ABSTRACT

The overall aim of this thesis was to investigate the risk of second primary malignancies - with a special focus on lung cancer - in a cohort of approximately 152,000 Swedish women diagnosed with breast cancer between 1958 and 2000. With recent advances in early diagnosis and treatment, breast cancer is becoming an increasingly survivable disease. Women with breast cancer normally receive post surgical adjuvant therapy, either as radio-, chemo-, or hormonal therapy, or as a combination of any of those modalities. Adjuvant radiotherapy reduces the risk of local recurrence, and its use is increasing as more women today choose partial mastectomies as their surgical choice. However one of the growing concerns is the chronic or late-occurring complications to the normal tissue from treatment of primary malignancies, among them therapy-related second primary cancer.

We found a statistically significant increased risk of second primary lung cancers more than 5 years after breast cancer diagnosis. The highest risk of a second primary lung cancer was observed among women <50 years of age at the time of breast cancer diagnosis. The risk of lung cancer increased with time between breast cancer diagnosis and the diagnosis of second primary lung cancer, independently of the age at breast cancer diagnosis. In addition, the risk of lung cancer increased with birth year cohort, which mirrors the increasing smoking prevalence seen among women in Sweden.

The completeness and quality of the information on tobacco use is most important when studying the risk of lung cancer. We contacted next-of-kin and living patients by mailed questionnaire to validate the quality of smoking information of the studied patients given in patient records. The total response rates were 89% and 93% for next-of-kin and living patients respectively. When information about overall smoking history from patient records and next-of-kin was compared, an almost perfect agreement was found (kappa=0.83), and similar result was found for living patients (kappa=0.86). Our results demonstrated that next-of-kin data are reliable and that the time between patient death and contact with next-of-kin did not affect the response rate nor the agreement.

Patient records and radiotherapy charts were abstracted for detailed information about treatment for 182 cases. Information about smoking history was identified in patient records or retrieved from next-of-kin. Our results demonstrated that in women treated with radiotherapy the risk of lung cancer increased after a follow-up time of more than 15 years. This risk was mostly confined to squamous cell carcinomas. In addition, the increased risk was restricted to women who smoked at the time of radiotherapy. Notably, non smoking women who received radiotherapy were not found to have an increased risk of lung cancer. The estimated excess relative risk for women with follow-up time ≥10 years after radiotherapy for breast cancer was 0.11 per gray.

Women previously diagnosed with breast cancer have a 20% increased risk of a second primary malignancy except breast cancer. The overall risk for second primary malignancy did not vary by follow-up period, but large differences were noted between individual cancer sites, probably reflecting different etiologies. Women with a breast cancer diagnosis before the age of 50 years and women with a family history of breast cancer had elevated risks of developing a number of second primary cancers indicating a genetic predisposition to develop multiple tumours and/or susceptibility to the carcinogenic effect of breast cancer therapy.

In conclusion, we have been able to establish an association between radiotherapy, smoking and risk of second primary lung cancer. We have shown that next-of-kin can provide reliable information on lifetime smoking status and should be considered as a valuable resource in studies where information on tobacco use is missing. We confirmed that women diagnosed with breast cancer have increased risks of most second primary malignancies. Finally, we showed that family history of breast cancer as well as young age at the time of breast cancer diagnosis increases these risks.

Keywords: breast cancer, second primary malignancy, lung cancer, radiotherapy, smoking, validation study, familial risk

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LIST OF PUBLICATIONS

This thesis is based on the following papers, which will be referred to by their Roman numerals.

I. Lung cancer risks in women with previous breast cancer

Michaela Prochazka, Fredrik Granath, Anders Ekbom, Peter G. Shields, Per Hall

European Journal of Cancer. 38, 1520-1525 (2002).

II. Validation of smoking history in cancer patients

Michaela Prochazka, Kamila Czene, Fredrik Granath, Peter G. Shields, Per Hall

Submitted

III. Ionizing radiation and tobacco use increases the risk of a subsequent lung carcinoma in women with breast cancer: case-only design

Michaela Prochazka, Per Hall, Giovanna Gagliardi, Fredrik Granath, Bo Nilsson, Peter G. Shields, Meredith Tennis, Kamila Czene

Journal of Clinical Oncology. 23(30):7467 (2005).

IV. Family history of breast cancer and young age at diagnosis of breast cancer increase risk of second primary malignancies in women: a population-based cohort study

Michaela Prochazka, Per Hall, Fredrik Granath, Linda M. Brown, Kamila Czene

Submitted

CONTENTS

LIST OF ABBREVIATIONS

CI	Confidence interval
DNA	Deoxyribonucleic acid
SIR	Standardized incidence ratios
RR	Relative risks
ERR	Excess relative risk
Gy	Gray
mSv	milli Sievert
Bq	Becquerel
ER	Estrogen receptor
BRCA	Breast cancer gene
ATM	Ataxia telangiectasia mutated
CDKN	Cyclin-dependent kinase inhibitor
TTF	Thyroid transcription factor
IMC	Internal mammary chain
CT	Computed Tomography
^{60}Co	Cobalt- 60 gamma-radiation
3D TPS	three-Dimensional Treatment planning Systems
SAMBAL	Swedish and American Breast and Lung cancer study
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
SCR	The Swedish Cancer Registry
ICD	International Classification of Diseases

GENERAL BACKGROUND

Main studied risk factors

Ionizing radiation

Radiation is described as energy emitted from a source. Some examples are heat from the sun, radio frequency waves from antennas, x-rays from an x-ray tube or gamma rays from radioactive material. Radiation that produces ionisation in matter is described as ionising radiation. When these rays pass through the body they have sufficient energy to damage DNA. Ionizing radiation may occur in the form of electromagnetic rays, such as x-rays and gamma rays, or as particles (e.g. alpha and beta particles). It occurs naturally (e.g. from the radioactive decay of natural radioactive substances such as radon gas and its decay products) but can also be produced artificially, as in the case of medical radiotherapy.

The annual global effective radiation dose per individual is estimated to be approximately 3 mSv. About 15 percent of ionizing radiation exposure to the general public comes from artificial sources, mostly from medical diagnostic radiation.[1] Radiation was used in the diagnosis and treatment of patients as early as 1896.[2] From this time significant improvements in diagnostic and therapeutic radiation have been made. The aging of our population increases the use of medical imaging technology and radiotherapy. The great benefits to patients from properly conducted procedures have resulted in the widespread practice of medical radiology. There is an indication that worldwide population exposure to medical radiation is increasing, especially x-ray, but also the radiotherapy treatment.[1]

The effects of a given dose of ionizing radiation on humans can be separated into two broad categories - acute and long-term effects. Acute effects seen early after large doses of radiation delivered over short period of time include radiation sickness, radiation burns and cataract. The severity of effect increases with dose, but depends also on fractionation and exposed volume. For example, a single acute dose of 5 gray (Gy) to the whole body results in death of at least half the irradiated individuals, while the same dose delivered over a suitably long time has no effect and causes only a slight redness of skin when given as a single dose to a small area.[3]

Damage to DNA is the initiating event by which radiation causes cancer. Exposure to ionizing radiation has been associated with most forms of malignancies. The red bone marrow, premenopausal breast, lung, and thyroid tissue are considered the most susceptible tissues in the body. Radiation-induced cancer may manifest itself decades after the exposure and does not differ from cancers that arise spontaneously or are attributable to other factors. The major long-term evaluation of populations exposed to radiation is the study of the approximately 86,500 survivors of the atomic bombings of Hiroshima and Nagasaki, Japan.[1]

Tobacco

Tobacco was introduced into Europe from America at the end of the fifteenth century. At first it was used mainly for medicinal purposes, but after about 100 years it came to be burnt in pipes for pleasure on a large scale, at first in England and later throughout the world. Cigarette smoking became the predominant form of tobacco use in most of the industrialised countries between the two world wars.

There is significant evidence that tobacco smoking is related to disease processes in most organ systems in the human body. No less than 40 diseases or causes of death have been associated with tobacco smoking.[4] In 1954, Doll and Hill[5] presented the first results of the prospective cohort study of British doctors, designed to investigate the relationship of tobacco smoking and lung cancer. Many studies published since 1950 have clearly shown that tobacco smoking is strongly related to the risk of developing lung cancer.[6-8] The consequences of tobacco smoking became known worldwide in 1964, soon after a report entitled "Smoking and health" was presented by the Advisory Committee to Surgeon General in the USA.[9]

In the early 1990s, Sweden was the only country in the European Union where women smoked more than men. [10] At present, more than one billion people use tobacco worldwide. The number of smokers continues to increase in Asia, Latin America and Eastern Europe,[11] while tobacco consumption has started to decline in North America and northern Europe.[11, 12]

Why study multiple primary malignancies?

Multiple primary cancers are defined by the International Association of Cancer Registries as the occurrence of two or more primary cancers, where each cancer originates in a separate primary site and is neither an extension, recurrence or metastasis.[13] Multiple primary malignancies have been described since the last century,[14] firstly in case reports, then in clinical series[15] and, more recently, quantified as incidence rates in population-based studies.[16-19] The occurrence of multiple primary malignancies is relatively common among cancer patients.[20] [21] Several studies have focused on frequency of the different combinations of cancers.[17, 22, 23] In a large study from Connecticut, a new primary malignancy developed in 6.6% of cancer patients.[16] Cancer patients had a 31% higher risk (23% when cancers of the same site were excluded) of developing a new cancer, compared to the general population.

Many reasons have been proposed for the occurrence of second primary malignancies. These cancers may have common etiologic factors. The treatment of one cancer may induce or prevent others. More intensive surveillance of cancer patients may lead to the detection of pre-malignant lesions or invasive cancers, which may otherwise have escaped detection.

In addition, inherited mutations in genes involved in known cancer syndromes, such as *BRCA*-related breast cancers and mismatch repair gene-related non-polyposis colorectal cancers increase risks of other malignancies and will therefore contribute to the elevated risks of second primary cancers, especially in women at a young age.[24-26] About 1% of cancers are due to known cancer syndromes, most of which are monogenic and have high penetrance.[27] However, a much larger proportion inheritable cancers have yet to be characterised.[28]

Due to improved diagnostic procedures and/or treatment, the time from the first cancer diagnosis until the patient's death has increased. The number of people experiencing diagnosis of multiple malignancies is therefore increasing. This makes it important to identify the cause of different secondary malignancies, in order to be able to prevent them, or at least to detect them as early as possible.

Breast cancer

Breast cancer is a major public-health issue globally, with more than a million new cases and 370,000 deaths worldwide annually. In spite of an increasing incidence, breast cancer mortality has been declining in most developed countries which means that more women then ever before are alive with a diagnosis of breast cancer.[29] There has been an increasing interest in the long-term effects of treatment therapy.[30] Most of breast cancer patients will die of causes other than breast cancer, and are actually "cured" from breast cancer.

In Sweden about 6,870 women were diagnosed with breast cancer, corresponding to about 30 percent of all malignant diseases in Swedish women (Figure 1).[31] The annual increase in breast cancer during the last 20 years has been 1.6 % (Figure 2). The lifetime risk of developing breast cancer has been estimated to be one out of nine women. At present around 75,000 women live after treatment for breast cancer and about 1,500 die from the disease every year in Sweden.[31]

What causes breast cancer?

General risk factors

Thousands of research papers have been written about breast cancer, and we have learned a lot about the lifestyle and genetic factors that influence breast cancer risk.[32-34] The incidence of breast cancer increases with age and is doubling about every 10 years until menopause, when the increase is not as pronounced.[34, 35] Compared to lung cancer, the incidence of breast cancer is higher at young ages. [36] The incidence of breast cancer varies by up to a factor of five world wide, with the highest rates observed in Europe, North America and the lowest in Far Easter.[37-39] Studies of migrants show that women who move from low a risk country to a high risk country or vice versa, assume the rate in the host country within one or two generations.[34] This suggests that environmental

Figure 1. Breast cancer incidence in Sweden. The ten most frequent cancer sites in per cent among women diagnosed with cancer in Sweden 2003.[31]

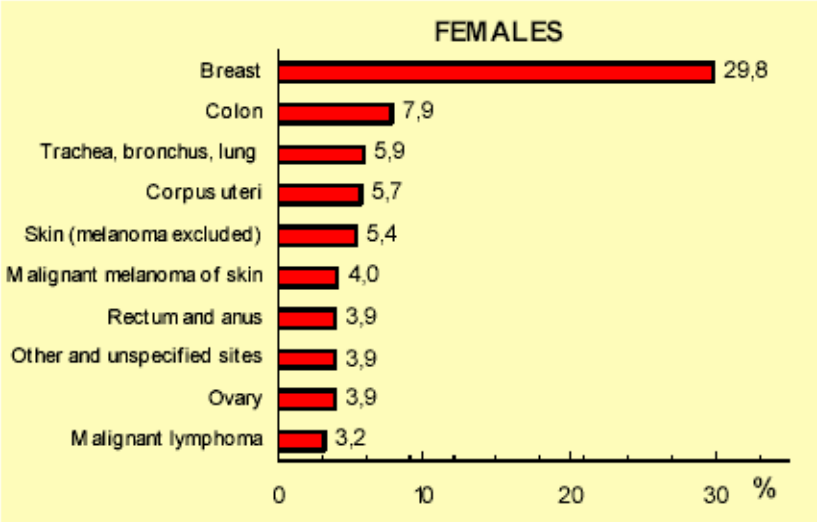
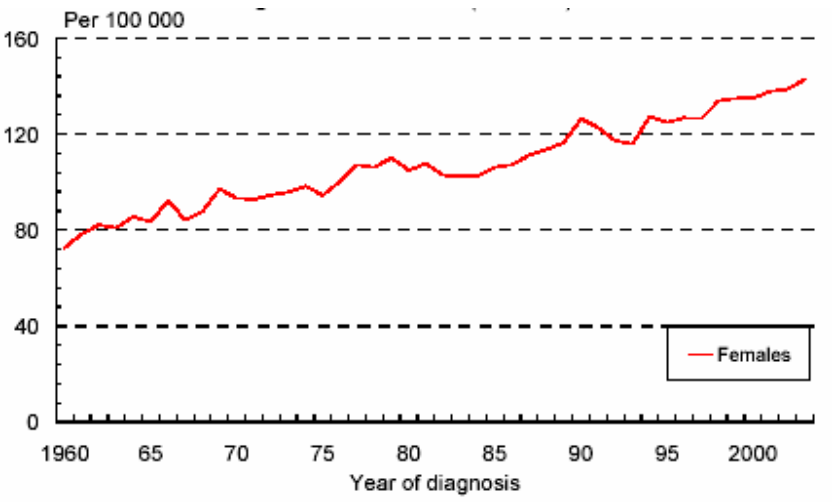


Figure 2. Breast cancer incidence per 100 000 women in Sweden.[31]



and lifestyle factors, rather than inherited genetic susceptibility, influence the risk of breast cancer.

Breast cancer is clearly associated with sex hormones, particularly exposure to estrogen. The majority of breast cancer tumours in postmenopausal women express the estrogen receptor (ER) and this is associated with favourable tumour characteristics.[40, 41]

An earlier age at menarche and late menopause has been consistently associated with increased risk of developing breast cancer.[42, 43] The risk of breast cancer is also influenced by pregnancy, where nulliparity and late age at first birth both increase the lifetime incidence of breast cancer.[43, 44]

An increased risk of breast cancer has been shown in women exposed to moderate to high levels of ionizing radiation, including women treated with radiotherapy towards the thoracic region,[45] and among survivors of the nuclear bombings in Japan.[46]

A number of studies have evaluated the influence of tobacco smoking in breast cancer, and the data do not support any important relation.[47-49] Theoretically cigarette smoking could increase the risk of breast cancer, because it is a known human carcinogen and studies have showed metabolites of cigarette smoke in the breast fluid of smokers.[50] On the other hand smoking can decrease the risk, as it is known to have an antiestrogenic effect, smokers have an earlier age at menopause.[51]

Other risk factors are hormone replacement therapy and socioeconomic status.[52-55] The identified and established risk factors can however not explain all breast cancer cases and other suggestions that have been put forward are alcohol intake and dietary fat.[56]

Several studies have provided evidence that women with breast, ovarian or endometrial cancer are at increased risk of developing each one of the other cancers suggesting a common hormonal etiology. [57-60] Numerous other risk factors, such as alcohol and obesity, are likely to account for some of the increased risk with regard to second primary malignancy. Alcohol is a common risk factor for cancer of the esophagus, pharynx, liver, oral cavity and breast.[61-65] Obesity is a shared risk factor for colorectal cancer, kidney cancer, and postmenopausal breast cancer.[66-68]

Genetic risk factors

Studies on familial aggregation of breast cancer cases place family history of breast cancer as one of the strongest risk factors for the disease. Familial risks in female breast cancer have been the subject of numerous epidemiological studies. A recent study reanalyzed 52 epidemiological studies on familial breast cancer and presented summary risk ratios of 1.80 and 2.93 for one and two affected first-degree relatives, respectively.[69] An estimated heritable proportion of 25 to 27 %, found in the twin and family studies[28, 70, 71] cannot be fully attributed to the known breast cancer causing genes (e.g. *BRCA1, BRCA2* and *ATM*). A strong family history for breast cancer is associated with an 80% absolute risk before 70 years of age. Still, little is known about the possible interaction

of the environmental exposures with genetic factors that would modify the familial risks.

Breast cancer patients with mutations in *BRCA1* experience an approximately 50 % increased absolute risk of developing second primary ovarian cancer before the age of 70 years, while in patients with mutations in *BRCA2* the absolute risk estimates seems to be smaller.[72-75] In addition, mutations in *BRCA2* and CDKN2A have been associated with a higher incidence of melanoma among breast cancer patients.[76-78] Genetic mechanisms for a predisposition towards second primary cancers after breast cancer have been described in the Li-Fraumeni syndrome.[24] This is an autosomal-dominant disorder, associating breast cancer in young women with soft tissue sarcoma, lung, leukemia, ovary, stomach and other cancers.

However, most cases of breast cancer are not associated with mutations in known high-penetrance genes, indicating the involvement of multiple low-penetrance risk genes. Low penetrance genes, sometimes called modifier genes, are defined as genes in which subtle sequence variants or polymorphisms, may be associated with a small to moderate increased relative risk for breast cancer.[79] It is most likely that a number of these genes have to work in concert and interact with non-genetic factors to increase the risk of breast cancer.

Breast cancer treatment

Surgical removal of the tumor remains the primary treatment. Adjuvant chemotherapy, modern endocrine therapy and radiotherapy provide a significant contribution to the survival of breast cancer patients.[33, 80]

Surgery

The surgical management of primary breast cancer underwent significant evolution in the last quarter of the 20th century as a result of changes in biologic understanding and clinical presentation of the disease. Partial mastectomy is currently the most used treatment (Figure 3A). This is possible since most breast cancers have a limited size and large tumors could be reduced in size by primary chemotherapy.[81] Total mastectomy (Figure 3B) is needed, when more than one tumour occurs, with extensive intraductal carcinomas, inflammatory carcinomas, and large primary tumours that did not reduce enough in size by neoadjuvant chemotherapy.[33]

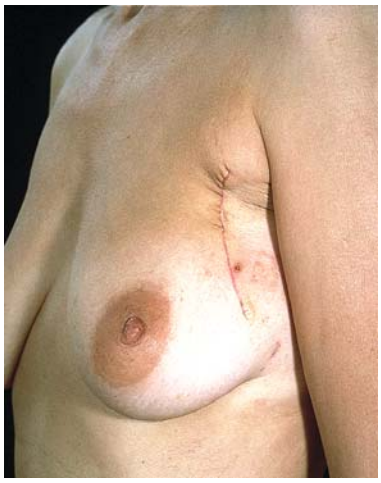


Figure 3A. Partial mastectomy.

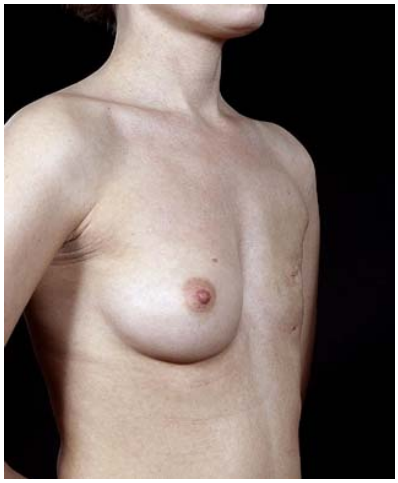


Figure 3B. Total mastectomy.

Chemotherapy

The main aim of adjuvant chemotherapy is to control any probable micrometastatic disease, thereby reducing the recurrence rate and improving long term survival. However, most agents used in chemotherapy for cancer treatment are carcinogenic in animal models. In humans, leukemia is found to be the primary feature of chemotherapy-related second primary malignancies and found in excess after treatment with most types of established agents.[82, 83] Solid tumours are rarely found in association with chemotherapy.[84-88]

Endocrine therapy

Endocrine therapy is the ideal treatment choice for postmenopausal women with estrogen receptor (ER)-positive breast cancer due to its demonstrated efficacy and favourable safety profile. Although tamoxifen has been the established treatment for more than 20 years, its long-term use is associated with several tolerability concerns and may lead to increased risk of endometrial cancer.[89] Five years of tamoxifen use increases the risk of endometrial cancer by two to threefold, and reduces the risk of new primary breast cancers by about 50 %.[90, 91]

Radiotherapy

Radiotherapy is widely used to reduce the risk of local recurrence. After breast-conserving surgery, postoperative radiotherapy is given routinely to nearly all patients. Early studies of mastectomy specimens demonstrated that microscopic disease could extend up to 2 to 4 cm beyond the primary site of the tumor within the breast tissue.[92] Trials comparing mastectomy to breast-conserving surgery plus radiotherapy demonstrated equivalent survival, confirming the effectiveness of this combined approach.[93, 94] Other studies that have compared breast-conserving surgery alone to breast-conserving surgery plus radiotherapy verified a substantial decrease in the risk of

local recurrence and the prevention of mastectomy with breast irradiation.[93, 95] However, both mild to moderate (skin erythema and irritation),[96] and serious long-term adverse effects (secondary malignancies)[58, 97, 98] of radiotherapy have been reported.

Radiotherapy has been shown to significantly reduce the risk of locoregional recurrence and to improve disease-specific survival in high-risk women with early stage breast cancer.[99-103] Other studies have shown the importance of radiotherapy in maintaining optimal locoregional control in patients with locally advanced disease.[104] Prevention of locoregional recurrence is an important goal in cancer management. Randomized trials have time after time shown a highly significant two-thirds reduction in locoregional recurrence with the addition of radiotherapy. [102, 103] Despite the advantage in locoregional control, the effect of radiotherapy on disease-specific and overall survival has varied. Early studies suggested decreased survival with radiotherapy.[105, 106] However, in 1995 the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) reported a significant decrease in breast cancer deaths due to radiotherapy (odds ratio 0.94), resulting in overall mortality rates of 40.3% with radiotherapy versus 41.4% without radiotherapy.[102] The 2000 Early Breast Cancer Trialists' Collaborative Group overview provided 20-year results from 40 unconfounded randomized trials of radiotherapy for early breast cancer.[103] They found a reduction of approximately two-thirds in local recurrence (9% vs. 27% local recurrence by year 10). Furthermore, breast cancer mortality was reduced (p=0.001), but other non-breast cancer mortality (particularly vascular) was significantly elevated (p=0.0003).

Adverse health effects of breast cancer treatment

Management of patients with breast cancer is a complex process. In the preventive, primary care, and adjuvant settings, decisions are made for individuals based on the hope that, we generally help more patients than we harm. For women with moderate risk of developing metastatic disease, such as those with small, hormone-dependent, node-negative breast cancers, one never really knows if one has helped a particular patient. In fact, a majority of these patients would probably survive without treatment (will not recur regardless of our treatment, not because of it).

Prognostic (estimate of risk for failure after therapy) and predictive (estimate of benefit from specific therapy) information have been of value to help individualize therapy of breast cancer more than for any other solid tumors.[107] The benefits of adjuvant systemic therapy have been reported for over 30 years.[107, 108] Breast cancer is a disease where different therapies are beneficial in various groups. For instance, adjuvant chemotherapy reduces the annual probability of recurrence approximately 25% to 30% for all patients.[108] However, in women with an initially poor prognosis, such as women with positive axillary lymph nodes, this reduction can result in an absolute improvement of 10% to 20% or more in the probability of being disease free after 10 to 15 years of follow-up. On the other hand, in women with small, node-negative, estrogen receptor positive cancers, this improvement is only a few percent.[107]

Breast irradiation is generally well tolerated. Common early adverse effects are tiredness, breast edema, erythema and irritation, which can influence quality of life.[96] Mild to moderate long-term effects are relative uncommon. About 5% to 10% of women experience limited breast pain attributed to radiotherapy or adverse cosmetic outcome, such as scar retraction and telangiectasia.[109] Serious long-term adverse effects are relatively rare (less than 1%) and include radiation pneumonitis, rib fracture, and cardiovascular disorder.[103, 110-113]

Radiation associated cardiovascular disease involves a spectrum of clinical diagnosis, such as cardiomyopathy and coronary artery disease, with ischemic heart disease being of greatest clinical significance.[114] The Early Breast Cancer Trialists' Collaborative Group demonstrated a significant increase in cardiovascular mortality by radiotherapy (death rate ratio 1.3).[103] Other studies have shown similar results of the effect of radiotherapy on cardiovascular risk.[115-118]

Radiation pneumonitis has been associated with increasing volume of irradiated lung and chemotherapy use. In a study by Lingos at al.,[119] radiation pneumonitis has been observed in 0.2% of women treated with tangent breast fields alone compared to 1.4% in women treated with nodal radiotherapy. Chemotherapy treatment elevated the incidence of radiation pneumonitis to about 3%, and this risk increased to approximately 9% when treated with both chemotherapy and radiotherapy.[110] Approximations of the risk for radiation pneumonitis vary because of differences in radiotherapy treatment techniques. This largely reflects variations in the volume of irradiated lung.[120, 121]

'Late effects' of breast cancer treatment are being increasingly documented as more patients survive their disease. Arguably the most serious of these late effects is the development of a second primary malignancy. Both radiotherapy and alkylating chemotherapy are themselves carcinogenic, and hence second malignancy after treatment is important to characterize and try to prevent.

Previous studies performed on population- and hospital-based data have shown that breast cancer survivors are at a 10 to 60 percent greater risk of developing a second primary cancer at other sites, compared to the general population.[98, 122-125] In the treatment for breast cancer it is recognized that chemotherapy and radiotherapy are carcinogenic. The level to which they do cause secondary primary cancers is dependent on many factors. Both genetic and hormonal factors may play an etiological role in this increased risk, as certainly may the treatment therapy for breast cancer, such as hormonal therapy, chemotherapy and radiotherapy.

The latency time, or the time between first and second malignancy, is around 10 or more years for radiation-induced cancers. This may also be true for some chemotherapy-induced second primary cancers.[1, 97, 126] Thus, many important considerations are related to the time between first and second primary cancer. For example, the second primary cancers may identified today outdated treatments. For instance, the technique of radiation therapy, the fraction size and surgery has changed during the past 40 years.

Today, radiotherapy technique uses higher energy sources and the fraction size is reduced.

Finally, despite the limitations of assessing treatment related second primary cancers, it is beyond doubt that treatment for breast cancer may cause second primary cancer.

Lung cancer

Lung cancer is the leading cause of cancer death in both developed and developing countries.[127] Because of the high mortality rate of lung cancer, the incidence and the mortality rates are nearly the same. The cumulative incidence rate of disease from 0 to 74 years of age ranged from 1.5 % to 14.0 % among men and 0.2 % to 8.5 % among women in different countries around 1980.[128] In Sweden the corresponding rates were 3.2 % and 0.9 %, respectively.[128] Ten years later the international range was similar and the corresponding rates in Sweden were 3.2 % among men and 1.4 % among women.[129] Lung cancer incidence is gradually levelling off in Swedish among men, but is continuously increasing in Swedish females.[31] During the last two decades the annual lung cancer incidence in women increased with 2.7 % and is now the third most common cancer in Swedish women (Figure 1). [31]

What causes lung cancer?

Tobacco

Tobacco smoking is identified as the single most predominant cause of lung cancer.[130] However, other causes have been identified, including workplace exposure (e.g. asbestos, nickel and radon)[131, 132] and other environmental factors (passive smoking, air pollution, and indoor radon).[133-135] Many studies suggest that women may be more predisposed than men to molecular aberrations resulting from the carcinogenic effects of tobacco smoke, [136, 137] and that women are about 2-fold more sensitive to men for similar smoking levels.[138-140] However, more recent cohort data have not supported pronounced sex differences in susceptibility.[141-143]

Ionising radiation

Ionising radiation has been shown to increase the risk of lung cancer in a variety of population, including Japanese atomic bomb survivors,[144] underground miners exposed to uranium,[145 146] and patients who have received radiotherapy for ankylosing spondilitis.[147] In addition, there are reports of an increased risk of lung cancer among patients receiving radiotherapy for breast cancer and Hodgkin's disease.[88, 148-150]

Interaction of ionising radiation and tobacco

There is evidence that tobacco smoking and radon decay products synergistically influence lung cancer risk.[135, 151 152] Radon exposure at high levels has been shown to cause a risk for underground miners. Many studies have revealed evidence indicating that exposure to residential radon at lower concentrations carries a risk of lung cancer.[153]

Based on linear relative risk model, an excess relative risk of 10 % per 100 Bq per cubic meter radon concentration was estimated in Sweden.[152] The average radon concentration in Swedish houses is about 100 Bq per cubic meter.[154] Radon exposure has a tendency to be higher in rural than in urban areas, since more houses are influenced by ground radon.

Several studies have shown an increased risk of second primary lung cancer after radiotherapy for cancer sites located close to the lungs, such as Hodgkin's disease[150, 155] and breast cancer.[97, 149, 156-158] For second primary lung cancer risk in women with a history of breast cancer, non-smoking women undergoing breast cancer radiotherapy have 2-3 fold increased risk of lung cancer. In smoking women however, there is a 30-fold effect of smoking and radiotherapy (versus 13 to 20 for lung cancer without radiotherapy).[149, 158] Overall, radiotherapy causes about 7-9 additional cases of lung cancer per 1,000 women over 10 years.[58, 149]

A relationship of chemotherapy to lung cancer risk has been addressed in studies of Hodgkin's disease, and the data is conflicting.[159] In a study by Foss Abrahamsen[160] and co-workers, radiotherapy led to a 6.6-fold significantly increased risk for lung cancer, while chemotherapy alone led to a non significant 2.5-fold risk. Chemotherapy and radiotherapy combined resulted in a 5.6-fold significantly increased risk for second primary lung cancer. Importantly, the chemotherapy treatments for Hodgkin's disease are known to be more carcinogenic than for breast cancer.

The effect of environmental risk factors, such as tobacco smoking and other exposures discussed above, may be modulated by host factors which determine individual susceptibility to environmental carcinogens. The p53 gene is involved in many cellular processes including maintenance of genomic stability, programmed cell death, DNA repair and cell cycle control.[161-163] It is upregulated in response to DNA damage, including radiation.[164, 165] Cell lines with mutated p53 are hypersensitive to point mutations following radiotherapy.[166] The p53 mutation frequency in cancer varies by organ site and histological subtype,[167] showing that cancer occurs through different pathways. There are many examples of specific carcinogenic exposures linked to cancers via a specific p53.[168, 169] In lung cancer, about 50 % of tumours have p53 mutations[167, 170] and there is a correlation of smoking with G→T transversions.[171] In breast cancer, up to 40 % of tumours have p53 mutations,[172, 173] and the presence of a p53 mutation is a poor prognostic marker for breast cancer.[174, 175] Studies around the world indicate that the p53 mutational spectrum for breast cancer varies by race and geography,[173, 175, 176] suggesting differences in aetiology are environmental (e.g., lifestyle, diet and occupation) and/or genetic.

Histology of lung cancer

Lung cancer occurs in multiple histological types, but the four major types include squamous cell carcinoma, adenocarcinoma, large cell carcinoma, and small cell carcinoma.[177] Other types include carcinoids, which are neuroendocrine tumors, and

mesotheliomas, which are strongly associated with asbestos exposure. Tobacco smoking has been shown to cause each of the major histological types of lung cancer. The associations are strongest for small cell carcinoma, squamous cell carcinoma and large cell carcinoma than for adenocarcinoma.[137, 178] However, recent findings indicate that adenocarcinomas are more strongly associated with smoking than has previously been recognised.[179] In recent years the proportion of adenocarcinomas has increased. This may be partly due to changing diagnostic criteria, but it also appears to represent a true increase which could be related to changes in inhalation practices and modern cigarette design.[180] Women more commonly have lung adenocarcinoma, a ductal cancer similar to breast cancer.[181]

Diagnosis of lung cancer

Diagnosis is usually made by clinical examination, x-ray, CT scan, and in most cases bronchoscopy, whereby the lungs may be inspected through a fiberoptical instrument and tissue samples obtained. Sometimes an examining operation is performed to obtain tissue samples. In Sweden around 98 % of all lung tumours have received a histological or cytological diagnosis during the last decades.[36] It is sometimes problematic to determine if the tumour is a primary lung malignancy, particularly for adenocarcinomas and among women.

The majority of the lung cancer patients (75 %)[182] are diagnosed late with advanced disease. The symptoms of lung cancer may be local, such as cough, hoarseness or chest pain, or they may be general, such as weight loss, fever, dyspnoea, tiredness and sweating.[182] The characteristics of the disease and the often late diagnosis combine to make the prognosis poor.

AIMS

The overall aim of this thesis was to investigate the risk of second primary malignancies -with special interest in lung cancer - in women previously diagnosed with breast cancer.

The specific aims were:

- to evaluate the risk of lung cancer in Swedish female breast cancer patients in relation to age at and time since breast cancer diagnosis, and calendar period (Study I)
- to investigate the completeness and accuracy of the smoking history in the patient records, the agreement between patient records and the information reported from relatives, and to investigate how relationship and time since women's death affected the response rate and the quality of the data (Study II)
- to analyze the risk of lung cancer in women treated with radiotherapy for breast cancer, to evaluate the influence of tobacco use and to provide excess relative risk estimates for radiation associated lung cancer (Study III)
- to assess the risk of other second primary malignancies among women diagnosed with breast cancer in relation to age at and time since breast cancer diagnosis, and family history of breast cancer (Study IV)

MATERIAL AND METHODS

Setting

All studies were based on Swedish data. Sweden provides excellent opportunities for epidemiological research and has been described as a "paradise for epidemiologist".[183] The most important factors are the existence of nation-wide population-based health registers, a public health care system with transparent referral systems, and most importantly the use of national registration numbers. Further, Sweden has an ethnically and socio-economically homogenous population, with a high public acceptance to registration.[183]

Data-Sources

The Swedish Cancer Registry

The Swedish Cancer Registry (SCR) was started at the National Board of Heath and Welfare in 1958. All newly diagnosed malignant tumours must be reported to the SCR both by the pathologist or cytologist and the physician.[31] As a result, most cases included in the SCR are reported from two sources. During the first five years after the establishment of the SCR the frequency of underreporting decreased to a level of about 5 percent.[184] However, the majority of the missing patients were deceased cases where the diagnosis was found on death certificates. Today, cancers found incidentally at autopsy are entered with a special notation of their origin. Cancers only reported at death certificates are not entered, as the validity of such records is considered too low. The total insufficiency today is probably under one per cent. Nation-wide rates of the diseases covered by the registry are annually published in "Cancer Incidence in Sweden".[36] The cancer diagnoses are recorded according to the *International Classification of Diseases*, seventh revision (ICD-7), and in later year's also newer versions of ICD. Data from the Death and Emigration registries are regularly linked to the Cancer Registry, making it possible to obtain the date and cause of death or if the subject emigrated during follow-up.

The Multi-Generation Register

In the early 1990s, Statistics Sweden created the Multi-Generation Register by linking data from several different population-based registers. The register provides information on all first-degree relatives for residents born in Sweden 1932 or later (index person). [185] To be included in the register, the index person had to be alive in 1960 or born thereafter. Adoptions and other non-biological relations are flagged. Each index person has information on the year of birth or immigration, year of death, sex, country of birth and the personal identity number on biological (or adoptive) parents. The Multi-Generation Register is unique also in an international perspective. At present it includes more than 11 million individuals who are structured in 3.1 millions of nuclear families.

The Register of Population and Population Changes

This register started in 1960 and contains the official Swedish census. Information on name, personal identification number, parish, community, and county of residence is recorded each year for all living Swedish residents, as well as the date of death for individuals who have died during the year. Information on emigration is included since 1969.

The Emigration Register

The emigration register is an extension of the Register of Population and Population Changes, and contains information on the date of emigration for all Swedish residents who have emigrated since 1968.

The Cause of Death Registry

The Cause of Death register is kept by the National Board of Health and Welfare and records information on all deceased individuals registered as residents in the country at the time of death, irrespective of whether death occurs in Sweden or abroad. The register was initiated in 1952 and provides information on date of death, age at death, and underlying and contributing causes of death. All causes of death are coded in accordance with the International Classification of Diseases, Injuries, and Causes of Death (ICD). The completeness is estimated to be over 99 %.[186]

The National Registration number

Since 1947, all living residents in Sweden have a unique ten-digit national registration number.[187] At the start, it consisted of nine digits of which the first six digits contain information of the birth date (yy-mm-dd), two digits on county of birth (nowadays assigned without relation to the place of birth), or for those born before 1947, county of residence at time of registration, and the last ninth digit denotes sex. Later, a check-digit which can be calculated from the previous ones was added. The national registration number is a unique personal identifier, and is used in all Swedish registries as well as in patient records. This provides opportunity to link information from various sources.

Paper I

The Swedish Cancer Register was used to identify approximately 141,000 women with breast cancer, diagnosed between 1958 and 1997, and followed up for the occurrence of lung cancer. In all, 613 women with second primary lung cancer were included in the study. The person years at risk were calculated starting 30 days after the date of breast cancer diagnosis and ending at the date of death, emigration, lung cancer diagnosis or December 31, 1997, whichever date came first. To estimate the possibility of chance affecting the results, 95% confidence intervals were computed and presented together with SIRs. The effect of birth year cohort was studied by Cox' regression, with attained age as the time scale, adjusting for age at breast cancer diagnosis. In order to study the potential impact of radiation therapy on the lung cancer risk, the predictive value of

laterality of breast cancer on the laterality of subsequent lung cancer was analyzed. The concordance (the breast and lung cancers on the same side) was possible only on a restricted set of patients since laterality for breast cancer was not reported to SCR until 1970 and gradually for lung cancer from 1986 and onwards.

Paper II

We studied the agreement between smoking history in patient records and the information reported from next-of-kin. This validation study was performed within the framework of a study of lung cancer risk in women previously treated for breast cancer in the Stockholm County during the period 1958-2000. In the Swedish Cancer Register, we identified 192 women diagnosed with breast cancer and subsequent lung cancer in Stockholm County. Controls consisted of women diagnosed with breast cancer, who survived the corresponding medical date of lung cancer diagnosis. The information about smoking habit was collected from patient records at the time of breast cancer diagnosis, therefore cases and controls were considered as one group. The total number of women were 401, 306 deceased and 95 still alive.

Patient records for all patients were identified and reviewed. Information about smoking habits was recorded in 233 out of the 401 patient records. Of the 306 deceased patients, we identified next-of kin for 270 women. Selection of the relative was done in the order: spouses, children, siblings, and other relatives. The lifetime smoking habits of the study participants were validated by a mailed questionnaire. All living patients received the same questionnaire as next-of-kin. To evaluate the quality of agreement between the reports of next-of-kin and patient records, we calculated Kappa statistics, along with its 95% confidence interval.[188] Landis and Koch [189] have classified kappa values into three groups with respect to the degree of chance-adjusted agreement. A kappa statistics representing less than 0.40 should be taken as a poor agreement, between 0.40 and 0.75 fair to good agreement, and greater than 0.75 almost perfect agreement.

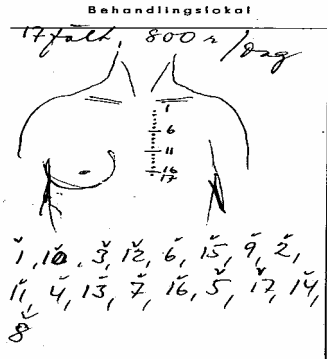
Paper III

Using the Swedish Cancer Register, 191 women diagnosed with breast and subsequent lung cancers were identified in Stockholm County between 1958 and 2000. Nine patients were excluded since they were diagnosed with lung cancer within 12 months of the initial breast cancer.

Information about smoking history was identified in case records from departments of oncology, surgery and thoracic medicine. For patients lacking information, approximately 29%, lifetime smoking habits were retrieved by asking spouse or next-of-kin through a mailed questionnaire.

For each patient case records and radiotherapy charts were identified and reviewed. Radiotherapy charts were abstracted for detailed information about physical and geometrical irradiation parameters, such as radiation quality, treatment technique, total

dose, fractionation schedule, and treatment field size. Detailed information about radiotherapy was available for 106 patients. The criteria chosen for organizing the radiotherapy information was grouping the patients according to the target definition and consequently to the used treatment techniques. In most clinical charts the exact definition of target was not given. Target was defined in general terms such as breast parenchyma, chest wall, lymph nodes of the internal mammary chain (IMC), of the supraclavicular region, and of the axillary region. We identified nine different treatment groups.



Group I consisted of patients irradiated towards the IMC. The treatment was given with overlapping rectangular cobalt- 60 gamma-radiation (^{60}Co) fields using a short-distance gamma beam unit. The treatment technique is described in detail elsewhere.[190]

Figure 4. Treatment fields for patients in group I.

In group II patients were treated with Orthovoltage x-ray beams. Ten of the patients were treated with two adjacent anterior-posterior fields to the fossa-supraclaviculary lymph nodes and to the chest wall. Additionally, two patients were treated with a field covering the IMC and one field covering the fossa-axillary lymph nodes. Treatments were given with a source skin distance of 60 cm, 0.5mm Cu filtration.

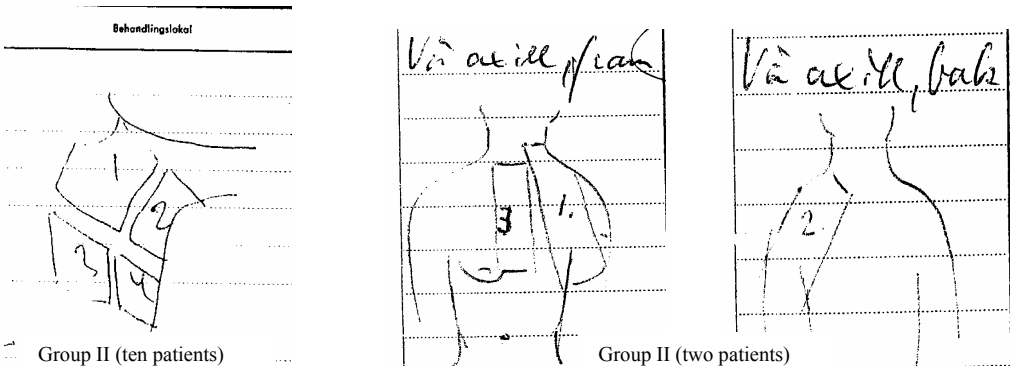


Figure 5. Treatment fields for patients in group II.

Group III consisted of patients treated with electron beams covering the fossa-supraclaviculary lymph nodes.

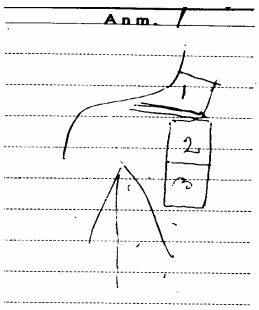


Figure 6. Treatment fields for patients in group III.

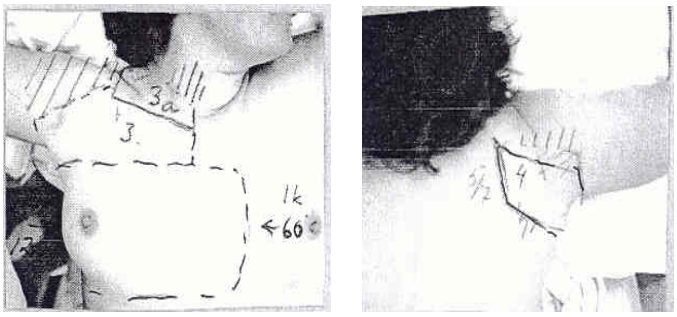


Figure 7. Treatment fields for patients in group IV.

Further, patients in group IV received radiotherapy to the breast parenchyma/chest wall and the IMC lymph nodes; they were treated with extended tangential photon fields. A shield for the apical part of the lung was often used.

Group V consisted of patients where the IMC, fossa and axilla were treated with an anterior-posterior ^{60}Co beam.

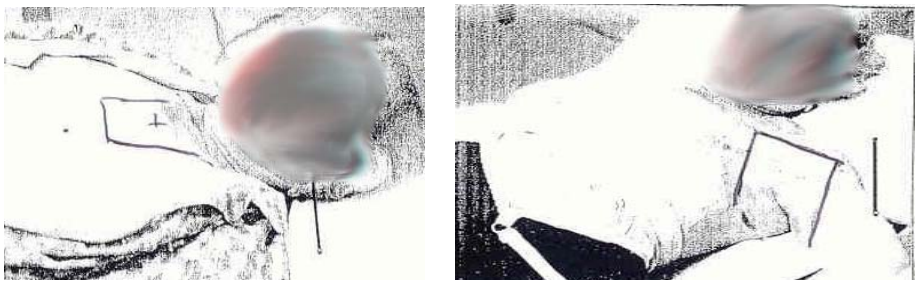


Figure 8. Treatment fields for patients in group V.

Patients in group VI were treated as patients in Group V, but also received an oblique ^{60}Co beam to the thorax region.

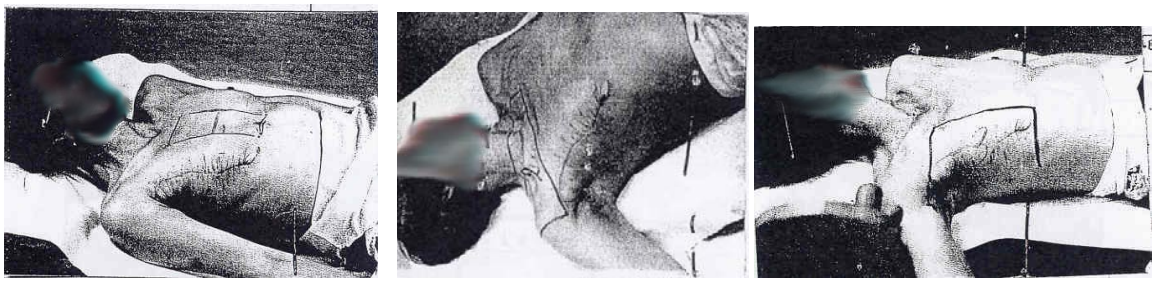


Figure 9. Treatment fields for patients in group VI.

In the treatment group VII the chest wall and the lower part of the IMC were treated with an oblique electron field. The lymph nodes in the lower part of the IMC, fossa, supraclavicular and axillary regions were treated with an anterior photon field, while a posterior photon field was added to the axillary region.

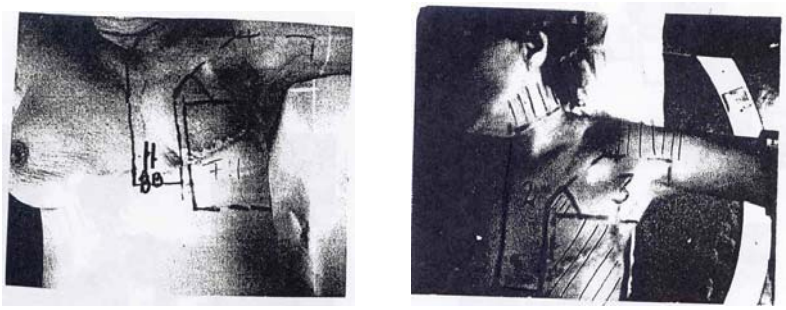


Figure 10. Treatment fields for patients in group VII.

In group VIII, the chest wall and the caudal part of the IMC lymph nodes were covered by an anterior electron field. An anterior photon field was used for the cranial part of the IMC, axillary, fossa and supraclavicular lymph nodes.[191]

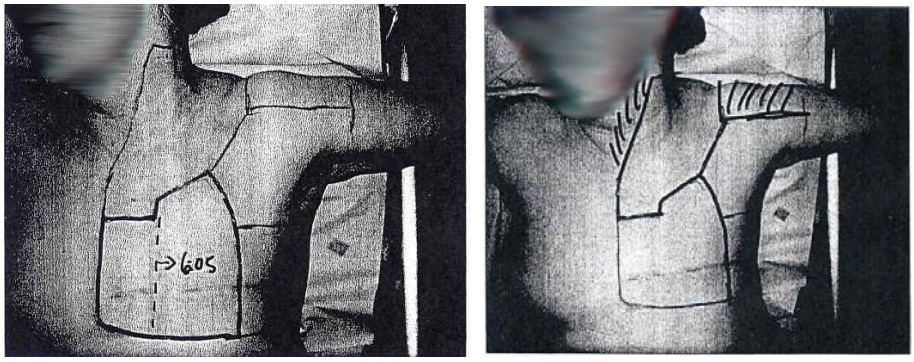


Figure 11. Treatment fields for patients in group VIII.

Finally, patients in group IX received radiotherapy to the remaining breast parenchyma after partial mastectomy, and were treated with tangential ^{60}Co beam or with x-rays photon fields.

Figure 12. Treatment fields for patients in group IX.

Radiation treatments were generally given in five fractions per week, for 3 to 6 weeks. The highest dose per fraction was given to patients in Group I, and the lowest in Group

IX. The treatment techniques of groups IV, VII, and IX have previously been described in detail.[192]

Calculation of lung dose

For most of the patients, original individual three-dimensional dose distributions in the lung were not available because patients were treated before the introduction of three-dimensional treatment planning systems (3D TPS). The reconstruction of treatment techniques on 3D TPS has already been used in studies both on radiation induced secondary cancer[149] and on dose-volume complications relationships.[112, 192, 193] Based upon the irradiation parameters given in the radiotherapy charts (Figure 13), we were able to quantify the ipsilateral and contralateral absorbed lung dose for all groups except group II, where only ipsilateral lung dose was estimated.

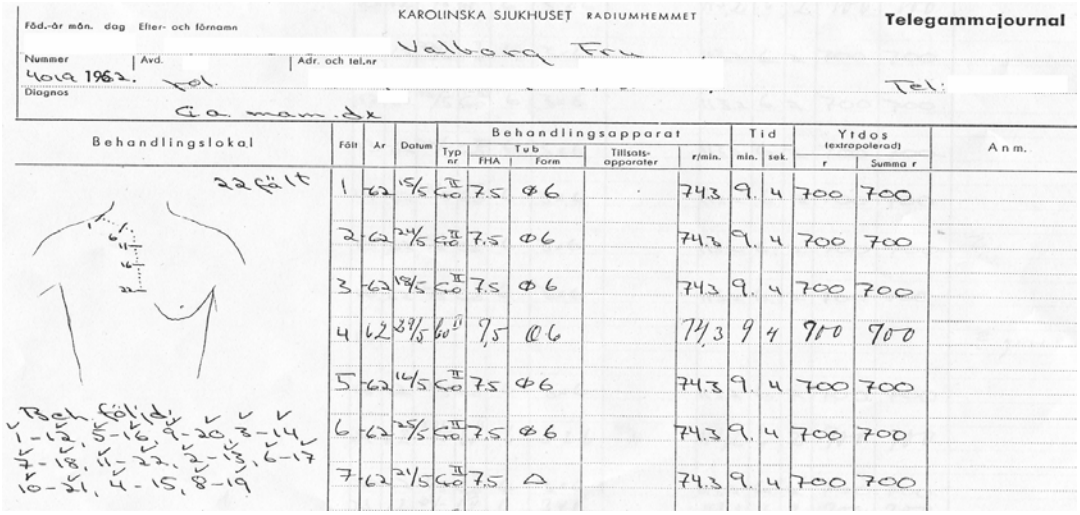


Figure 13. Example of a patient's radiotherapy chart. This patient was irradiated to the IMC-group I. The first column gives information of location for treatment and direction of the beams. The second column gives treatment field. Thereafter year of treatment, day of treatment, type of treatment (here ^{60}Co beam), focus-skin distance in cm, type of tube, additional equipment used, exposure to the skin per minute, irradiation time in minutes. The next last column contains exposure to the skin and the last column is for remarks.

The risk of lung cancer was assessed in a case-only approach where each woman contributed a pair of lungs, which can be considered matched for genetic and environmental factors (primarily smoking). The lung on the breast cancer side was considered as exposed and the contralateral lung as unexposed. The concordance rates with 95% CI were calculated as proportion of the lung cancer cases on the same (concordant) side as breast cancer. The relative risks (RR) and 95% CI were estimated as in a twin-study design, by conditional logistic regression.[194] Heterogeneity of the radiation effect by latency, smoking and histopathology were tested by likelihood ratio tests. The excess relative risk (ERR) per gray (Gy) was calculated for the patient group with latency ≥10 years since exposure.

Paper IV

We used the Swedish Cancer Registry to identify all women with a histologically confirmed invasive breast cancer during the period 1958 to 2000 and 152 586 women were included in the study. Information from the Swedish Cancer Registry Register was then linked to the Multi-Generation Register.

Standardized incidence ratios (SIR) were calculated as the ratio between observed and expected number of second primary malignancies. The observed number of cases was assumed to be Poisson distributed,[195] and 95% confidence intervals (CI) for SIR were calculated. The person years at risk were calculated as starting at date of breast cancer diagnosis and ending at date of death, emigration, second cancer diagnosis or December 31, 2000, whichever date came first. Expected number of cancers was calculated multiplying the age-, sex-, and calendar year specific rates from the Swedish Cancer Registry with the generated person years at risk. The overall SIRs are based on cancer sites presented in each table.

Family history SIRs for second primary malignancies were calculated in a similar way, starting at the follow-up from the diagnosis of the breast cancer. Family history information was collected on all first-degree relatives, parents, siblings, and offspring. Ratio between SIRs with family history of breast cancer and SIRs without family history of breast cancer was calculated to get a comparison between these two groups, and 95% confidence intervals were calculated. [196]

General methodological considerations

Epidemiological studies are in general categorized as descriptive (deals with the frequency and the distribution of risk factors and allows to assess the extent of a disease), analytic (aiming to examine associations, commonly hypothesized causal relationships), and experimental (a term often equated with clinical trials of treatments and other interventions). The goal of all research is to get valid evidence concerning the hypothesis under study. The choice of study design depends on the nature of the dependent variable under investigation, type of exposure, feasibility, ethical considerations, and the available resources. The two most widely used are cohort studies and case-control studies, which are the designs used in this thesis.

Cohort studies

Cohort studies are well suited for investigations of rare exposures and provide opportunities for assessment of multiple outcomes. A cohort study is a study in which individuals are followed over time. Measures of exposure are made when entering the cohort and measures of outcome are made during or after the time under study. Cohort studies, sometimes referred to as follow-up studies, can be made retrospectively or prospectively. The association between exposure and the disease is most often presented as the relative risk of developing the disease following exposure to the factor under

study and calculated as the relation between the occurrence of the disease in the exposed and unexposed. Occurrence can be measured as incidence rates, where person-years are the denominator used.

We used a cohort design to study the risk of second primary lung cancer (Paper I), and other primary malignancies in women previously diagnosed with breast cancer (Paper IV). The advantage of register-based studies is medical verification of all cancers including those in family members. Importantly, both cancer and family data have a practically complete national coverage, resulting in large numbers and guarding against bias. The main limitation of register-based studies is that we are restricted to information included in the registry. In the Swedish Cancer Registry the exposure information, such as radiotherapy, chemotherapy and hormonal therapy is not registered. The prerequisite for valid register-based studies is a close to complete inclusion of the study subjects and few subjects lost during follow-up.

Case-control studies/case-only design

Case-control studies are preferable for studies of rare outcomes, and allow evaluation of multiple exposures. Case-control studies are studies in which patients who already have a certain condition are compared with people who do not. Differences in certain exposures between groups are looked for. The case-control study is the most efficient study design when investigating a rare outcome, such as cancer. It is also cost-effective, and provides the ability to study many exposures related to an outcome, and their potential interaction. However, it is important that exposures of the control group are representative of the source population from which cases are obtained. The controls should not have the outcome under study. There are many ways of selecting controls and the method used is important for validation of any associations between exposure and outcome revealed in the study. Matching cases to controls is used to avoid confounding. However matching on too many factors, so called over-matching, can be contra-productive, and may even introduce bias.

Paper III was based on a large nation-wide case-control study, called SAMBAL (Swedish and American Breast and Lung cancer study). The cases in the SAMBAL study encompass all Swedish women diagnosed with breast cancer, and who were later diagnosed with lung cancer during the period 1958 to 2000. Lung cancers diagnosed within 12 months of the initial breast cancer were excluded. Controls consist of women diagnosed with breast cancer, and who survived the corresponding medical date of lung cancer diagnosis. Controls were matched by age and decade of breast cancer diagnosis.

In the first analyses of the SAMBAL data we performed a case-control study with a case-only design (Paper III) in women diagnosed with breast and lung cancer in Stockholm County during the period 1958 through 2000. The design looks like an affected-unaffected monozygotic twin design. By utilizing the fact that the two organs are paired, these data could be used to assess the lung cancer risk in a similar fashion as

in a disease discordant twin pair study. In contrast to a twin study, all of our radiation-treated lung cancer patients contributed an informative pair because they were exposure discordant. Each woman contributed a pair of lungs and the lung on the breast cancer side was considered as exposed (case), and the lung on the opposite side was considered as unexposed (control). The main advantage is that this way cases and controls, i.e. the lungs, can be considered matched for both genetic and environmental factors. The main disadvantage is that the only estimable main effect is the effect of radiotherapy.

Validity

The validity is usually divided into two parts, namely internal and external validity. *Internal validity* can be defined as the degree at which we are able to avoid bias and confounding. Our aim in conducting studies is most often to state a (causal) relationship between exposure and effect. We often try to do this so that it enables us to make inferences about populations in general. How well we can do these generalisations is called the *External validity*. External validity thus deals with the question if the results are applicable to other populations or patients than the ones included in the study.

Bias

There are three main categories of bias: selection bias, information bias and confounding. Selection bias is a systematic error that stems from the procedure used to select subjects and from factors that influence study participation.[197] This is usually not a big concern in population-based cohort studies.

Information bias (also called misclassification) deals with exposure measurements and classification of individuals in healthy or diseased, and can occur in any study. Misclassification of either exposure or outcome can be differential or non-differential, depending on whether measurement of one variable is related to measurement of the other. If misclassification is non-differential, that is, not different and equally likely to occur in all the groups involved in the analysis, the results will be diluted and any connection between exposure and outcome will be underestimated. On the other hand, if misclassification is differential, affecting one group more than the other, the distortion of the results might take any direction.

Misclassification of the outcome, that is, the second primary malignancies registered among women with a primary breast cancer would be a main methodological consideration concerning Paper I, III and IV. The observed increased risk of second primary malignancies might be misclassified metastases. The common sites of metastasis from breast cancer are skeleton, lung, liver and brain. This consideration is most likely to be important for cancers occurring within the first year after the primary malignancy. In Paper III and IV the first year after breast cancer diagnosis was excluded. On the other hand, some second primary malignancies can be classified as metastases and therefore never reported to the Swedish Cancer Register.

Differential misclassification of outcome can arise in cohort studies if follow-up is incomplete and the loss is related to exposure. In our cohort studies (Paper I and IV), registration of outcome (second primary malignancy) was independent of exposures and follow-up was considered complete.

A confounder is a variable that is associated with the disease and with the exposure, but must not be an effect of the exposure.[197] A confounding factor may mask an actual association or falsely demonstrate an apparent association between the study variables where no real association between them exists. In registry-based studies, available information on potential confounding is limited. Thus, in our paper I and IV we were not able to adjust for any confounders other than age, and calendar period. The major strength of our case-only design (Paper III) was that a woman was both a case and control, this design allowed control for all genetic and environmental confounders.

In Paper II we performed a validation study of smoking information in patient records and information collected by mailed questionnaires from next-of-kin, and living patients. The response rate is of critical importance for validity, and a low response rate has the possibility to cause a selection bias. In our study the response rate was 89% for next-of-kin and 93% for living patients. Furthermore, the overall agreement was almost perfect after correction for possibility of correct guessing (chance).

RESULTS

Paper I

The mean time between breast cancer diagnosis and the development of primary lung cancer was 12.2 years. The overall SIR was 1.32 (95% CI: 1.21-1.42). Throughout the first 5 years there was a significantly decreased risk of lung cancer followed by significantly increased risks in the subsequent periods, reaching its maximum >20 years after breast diagnosis, SIR = 2.53 (95% CI: 2.10 – 3.04, Figure 14). The highest risk of a subsequent lung cancer was observed among women <50 years of age at the time of breast cancer diagnosis (SIR=2.30; 95% CI: 1.97-2.63). Overall, the risk of lung cancer increased with time between breast cancer diagnosis and the diagnosis of primary lung cancer, independently of the age at breast cancer diagnosis.

There were 174 lung cancer cases with information on laterality of both lung and breast cancer. The risk of developing lung cancer on the same side as the breast cancer compared to the contra lateral side was increased after more than 10 years from breast cancer diagnosis (relative risk, 2.0; 95% CI: 1.3-3.0). There was no elevated risk within 10 years from breast cancer diagnosis. However, the risk estimation in this approach is biased towards the null since we included a fraction of patients not receiving radiotherapy, anticipated to show no association with laterality. The risk of lung cancer increased in later birth year cohorts, which mirrors the increasing smoking prevalence among women seen in Sweden.

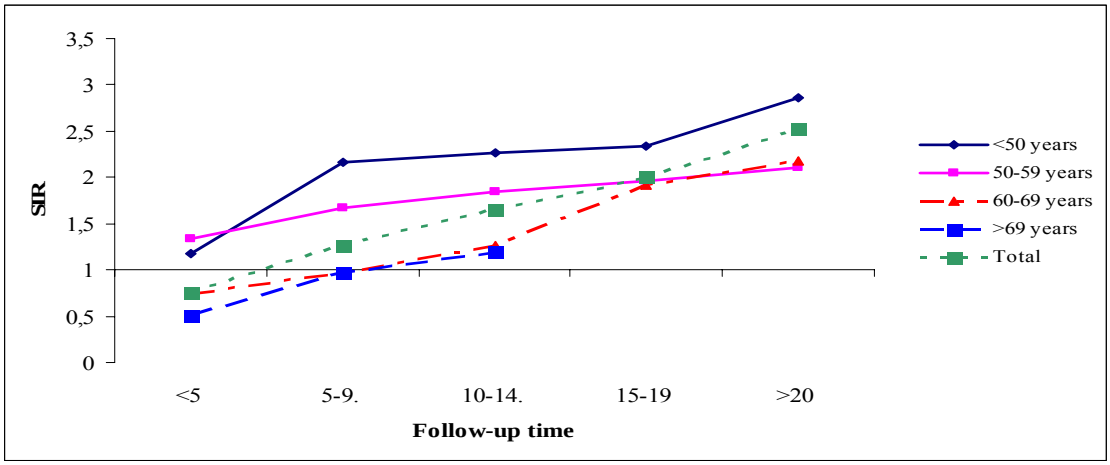


Figure 14. Standardized incidence ratio (SIR) in relation to age at breast cancer diagnosis and time (years) after initial breast cancer diagnosis.

Paper II

Of the 270 questionnaires sent to next-of-kin, 240 were returned, and one answered by telephone, resulting in response rate of 89 %. For the 95 living patients the response rate was 93 %, two of the living patients were too ill to answer. Of the 83 % of next-of-kin

who were able to answer about the patient's overall lifetime smoking status, 69 % were children of the deceased woman. The response rate from next-of-kin was not affected by the time since the woman's death, and varied between 86 to 95 %. The trend test showed no evidence of changes in the response rate (p = 0.31). The average interval between death of the patient in the study and next-of-kin questionnaire was 14 years, and the time interval varied between 1 and 38 years.

Validation of the information in the patient records and from next-of-kin could be done for 132 patients with complete information from both sources. Among these patients 11 (8 %) were classified differently by next-of-kin. When the smoking history was not stated in the patient record (for a total of 119 patients) 26 % were smokers, and 50 % were non smokers as reported from next-of-kin. For 28 (24 %) of the women the smoking status remained unknown.

	kappa value	95% Confidence interval	McNemar *p*-value
Information from Next-of-kin	0.83	0.73-0.92	0.13
≤10 years since patients death	0.80	0.64-0.95	1.00
>10 years since patients death	0.83	0.70-0.97	0.03
Quantitative smoking information	0.46	0.21-0.71	0.78
Information from living patient	0.86	0.72-1.00	0.56

Table 1. Measures of agreement of smoking history between patient records and next-of-kin, and between patients records and information from living patients.

In Table 1 the agreement for next-of-kin and living patients is summarised. When information from patient records and next-of-kin was compared, the kappa value was 0.83. McNemar's test of symmetry revealed no evidence of a trend toward under-/over-reporting among all next-of-kin. When time between death of the patient in the study and the next-of-kin questionnaire was divided in median intervals, a high agreement was present in both groups. In the interval ≤10 years since death with kappa value 0.80 and 0.83 in the interval of >10 years.

Quantitative information on smoking from both patient records and next-of-kin was available for 50 women. Among the 21 women who in the patient records had smoking information of ≤15 cigarettes a day, seven were found for whom the next-of-kin reported a greater amount, with kappa value 0.46 (Table 1). For most of the 13 women who were classified differently by next-of-kin, the difference in tobacco smoking was small and arose mainly from differences close to the cut-off point.

Among the 46 living patients with information from both sources, 39 % self-reported a positive overall smoking history, and 57 % were non smokers, resulting in a kappa value 0.86 (Table 1), with no evidence of asymmetry (McNemar *p*-value = 0.78). When the smoking status was missing in the patient record, 27 % (13 of 49) self-reported a positive smoking status, and 59 % were non smokers.

Paper III

The mean dose to the ipsilateral lung varied between 7.9 and 26.8 Gy, depending on the treatment group. In the first part of our study period, most of our patients received a mean dose to the lung of about 15 Gy, while in the 1970s the mean dose increased to around 25 Gy. In the latter part of the study period (1990s), the mean dose decreased to around 8 Gy. The mean latency period between breast and lung cancer in women not treated with radiation therapy was 9.7 years, with no difference between concordant and discordant laterality. In patients treated with radiotherapy, lung cancers diagnosed on the concordant side showed a mean latency of 17.6 years compared to 13.0 years for discordant lung cancers.

We compared latency and risk for lung cancer on the breast cancer side (=concordant side) with lung cancer on the contralateral side (=discordant side). Among 116 lung cancer cases that received radiotherapy, there were four women with bilateral tumours in the lung, and in six women the laterality of lung cancer was not specified, leaving 106 women to be included in the statistical analyses.

In patients treated with radiotherapy, the risk of developing lung cancer on the same side as the breast cancer compared with the contralateral side was significantly increased after more than 10 years from the breast cancer diagnosis (RR=2.04; 95% CI: 1.24-3.36; Table 2).

	Relative risk	95% CI	ERR per Gy	95% CI	P-value for Dose^2
All women	2.04*	1.24-3.36	0.11*	(0.02-0.44)	0.63
Smokers	3.17*	1.66-6.06	0.23*	(0.04-2.13)	0.34
Non-smoker	0.9	0.37-2.22	-0.0006	(-0.04-0.21)	0.61

*Statistically significant

Table 2. Relative risk for lung cancer in women previously diagnosed with breast cancer in the irradiated study group with a latency time of 10 or more years between breast and lung cancer.

Further analysis of the irradiated study group with a latency time ≥10 years since exposure after breast cancer treatment demonstrated that the increased risk was most evident for the squamous cell carcinoma of the lung (RR=4.00; 95% CI: 1.50-10.66). This association was not seen in any other histopathological subtype of lung cancer,

including adenocarcinoma. Separate analysis by smoking showed that the increased risk of lung cancer was present for smokers (RR=3.17; 95% CI: 1.66-6.06), but there was no observed increase in risk for non smokers (Table 2). In these analysis evidence of heterogeneity was found for smoking *(p*=0.026), while heterogeneity among histologies did not reach statistical significance (*p*=0.07).

The excess relative risk (ERR) per gray was calculated for the irradiated patient group with latency ≥10 years since exposure for all women and in relation to smoking. In the analysis, the individual doses to the ipsilateral as well as contralateral lung were used and therefore patients from treatment techniques with known dose to the contralateral lung were selected (group II was excluded). The estimated ERR/Gy for all women was 0.11 (95% CI: 0.02-0.44) assuming that risk increases linearly with dose, and a significant ERR/Gy was found for smokers 0.23 (95% CI: 0.04-2.13).

Paper IV

Of the 152 586 women in our study population, 10 725 women (7.0%) developed a second primary malignancy other than breast cancer between 1958 and 2000, giving an overall SIR of 1.20 (95% CI: 1.18-1.22). Figure 15 gives the estimated SIR for all second primary malignancies separately by sites for the entire follow-up period. The greatest increase in risk was found for connective tissue (SIR=1.69), followed by salivary glands (SIR=1.63) and thyroid (SIR=1.55).

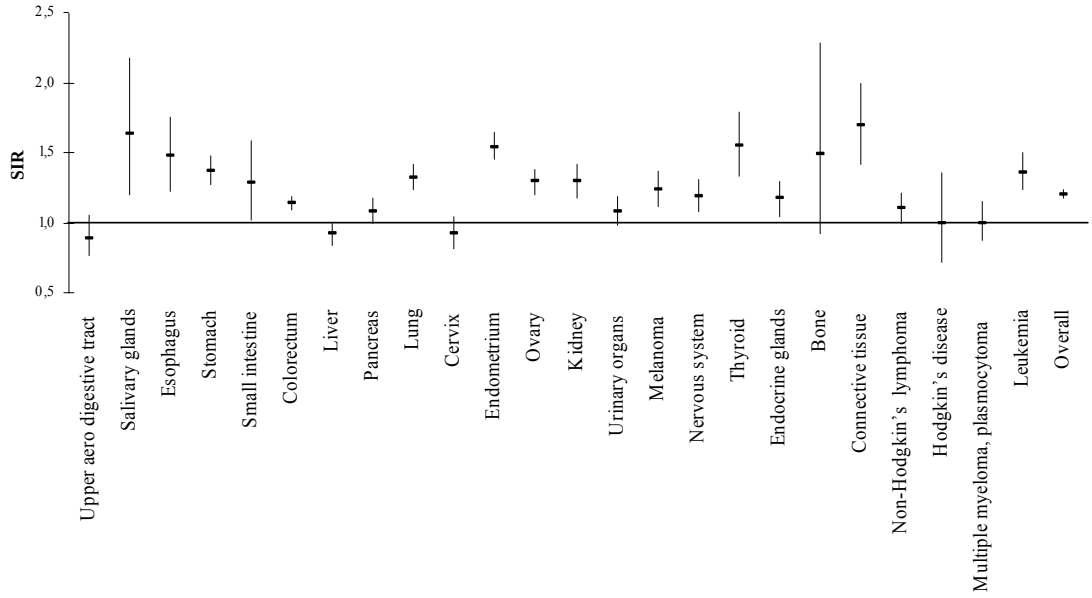


Figure 15. Standardized incidence ratios (SIR) and 95% confidence interval of second primary cancers among women (n=10725) diagnosed with breast cancer between 1958 and 2000.

For the majority of second primary cancers, the risk decreased with increasing age at time of breast cancer diagnosis and the overall SIR for women < 50 years of age was 1.64 compared to 1.20 among those above this age. A significant difference in risk when comparing younger and older women at the time of breast cancer diagnosis was seen in esophagus (SIR=2.63 vs. 1.35), stomach (SIR=2.15 vs. 1.30), lung (SIR=2.30 vs. 1.11), ovary (SIR=1.98 vs. 1.11), connective tissue (SIR=3.11 vs. 1.42), particularly thorax and upper limbs (SIR=7.57 vs. 3.06) and non-Hodgkin's lymphoma (SIR=1.49 vs. 1.04). For cancer of the endometrium and acute lymphatic leukemia the tendency was the opposite, but the difference was not statistically significant.

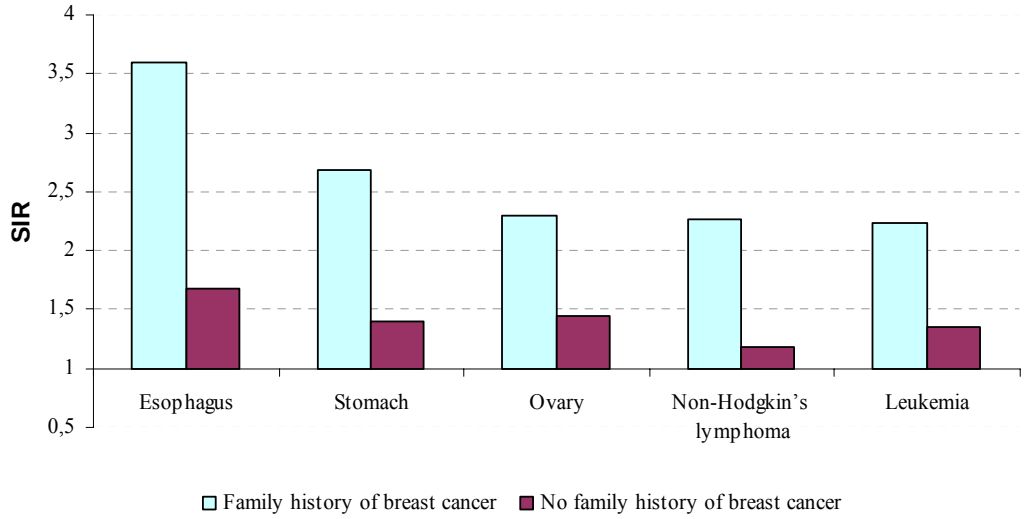


Figure 16. Standardized incidence ratios (SIR) for second primary malignancies following breast cancer diagnosis in women with and without family history of breast cancer and with a significantly increased ratio between these two groups.

A family history of breast cancer significantly increased the risk of being diagnosed with a second primary malignancy. The most elevated risk was seen in the esophagus, stomach, ovary, non-Hodgkin's lymphoma and leukaemia (Figure 16). Esophagus, non-Hodgkin's lymphoma, and stomach showed an approximately 2-fold higher risk in women with a family history of breast cancer compared to those without.

Table 3 shows that young age at breast cancer diagnosis as well as family history of breast cancer significantly increased overall risk of being diagnosed with second primary malignancy. The greatest risk was observed for young women with a family history of breast cancer (SIR=1.9), whereas the smallest risk was seen for older women without a family history of breast cancer (SIR=1.26). This difference was even more pronounced in the follow-up period 1-9 years after breast cancer diagnosis (SIR=2.10 vs. SIR=1.23).

Table 3. The overall standardized incidence ratios (SIR) in relation to family history of breast cancer, and age at breast cancer diagnosis.

Family history of breast cancer	Age at breast cancer diagnosis <50 years Obs	SIR (95% CI)	≥50 years Obs	SIR (95% CI)
	Follow-up time 1-9 years			
Yes	53	**2.10** (1.57-2.70)	125	**1.36** (1.13-1.60)
No	418	**1.59** (1.44-1.75)	2369	**1.23** (1.18-1.28)
	Follow-up time ≥10 years			
Yes	46	**1.81** (1.33-2.37)	65	**1.62** (1.25-2.04)
No	734	**1.57** (1.45-1.68)	1142	**1.25** (1.18-1.32)
	Total			
Yes	100	**1.92** (1.56-2.31)	204	**1.44** (1.25-1.64)
No	1181	**1.58** (1.49-1.67)	3808	**1.26** (1.22-1.30)

Obs=number of observed cases; bold: statistically significant; CI= Confidence interval

Unpublished data

The accuracy of cancer registration is of crucial importance for epidemiological studies of cancer incidence and risk calculations. In studies of second primary malignancies after any primary cancer, validity of registration is of no less importance.

We performed a validity test of the Swedish Cancer Register. Of the 182 women diagnosed with breast and subsequent lung cancers identified in Stockholm County between 1958 and 2000, we found 94 tumour cell blocks from both breast and lung cancer. To establish the reliability of cancer registration of second primary lung cancer, histopathological slides from 94 breast and 94 lung cancers were re-examined. The histology notified in the primary pathology reports for lung cancer were compared with re-classification of the lung cancer tumour tissue, and also compared with a breast cancer tumour cell block of the case. The thyroid transcription factor 1 (TTF1) status, estrogen and progesterone receptor status analysis were performed to distinguish a possible breast cancer metastasis. The TTF1 is a highly specific marker for primary lung adenocarcinomas, and is recommended to be included in a panel of antibodies for the differential diagnosis between primary and metastatic adenocarcinomas of the lung.[198]

According to existing primary pathological reports and the second histopathological evaluation in this study, 16 % (15 of 94) second primary lung cancers were, after re-examination, classified as possible breast cancer metastases. When time between breast and lung cancer was considered, 23% (10 of 43) of the possible breast cancer metastases occurred less than 10 years, and 10% (5 of 51) after more than 10 years after breast cancer diagnosis.

Our result of 16 % possibly incorrectly registered second primary lung cancers in women previously diagnosed with breast cancer is in agreement with an earlier study of second primary malignancies in ovarian cancer patients by Bergfeldt at al.[199]

Table 5. Distribution of the re-evaluated tumours of the second primary lung cancers in relation to years between breast and lung cancer diagnosis.

	Follow-up		
	<10 years	≥10 years	Total
Primary tumor	33	46	79
Possible breast cancer metastases	10	5	15
Total	43	51	94

DISCUSSION

Cancer is a curable disease for many and a chronic illness for most. With continued advances in strategies to detect cancer early and treat it effectively along with the aging of the population, the number of individuals surviving many years beyond a cancer diagnosis can be expected to continue increasing. Survival from cancer has seen dramatic improvements over the past 3 decades, mainly as a result of advances in early detection, therapeutic strategies, and the widespread use of combined therapy (surgery, chemotherapy, and radiotherapy).[200, 201] The 5-year relative survival rate after a diagnosis of cancer has increased steadily to reach almost 64% in the mid-1990s.[202]

Even though the treatment for cancer is beneficial and often lifesaving, most of the therapies for cancer are associated with a spectrum of complications that vary from minor and treatable (such as breast edema, scar retraction, and telangiectasia)[96, 109] to serious, or occasionally, potentially fatal.[103, 108, 110, 111, 113, 116, 203] The major non-malignant cause of death is mortality from cardio-vascular disorders, especially in the older age groups with early breast cancer.[103]

Late effects of breast cancer treatment are being increasingly documented as more women are surviving their disease. The most serious of the late effects are second primary malignancy arising as a result of genetic predisposition, and/or the mutagenic effects of therapy.

In *Paper IV,* the risk of second primary malignancy after breast cancer was studied. Women with a first primary breast cancer had a 20% increased risk of developing a second primary malignancy other than breast cancer. The association between breast cancer and other tumors is well documented,[58, 98, 122, 124, 125, 204, 205] and the reported overall risk varies between 20 to 30% for second primary non-breast cancers. In our study as well as in many others studies, the risk was higher among younger women.[58, 124, 205, 206] This pattern may reflect a genetic predisposition to develop multiple tumors and/or susceptibility to the carcinogenic effect of the breast cancer therapy. We found that family history of breast cancer and young age at breast cancer diagnosis were the strongest risk factors for selected cancer sites. It is well know that cancer treatment can cause second primary malignancies.[126] Examples include acute leukaemia from chemotherapy, and these and other cancers from radiotherapy.[17, 126] We were not able to identify potential treatment effects because this information is not given in the cancer register. However, our findings can generate hypothesis for future studies to test.

The risk of second solid cancers appears to increase with time after diagnosis,[1] which appears to be the major risk to long-term survivors of breast cancer. In Papers I and III, the risk for second primary lung cancer was studied. In the *first paper,* all Swedish women with breast cancer and second primary lung cancer were studied. Overall, an increased risk of lung cancer was seen >5 years after breast cancer diagnosis. Moreover, a significantly decreased risk of lung cancer within the first five years after breast cancer was found in women >60 years of age when diagnosed with breast cancer. Lungs are a

common site of metastasis from breast cancer, and therefore this decreased risk could be due to underreporting since a finding of an irregularity at pulmonary x-ray examination among breast cancer patients could be interpreted as metastases and not adequately diagnosed. Another explanation could be that radiotherapy for breast cancer has a therapeutic effect on pre-clinical conditions in the lung, and thereby postpones the manifestation of lung cancer in breast cancer patients. It could also be that tamoxifen has a protective effect on the development of lung cancer since hormonal treatment is more common in the elderly.

The prevalence of Swedish female smokers in age group 45 to 64 is currently 22%. This can be compared to all women (age 16-84), where the smoking prevalence is 17.5%.[207] Women between 45 to 64 years of age are at a high risk of being diagnosed with breast cancer. At the same time this group has the highest prevalence of daily smokers. We have shown that women with breast cancer have an increased risk of second primary lung cancer that could be related to treatment of breast cancer, especially radiotherapy and smoking. However, this study was register-based and we did not have individual data for the studied cases.

In *Paper III* we used detailed information on radiation dose and smoking to assess the risk of lung cancer. The origin of this study was the finding in study I of increased risk of lung cancer, and possible effect of radiotherapy and smoking. Our results show that women who received radiotherapy had an increased risk of developing lung cancer on the same side as breast cancer after at least 15 years of follow-up. This finding is in agreement with other studies which showed that radiation induced lung cancer develops after a substantial latency time.[58, 116, 148, 157, 158, 208] Notably, women who did not receive radiotherapy were not found to have an increased risk of lung cancer. Partial mastectomy, followed by radiotherapy is currently the most popular treatment.[81] We have shown that the lowest mean dose to the ipsilateral lung (lung on the same side as the breast cancer) was in the later part of our study, and was in women who were treated with partial mastectomy. However, newer radiotherapy using intensity modulated radiation therapy, might actually be increasing the risk for second primary malignancy.[209, 210] The goal of this methodology is to decrease doses to surrounding normal tissue and reduce radiation complications. Nevertheless, some clinicians are concerned that the risk for second primary cancer persists or is worse, because a greater volume of tissue is radiated at doses still considered to be potentially carcinogenic.[209, 211-213]

Previous studies have shown that the risk of second primary lung cancer among non-smoking women undergoing radiotherapy for breast cancer have a 2-3-fold risk of lung cancer, and 30-fold increased risk when the women was a smoker (versus 13-20 for lung cancer without radiotherapy).[158, 214] We found that the effect of radiotherapy was restricted to smokers, because no effect was seen in non-smoking women.

Validation of the 94 lung cancer tumor tissues included in this study showed than 10% of cases with follow-up of more than 10 years after radiotherapy for breast cancer could

actually be metastases of breast cancer. This should not be a problem in case-only design, but should be taken in consideration in the ongoing case-control study.

The quality of the exposure information is extremely important in all epidemiological studies. This information is often obtained from patient records, since data from other sources are not available. When studying the risk of lung cancer, information on smoking history is crucial. Mailed questionnaires are widely used to collect data in health research and are often the only financially possible option when collecting information from large, geographically spread populations. In *Paper II* we used a mailed questionnaire to collect smoking information from next-of-kin and living patients. The overall response rates in our study were 89% and 93% respectively. We have no information about the individual reasons for not returning the questionnaire. Whether and how the length of the questionnaire affects the response rate is a very important issue in most research areas, since more information might be obtained by using a longer questionnaire. On the other hand, short questionnaires probably increase the response rate.[215, 216] In addition, the topic of the study and how it concerns the participants may to some extent influence the response rate. In our study, the questionnaire send to next-of-kin was only one page. This small size could positively affect the high response rate. We found that the time interval between patient's death and the contact with next-of-kin did not affect the response rate. Interestingly, even when a long time had past since a women's death, response rate from next-of-kin was not affected. Our findings show that time did not affect the memory of next-of-kin with regards to patients overall smoking habit. However, the quantitative smoking information was of less quality. Patient's smoking history was missing in over 40% of patient records. The reason could be that there is no clear association between smoking and breast cancer, and the clinician does not consider this information relevant. In conclusion, health researchers using the information from next-of-kin and mailed questionnaires can improve the quality of their research.

Cancer patients are generally at increased risk of second primary malignancies. Hodgkin's disease is a cancer site where modern therapy has greatly improved survival. Second cancers are currently the primary cause of death among Hodgkin's disease patients.[217, 218] Both radiotherapy and/or chemotherapy are included in the treatment of Hodgkin's disease. In a large population-based study of Hodgkin's lymphoma patients, the overall risk of second primary cancers was 2.3 for women.[219] In our study, Hodgkin's disease patients have an almost 2-fold higher risk of being diagnosed with a second primary malignancy. However, it is important to remember that there are many differences between these two cancer sites. For instance, the average age in our study was 63 years, compared to 37 years among Hodgkin's disease patients. It is well known, that young age at cancer diagnosis is a risk factor, but also that younger patients tend to receive more aggressive treatment.

In this thesis, we have studied women who were diagnosed with breast cancer and later developed second primary malignancies. Why some patients are diagnosed with multiple malignancies have several potential explanations such as increased medical surveillance, previous therapy, shared etiological factors, life style factors, and genetic predisposition for development of multiple tumors. By studying risk of a second primary malignancy in relation to age at first cancer and follow-up (Paper I and IV), and also the influence of family history, and the interaction between some of these factors, we were able to speculate on the causative factors. We have shown that diagnosis of breast cancer and family history of breast cancer increases the risk of certain sites of second primary malignancies. We have been able to establish association between radiotherapy treatment for breast cancer and second primary lung cancer, and the effect of smoking (Paper III). Finally, the completeness and quality of the information on tobacco use is most important when studying the risk of lung cancer. We have shown that next-of-kin can provide reliable information on lifetime smoking status, and should be considered in studies where information on tobacco use is missing.

Clinical implications

The established and suggested associations between a first and second primary malignancy in breast cancer patients should be considered in clinical follow-up. The elevated risk for second primary malignancies appears to be protracted over time, and therefore a life long observation of these patients seems justified.

We convincingly show that radiotherapy for breast cancer increases the risk of the ipsilateral lung and that this risk is completely confined to women who smoked at time of radiotherapy. These findings raise two questions: are there subsets of women who do not benefit from radiotherapy and could smoking cessation decrease the risk? The benefits of radiotherapy most certainly outweigh its harmful effects for many women with breast cancer. Whether this is also true for very early post-menopausal breast cancers with a low metastatic potential remains uncertain. However, our results strongly suggest that women with breast cancer, especially those selected for radiotherapy, should be encouraged to give up smoking.

There are many of examples where identifying cancers that occur as multiple primaries can be useful. For instance, women with histories of uterine or ovarian cancer have been found to be at increased risk of breast cancer,[126, 220] which can lead to genetic testing or routine screening of the women at risk.[126, 130] In addition, by comparing treatment profiles according to whether second primaries were experienced, carcinogenic effects of treatment can be identified and safer treatment options adopted.[126]

Future research

Currently, a nation-wide Swedish case-control study of women with both breast and lung cancer is being conducted. The large sample size will allow more detailed analyses also of other factor, such as chemotherapy. A molecular part of this study is ongoing at Lombardi Cancer Center,A molecular part of this study is ongoing at Lombardi Cancer Center, Georgetown University Medical Center, US. The main issue is to determine the relationship of estrogen receptor positivity in the primary breast and second primary lung cancer of women treated with radiotherapy for breast cancer, and to reveal the *p53* tumor suppressor gene mutational spectra in the primary breast and second primary lung tumors of breast cancer radiotherapy treated women.

The future of breast cancer treatment will be determined by patient characteristics, as well as tumor biology. With further improvement of molecular diagnostics, the care of cancer patient might be individualized: treatment should be reserved for patients at greatest risk of recurrence, and therapy would be chosen according to its ability to target the abnormalities of a particular cancer while minimizing the effects on normal tissues.

Conclusions

- Women diagnosed with breast cancer had a 20% increased risk of developing a second primary malignancy, and the risk for all cancers together did not change over follow-up period. However, large differences were noted for selected second primary cancers, probably reflecting the influence of shared etiological factors and therapy.
- Women with a breast cancer diagnosis before the age of 50 years and women with a family history of breast cancer had elevated risks of developing a number of second primary cancers. This may reflect a genetic predisposition towards developing multiple tumours and/or susceptibility to the carcinogenic effect of breast cancer therapy.
- Radiotherapy for breast cancer significantly increases the risk of lung carcinoma more than 10 years after exposure in women who smoked at time of breast cancer.
- Next-of-kin can provide reliable information with almost perfect agreement with patient records on lifetime smoking status, and should be considered in studies where information on smoking history is lacking.

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