklart. I vissa studier har BMI snarare varit lägre bland magsäckscancerfall än bland kontrollpersoner. Flera betydande potentiella systematiska fel är dock förknippade med dessa studier, främst svårigheter att få korrekt uppgift om vikten innan diagnosen ställdes (kraftig ofrivillig viktnedgång är ett vanligt symtom vid magsäckscancer) och olika risk avseende anatomisk tumörlokalisation inom magsäcken. Få prospektiva kohortstudier har genomförts, men de som finns har också rapporterat en skyddande, eller avsaknad av ökad risk vid högt BMI. Om hög fysisk aktivitet påverkar risken för magsäckscancer är ofullständigt känt. Vi belyste dessa frågor i en studie på samma personer som vi följde upp i delarbete 1 (HUNT-1) där de medverkande personernas längd och vikt mättes objektivt av personal inom HUNT-verksamheten och detaljerad information om fysisk aktivitet på fritiden insamlades via frågeformulär. *Vi fann att en måttlig grad av fysisk aktivitet (motion) medför en halverad risk för magsäckscancer och att BMI inte verkar vara relaterat till ökad eller sänkt risk att drabbas av denna cancerform.*

Delarbete 4

Ett samband mellan högt saltintag och ökad risk för magsäckscancer har länge misstänkts, och vissa studier har också påvisat ett sådant samband. Andra studier har dock visat avsaknad av samband. Sammanfattningsvis kan sägas att resultaten är alltför motstridiga för att associationen kan anses vara säkerställd. Vi undersökte saltets inverkan i en studie av de personer som deltog i HUNT-1. Denna kustnära befolkning har ett högt generellt intag av salt fisk, vilket gav ett bra underlag för att studera just denna faktor i kohorten. *Vår studie gav inte stöd till hypotesen att ett högt intag av salt i kosten påverkar risken för att insjukna i magsäckscancer.*

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