IMPACT OF POST-DIAGNOSIS SMOKING ON CANCER SURVIVAL

A DISSERTATION
SUBMITTED TO THE FACULTY OF THE GRADUATE SCHOOL
OF THE UNIVERSITY OF MINNESOTA
BY

Li Tao

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

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August, 2012

Acknowledgements

I would like to first acknowledge the members of my dissertation committee. My committee members invested considerable amount of valuable time into my training and the development of this work. It was an honor and privilege to have the opportunity to learn from such great faculty members. This dissertation would not have been possible without the inspiration and persistent guidance of my advisor, Dr. Karen Kuntz, or the individual involvement, critiques, recommendations, and assistance of Dr. Beth Virnig, chair of my committee. I would like to thank Dr. Kristin Anderson for her invaluable and gracious support ever since I started developing an interest in cancer research; and to thank Dr. David Radosevich for his insightful comments and warm encouragement along the journey.

In particular, I am very grateful to Dr. Jian-Min Yuan. I have been working with him for the past three years, which has been a wonderful and important period of my academic life. Dr. Yuan enlightened me with consistent guidance, constructive directions, constant encouragement, extreme patience, as well as life lessons and genuine friendship. His availability, accessibility, and dedicated work ethic were exactly what I needed to begin, maintain, and complete research projects including this dissertation work. I would like to send a special and sincere Thank You to him for being such a kind and supportive person to his students and staff, myself lucky being one of them.

My appreciation also goes to the faculty members and coworkers who have assisted me throughout this dissertation process. Dr. Kim Robien was generous and kindly supportive for my analysis. Renwei Wang was always helpful and patient with all

the detailed questions that I had during data processing. Dr. Bradley Buchner and Dr. Xingfu Chen helped with technical writing of the dissertation. I acknowledge all other friends and coworkers for their help in the process of this dissertation work.

Special gratitude goes to my family. My parents and my husband always encourage me to be a hard worker, to pursue my goals, and to overcome stresses and strains that accompanied my academic aspirations. My parents, my husband, my son, and all other family members make sure I have all the support and love to accomplish this dissertation research and beyond.

Abstract

Cancer is a leading cause of death. Cigarette smoking is the most important preventable cause of cancer-related death. The impact of smoking on cancer survivors in the post-diagnosis setting is not well studied. In this dissertation, the association between cigarette smoking after cancer diagnosis and risk of all-cause death was examined among male cancer patients of the Shanghai Cohort Study and female cancer patients of the Iowa Women's Health Study. Cox proportional hazard regression models and Kaplan-Meier method were used to compare mortality risk and survival in association with post-diagnosis smoking. Following the two cohort analyses, estimates of the proportion of death that is due to cancer, the total remaining life expectancy for patients who quit smoking and patients who continue to smoke after cancer diagnosis, as well as gains in life expectancy due to post-diagnosis smoking cessation were provided by performing a decision analysis. Findings from this dissertation work suggest that smoking cessation even after cancer diagnosis may reduce the risk of death and extend remaining life expectancy for both male and female cancer patients. The magnitude of the effect of post-diagnosis smoking cessation varies by cancer type, gender, age and stage at diagnosis. The encouragement of cancer patients to quit smoking during clinic visits at or after cancer diagnosis could be an effective strategy to improve the prognosis of cancer patients. Findings of this dissertation fill a gap in existing knowledge base regarding impact of smoking among cancer survivors and have important public health implications to patients, healthcare providers, policy makers, health insurance and pharmaceutical identities, as well as the general public.

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CHAPTER 1: INTRODUCTION/LITERATURE REVIEW

Cancer is a leading cause of death both worldwide and in the United States [1]. Tobacco use is the most important known cause of cancer incidence and cancer-related death, accounting for 25% of all cancer cases in men and 4% in women worldwide [2], and approximately 30% of all cancer deaths in the U.S. [3,4]. There is sufficient evidence to infer causal relationships between smoking and increased risk for 10 types of cancers, including bladder, cervical, esophageal, kidney, laryngeal, acute myeloid leukemia, lung, oral, pancreatic, and stomach cancer [5]. In addition to higher risk, higher rates of *mortality* were found for smoking-related cancers as compared to non smoking-related cancers. For instance, in the U.S. 5-year relative survival rates for lung, pancreatic, and stomach cancers were 15%, 5%, and 23%, respectively, whereas 5-year relative survival rates for breast, colorectal, and prostate cancers were 88%, 63%, and 97%, respectively [6].

Despite the well-established harmful health effects of smoking and in spite of enormous efforts to reduce the prevalence of cigarette smoking, 21.5% of men and 17.9% of women in the U.S. are still current smokers (total 19.3%) [7]. While smoking prevalence has declined since the 1970s, the decline has slowed, and smoking prevalence has not changed significantly since 2004 [3]. Smoking has been estimated to be responsible for an average of 14 years of life-loss (13.4 years for male smokers and 14.3 years for female smokers), $96 billion in direct medical expenses, and $97 billion in lost productivity annually in the U.S. [4,8,9]. Furthermore, smoking prevalence in some other countries is still very high. According to the Global Adult Tobacco Survey (GATS), a cross-sectional survey of tobacco use among adults carried out by 14 most populated countries in collaboration with the World Health Organization, reported that smoking prevalence was

as high as 39.1% (60.2% of men and 21.7% of women) in Russian Federation and 28.1% (52.9% of men and 2.4% of women) in China [10] as of 2010. If current smoking patterns continue, the annual tobacco-attributable death toll from tobacco will rise from 4.6 million per year in 2000, to more than 10 million per year by 2030 worldwide [11].

At the same time that smoking-related cancer deaths are increasing, innovations in medical technology have led to earlier diagnoses and improved treatment for cancer, resulting in increased numbers of cancer survivors. Of the 11.7 million people living with cancer in 2007, 4.7 million (40%) have been diagnosed and have been living with cancer for 10 or more years [12]. In this growing population of cancer survivors, smoking persistence is as high as 20.2% in the U.S. [13]. Among cancer patients who are smokers, only a fraction of patients receive formal smoking cessation counseling from their physicians or healthcare providers at the time of diagnosis, during treatment, or on follow-up visits [14]. Less than half of the current smokers at the time of diagnosis eventually quit smoking after the diagnosis [14]. Only a few smoking cessation programs tailored to cancer patients were attempted and the efficacy of these programs was not consistent [15]. Clearly, there is considerable room for improvement of tobacco control in the post-cancer diagnosis clinical setting. However, to guide clinical practice in order to develop smoking cessation programs targeting cancer patients during surviving years, solid evidence of survival benefits of quitting smoking for cancer survivors is needed. Central to this dissertation is the premise that the extraordinary burden of cancer-related mortality caused by tobacco use can be reduced given that the pandemic is entirely manmade.

1.1. Hypothesis and outline of the dissertation

Although strong and consistent evidence supports the relationship between smoking cessation and the decreased risk of cancer incidence and cancer-related mortality, there are insufficient studies that examine the impact of post-diagnosis smoking on survival outcomes for cancer survivors. Smoking cessation may lower cancer mortality by preventing or delaying cancer from developing as well as by reducing mortality rate for those who already have cancer. In this dissertation, I will focus on the latter, which is the association between post-diagnosis smoking cessation and cancer mortality. I hypothesize that cigarette-smoking after cancer diagnosis is associated with increased mortality risk for cancer survivors. I will only focus on adult male and female cancer survivors who have been diagnosed during middle- to old- age, which is after the age of 55 for analyses of this dissertation.

In this chapter, I will begin with an introduction and a review of literature for evidence of the relationship between smoking and cancer incidence and prognosis, the health effects of pre- and post-diagnosis smoking cessation, the barriers of smoking cessation for cancer patients, and decision analyses approaches to estimate the effect of smoking. Following an overview introduction of method and materials of the two cohorts in chapter 2, the hypothesis of the dissertation will be tested in two independent cohort analyses. Based on results of the two analyses and published data, estimates of the proportion of death that is due to cancer, the total remaining life expectancy for patients who quit smoking and patients who continue to smoke after cancer diagnosis, as well as gains in life expectancy due to post-diagnosis smoking cessation will be provided by

performing a decision analysis in the third study. The three major analyses in this dissertation are:

1. Impact of post-diagnosis smoking among male cancer survivors in Shanghai, China a cohort analysis, Chapter 3;

2. Impact of post-diagnosis smoking among primarily white female cancer survivors in Iowa, U.S.A., a cohort analysis, Chapter 4;

3. Probabilities of death from cancer and impact of post-diagnosis smoking on life expectancy among cancer survivors: a decision analysis, Chapter 5.

The findings of the three studies complement each other and provide important public health implications. Conclusions of the dissertation will be summarized in chapter 6.

1.2. Tobacco smoking and cancer

1.2.1. Tobacco smoking and cancer

As early as the 1950's, the association between tobacco use and lung cancer risk was established [16]. The important role of cigarette smoking in the development of lung cancer and other diseases reported by the first Surgeon General's report in 1964 prompted a wide range of research interests as well as public awareness about the health effect of tobacco smoking [17]. Since then, evidence of diseases that are associated with tobacco has grown substantially, supported by research conducted in multiple health-related fields.

More than 100 case-control studies and 50 cohort studies have shown that tobacco smoke is carcinogenic to the lung in humans [18]. Smoking is the primary risk factor for

lung cancer. In the U.S., about 90% of lung cancer in men and 80% of lung cancer in women is attributable to cigarette smoking [19, 20]. Relative risk of death from lung cancer among current smokers compared to lifelong nonsmokers is about 23 times greater for men and 13 times greater for women [21]. The increased likelihood of lung cancer is proportional to the duration and intensity of the individual's smoking history [22]. Although smoking is more strongly associated with lung cancer than with any other types of cancer [5], the body of evidence for the relationship of smoking and other cancers is growing fast. Collective evidence has shown that cigarette smoking is a causal factor for cancers of the urinary bladder [23-26], cervix and uterus [27-30], esophagus [20, 31, 32], kidney and other urinary tract [33-36], larynx [20, 37-40], stomach [41-46], lip, oral cavity and pharynx [47-49], pancreas [20, 50-52], as well as acute myeloid leukemia [53-55]. The association between smoking and the above cancers is thought to be correlated with the duration and intensity of smoking. The IARC and the Surgeon's General report of 2004 makes conclusive statements that infer causal relationships between smoking tobacco products and the above 10 types of cancer [1, 5, 15].

Evidence of smoking as a risk factor for some other cancers is controversial and inconsistent. The relation between smoking and breast cancer risk has been extensively studied. Existing evidence is strongly against any major overall relationship. No substantial association between smoking and breast cancer risk has been shown, overall or within subgroups defined by menopausal status, estrogen receptor types or time to initiate smoking before first full-term pregnancy [56-58]. Although it is plausible that carcinogenic compounds to the mammary gland may be more actively taken up and metabolized by smokers, the relationship between smoking and breast cancer risk has been difficult to establish, probably because of the low carcinogen dose [59]. In fact,

smoking may have an anti-estrogenic effect to obscure carcinogenicity of tobacco smoke, which may result in a protective effect on breast cancer risk [60, 61]. For other cancer sites, the uncertainty about confounding with other main risk factors is a major issue in examining the association between smoking and cancer risk. In general, heavy smokers have an elevated risk for colorectal adenomatous polyps, but the induction period of cancer in the large bowel may be extraordinarily long compared with the progression of other cancers [62-64]. Studies have consistently shown no association between cigarette smoking and prostate cancer incidence [65, 66] but suggested a slightly higher prostate mortality rate among smokers [67, 68]. For three other cancer sites, liver, nasal cavity/paranasal sinuses, and nasopharynx, the IARC has designated a strong relationship with smoking [1], but the Surgeon General does not currently include them as causally related to smoking [5].

1.2.2. Effect of smoking on carcinogenesis and cancer prognosis

Cigarette smoke contains over 4000 characterized compounds, 250 of which are known to be harmful, and at least 60 of which are carcinogens [69, 70]. The most potent of these carcinogens are polycyclic aromatic hydrocarbons and nicotine metabolites. Several pathways of tobacco causing cancer have been proposed (reviewed in ref. [71]). Many carcinogens may form DNA adducts in the human body which ultimately lead to tumor growth. Tobacco carcinogens may also trigger unfavorable genetic responses which stimulate tumor growth at many sites, such as lung and bladder [72, 73]. Tobacco compounds are the major pre-carcinogenic resource of substrates for certain isoenzymes in the metabolic pathways that prompt a carcinogenic effect. In addition, cigarette smoking also induces angiogenesis, capillary growth, and dysfunction in coronary and peripheral

arteries [5, 74, 75], resulting in increased risk for many other diseases, such as cardiovascular disease and diabetes. Therefore, given the biological mechanisms of tobacco carcinogenesis, it is plausible that the termination of tobacco exposure, even after cancer diagnosis, may stop, or slow the biochemical and genetic progression of tumors, as well as decreasing the risk of other diseases [76, 77].

Existing evidence is not very consistent about whether smoking before cancer diagnosis has an impact on the prognosis of cancer. Some studies have reported that compared to nonsmokers, smokers were likely to be diagnosed with a more aggressive lung cancer [78, 79], have lower 5-year survival rate [80], and have an increased comorbidity risk [81], while other studies suggested differently [82, 83]. Cigarette smoking was also suggested by some studies [84-86] to be strongly associated with an increased risk of an invasive bladder cancer as opposed to a low-grade superficial bladder cancer. Yet other studies were not able to detect similar association [87-89].

A few studies examined the impact of a smoking history on prognostic factors of other cancers. For example, in colorectal cancer patients, microsatellite instability was more likely to occur among smokers than among nonsmokers [90]. Breast cancer patients who had ever smoked did not suffer from higher grade or larger sized tumors, but had an overall slightly poorer survival compared to nonsmoking breast cancer patients [91]. More lifelong nonsmokers than current smokers had survived beyond 5 years among cervical cancer patients [92].

1.3. Smoking cessation

In response to mounting and irrefutable evidence of the harmful health consequences of tobacco use, many organizations have established tobacco control

policies. Federal and State governments, for example, have increased tobacco taxes, and enacted various legislations prohibiting smoking in work places as well as public places (e.g. supermarkets, restaurants, and bars) [93-97]. Other organizations, such as public and private colleges, have also restricted or prohibited smoking on campus [98, 99]. These and other similar efforts have broadly encouraged smoking cessation-related behaviors in the U.S. [100-103]. The impact is noticeable. Since the release of the landmark 1964 Surgeon General's report about the relationship between smoking and many diseases, more than 38 million Americans have successfully quit smoking, and nearly half of all living adults who ever smoked have tried to quit [104], with the vast majority being self attempts without the assistance of formal intervention programs or pharmacotherapy [8]. In 1990, a Surgeon General's report summarized the beneficial consequences of smoking cessation for different populations defined by gender, age, and other characteristics [104]. In the U.S., it is estimated that the general public gained an average of 15 years of life as a result of antismoking campaigns–induced decisions to quit or to not start to smoke in the first place [105].

However, smoking prevalence and tobacco-attributable mortality is still high in the U.S. Smoking prevalence is also surprisingly high among cancer survivors in spite of the established causal relationships between smoking and many cancers. Therefore, although public awareness of the health effects of smoking has increased substantially, important gaps in knowledge of the impact of smoking and smoking cessation still exist, especially among cancer survivors. Furthermore, it is essential to study the effect of smoking cessation among people who already have cancer. Many cancer patients and their healthcare providers might figure that it is not desirable and worth the effort to stop

smoking at a time when the damage of smoking is done and that patients have already

been diagnosed with cancer. It will be extremely important and meaningful to know that

smoking cessation after diagnosis might considerably improve survival outcomes for

these cancer patients.

1.3.1. Health benefit of pre-disease diagnosis smoking cessation

Smoking cessation has major and immediate health benefits for men and women

of all ages. The excess risk of death from cigarette smoking may decline soon after

quitting and continue to fall in the long run [1, 104].

Many detrimental effects of tobacco smoking such as increased cancer risk and

cancer mortality can be avoided or reduced by smoking cessation or smoking reduction

[22, 106]. As the first neoplasm causally linked with smoking, lung cancer has been the most

thoroughly studied cancer with respect to the benefits of smoking cessation [5]. Smoking

cessation reduces the risk of developing a primary tumor of all major histological types of

lung carcinoma, with the greatest reduction seen in small cell and squamous cell tumors

[107-111]. Former smokers experience a higher risk of developing lung cancer compared with

never smokers; but compared with current smokers, former smokers have a 20- to 90-

percent reduction in lung cancer risk [22, 112-114].

As cigarette smoking has been established as an important risk factor for many

other cancer sites, evidence of health consequences of cessation is also growing. Smoking

cessation reduces the risk of bladder cancer but the effect is not proportional to the

duration of abstinence [24, 26, 115]. Some studies suggested that the reduction in risk of

bladder cancer may occur within the first 2-4 years after stopping, but did not continue to

decline with increasing time since quitting [23, 26]. Risk of colorectal mortality is marginal

significantly higher for current smokers than for former smokers [116-118]. Risk of cervical

cancer is lower among former smokers than that of current smokers. Risk reduction may

occur rapidly after cessation: after the first year of abstinence, former smokers had lower

cervical cancer risk than current smokers [119-121]. Little consistency has been reached

about the health effect of smoking cessation on other cancer sites. Confounding effect

from risk factors other than smoking remains the major issue.

Besides cancer, a decreased risk and mortality rate following smoking cessation

was suggested for other diseases, including the coronary heart disease and vascular

diseases [1]. People who have ever smoked have about twice the risk of developing and

dying from coronary heart disease and stroke compared with lifetime nonsmokers [77, 122,

123]. The excess risk of developing cardiovascular diseases decreases after only 1 year of

smoking abstinence and after 15 years of abstinence, the risk was similar to that of

lifelong nonsmokers [104].

1.3.2. Smoking prevalence and quit rates of cancer patients

It is expected that the diagnosis of cancer serves as an incentive for patients to

quit smoking. Patients diagnosed with smoking-related cancers may be more likely to

quit after the cancer diagnosis than patients diagnosed with non smoking-related cancers

[124, 125]. The incentive of the cancer diagnosis, however, does not have a large impact on

smoking prevalence among cancer patients. National surveys suggested that smoking

prevalence in cancer survivors was similar to individuals without a history of cancer. The

survey showed that 20.2% of cancer survivors and a comparable 23.6% of the general

population without a self-reported history of cancer eventually quit smoking [13]. Among

all cancer survivors, those who were under the age of 40 had a substantially higher rate of

smoking compared to the non-cancer populations; whereas smoking prevalence was not different between cancer patients and non-cancer populations after the age of 40 [126]. Smoking cessation rate among current smokers at diagnosis range from 6% to 96% for lung and head and neck cancer patients, 50% for bladder cancer patients, and only 4% for breast cancer patients [127-132]. An estimated 13% to 20% of lung cancer patients still smoke during or right after treatments of surgery or chemotherapy [133, 134]. Reasons for the broad range and heterogeneity may be that some studies collected data on smoking status retrospectively; some hospital- or clinic- based studies have selection bias, sample sizes, and a one-time cross-sectional measurement of smoking status at the time of diagnosis or treatment without follow-up measurements. For long-term cancer survivors, the patterns of smoking behavior alterations, including initiation, relapse, and quit, on health outcomes are unknown [135].

1.3.3. Impact of post-cancer diagnosis smoking

The health benefit of smoking cessation at- or post- cancer diagnosis is uncertain. The majority of the existing evidence about the impact of continued smoking is focused on consequential cancer treatment efficacy within a relative short period of time for lung and head and neck cancer patients. Treatment-related adverse events of continued smoking specifically for lung or head and neck cancer patients include increased complications from general anesthesia, increased risk of severe pulmonary complications, detrimental effects on wound healing, reduced radiation treatment efficacy, increased toxicity and side effects of radiation and chemotherapy, immune suppression, weight loss, fatigue, pulmonary and cardiac toxicity from chemotherapy, increased incidence of infection, and increased probability of cancer recurrence or occurrence of a secondary

tumor [15, 136-143]. The impact of persistent smoking on cancer patients' general health includes lower quality of life, higher level of usual pain, and poorer general health and social functioning compared to nonsmoking patients [144-148]. Some studies, however, did not detect any negative health consequences of smoking after diagnosis for lung cancer patients [149, 150].

A few studies have examined the impact of post-diagnosis smoking for other cancer patients. Women with breast cancer who continued smoking after radiation treatment had a significantly increased risk of developing a subsequent lung cancer, but the interaction effect of radiotherapy and smoking was most likely the cause ([151-155], reviewed in ref. [156]). Patients with tobacco-associated superficial transitional cell carcinoma of the bladder had no significant differences of occurrence for adverse events (disease progression or other urinary tract tumor) between nonsmokers and the continued smokers after diagnosis [157].

Studies assessing the association between smoking after cancer diagnosis and survival outcomes are sparse. A few hospital- or clinic- referral based studies enrolled and followed early stage lung cancer patients who were current smokers before diagnosis and received concurrent chemotherapy, with or without radiation therapy. Except for one study [132], no significant differences in risk of all cause mortality of persistent smokers compared to quitters during the period of follow-up were reported for early stage small cell lung cancer patients [136, 149, 150, 158]. Patients diagnosed with early stage non-small cell lung cancer and who received thermotherapy had no difference in median survival time between continued smokers and nonsmokers up to 12 months after diagnosis [146, 159-161], with significant difference reported in one study [110]. Another study of head and neck

cancer patients suggested at 2 years after diagnosis, survival rates of patients who had quit smoking after diagnosis approached that of patients who never smoked, and that the persistent smokers had the poorest survival rates [162]. Overall, these hospital-based chart-review studies involved a relatively small number of patients, to look at the interaction effect of treatment and smoking on cancer survival. Design for these studies was subject to potential biases, and conclusions may lack impact and generalizing validity relative to other study designs.

Quit smoking cigarettes after a cancer diagnosis may also reduce mortality risk from other causes, including cardiovascular diseases. Cigarette-smoking is a major cause of coronary heart disease in the U.S. Smokers have a 70% increased death rate from coronary heart disease relative to non-smokers [1]. Also, former smokers have a reduced risk of current myocardial infarction or coronary heart disease death relative to persistent smokers [123]. There have been no studies that address the question of smoking-related cardiovascular disease mortality rate among cancer patients.

It is worth noting that the absolute effect of cancer mortality on survival may diminish with increasing age. Depending on the type of cancer, the remaining life expectancy can be dramatically different. For some cancers, the anticipated life expectancy may be very short, so that the benefit of smoking cessation is reduced. Given that smoking related cancers may have a poorer prognosis and lower life expectancy compared to non smoking related cancers, the smoking related cancers are the ones that are most likely to be affected.

1.3.4. Barriers to successful smoking cessation for cancer patients

Although the impact of tobacco use on disease incidence and mortality has been established, long term abstinence rates among smokers are low. Only approximately 2.5 million of the nation's 45 million smokers successfully stop smoking permanently each year, out of more than 30 million who have tried [1]. In fact, in the U.S., only about 4 -7% of all smokers are able to quit smoking in the long run [163]. The slowly declining rate in smoking prevalence may be attributable to many reasons.

Cancer survivors may face numerous disease or treatment imposed physical, psychological, social, spiritual, and financial issues during the remaining years of their lives. While these issues may mitigate towards cessation of smoking, there may be other issues that push people the other way. Barriers to smoking cessation may include heavy nicotine dependence, lack of strong motivation, fatalistic attitudes about cessation benefits, treatment factors, presence of smokers in the patient's social network, and high psychological distress related to typical survival outcomes and treatment effect [128, 138, 164]. On the other hand, physicians may be less motivated to advise patients who have developed smoking-related cancers to quit because of lack of evidence that a quitter could live longer and a fatalistic belief that the carcinogenic damage is already done [165]. In addition, as of today, efforts to develop strategies and policies for cancer survivorship programs lack strong data regarding the benefits of smoking cessation on survivors. The result is a shortage of successful smoking cessation interventions for cancer patients [166]. A recent study suggests that most institutions fail to offer smoking prevention (61%) or cessation (75%) programs to individuals diagnosed with cancer, and many even lack a referral system (42%) [167]. Therefore, it is clear that there is considerable room for

improvement in promoting a healthy lifestyle of smoking cessation for cancer survivors, which, ideally should be provided by healthcare providers. More formal cessation programs in the post-cancer diagnosis clinical setting are demanded.

1.3.5. Public health and policy implications of post-cancer diagnosis smoking cessation

The topic of this dissertation has important public health implications. With improvements in medical treatments and screening techniques, more patients face an early diagnosis of cancer than ever and the population of cancer survivors is expanding [12]. The need for survival research in this population is growing as well.

Establishing the role of cigarette-smoking in cancer survival will not only help to identify mechanisms for therapeutic purposes, but is also necessary for implementing and enforcing smoking cessation interventions in order for patients to increase their chances to achieve better outcomes. A few randomized controlled trials with longer interventions (longer than 3 months) have shown increased smoking cessation rates for patients who had an acute myocardial infarction [168-170]. Two randomized controlled trial of a surgeon–dentist-delivered intervention for patients with primary squamous cell carcinoma of the upper aerodigestive tract provided personalized risk factor information and strong advice for smoking cessation to both intervention- and control-group patients at medical visits demonstrated that physician's involvement and education during medical care was a powerful tool, although no significantly difference in quit rate was detected between the intervention and control group for both studies [15, 124, 171, 172]. A few non-randomize controlled intervention programs conducted within hospital settings showed some efficacy to bring down the smoking rate among cancer patients. The typical intervention used consisted of in-hospital visits, the provision of educational materials, and several

follow-up telephone calls. Findings indicated higher abstinence rates in the intervention group than in the usual-care control group [173-176]. However, quality of these studies and the abstinence rates varied greatly from study to study.

In addition, smoking cessation interventions for the general population have been considered cost-effective [177-179]. Studies of the cost-effectiveness of smoking cessation among cancer patients, however, are inadequate. I was able to locate only one study that suggested that smoking cessation programs initiated before surgical lung resection are cost-effective at both 1 and 5 years post-surgery [180]. The strong likelihood of substantial medical, psychosocial, and financial benefits of smoking cessation for cancer patients provides a rationale for clinical intervention in smoking behavior. In addition, motivation for smoking cessation is expected to be greatly increased after the diagnosis of cancer, particularly for patients diagnosed with smoking related-cancers [124, 125, 129, 131, 135]. Thus, after a patient is diagnosed with cancer, there is a great "teachable" opportunity that healthcare providers can intervene and emphasize on the importance of quitting smoking at a time when survivors' health is salient [135, 138].

The important role of healthcare providers in counseling patients to embrace healthy lifestyle and preventive behaviors is well recognized [181-183]. Approximately 70% of all smokers visit a physician annually [184], but less than 50% of the smoking patients receive cessation counseling on physician visits [185]. Compared to the general population, cancer patients are more likely to receive treatment on an inpatient basis or for regular or prolonged outpatient visits, so that they are in more frequent contact with healthcare providers during diagnosis, treatment, and follow-up care. Physicians, oncologists, oncology nurses, pharmacists, and other healthcare providers have an opportunity to

engage in tobacco use counseling on an ongoing basis for cancer survivors during these visits [104, 186]. To date, several hospital-based studies examined the efficacy of nurse-managed smoking cessation interventions [173-176], while a few studies tested physician-delivered cessation interventions for adult cancer survivors [171, 172, 187, 188]. Overall, these studies have reported marginal or non-significant difference in quit rate between intervention group and control group. These smoking intervention attempts all emphasized the importance of education materials which should be based on a theoretical framework to match the need of cancer patients. One of the reasons for the unproductive intervention results is the lack of a strong evidence of survival benefits to construct the theoretical framework (reviewed in ref. [186]).

Tailored and targeted smoking cessation programs for cancer survivors are desirable [138]. It is suggested when implementing smoking cessation interventions among cancer survivors, physicians should pay special attention to the physical limitations imposed by cancer treatment. Psychological assistance with mental issues arising in response to cancer diagnosis and medication management for cancer patients should also be properly adjusted [135]. There is considerable demand on the healthcare providers' end to communicate with patients to sustain anticipated effects of smoking cessation during the surviving years after the diagnosis.

As of today, the body of literature is insufficient for healthcare providers to draw a firm conclusion or convey a strong message about the impact of smoking intervention on cancer patients. Patients diagnosed with cancer may have strong disease-related and treatment-imposed individual issues, risk perceptions, and cognitive beliefs regarding smoking, all of which should be respectively addressed by healthcare providers.

Additional research is warranted to assist healthcare providers as well as policymakers to gain appropriate knowledge about survival benefits of smoking cessation so as to facilitate the implementation of personalized intervention on cancer patients.

1.4. Using simulation models to estimate life expectancy gain due to post-diagnosis smoking cessation

A decision analysis using simulation models is another useful approach to estimate the impact of post-diagnosis smoking cessation. Relative hazard rates derived from traditional cohort analysis are derived based on the comparison of the mortality risk for groups of patients defined arbitrarily according to usually self-reported smoking status, with one of the groups being the reference. The relative measures in the multiplicative scale may be difficult to interpret and misleading to the general cancer patients and policy makers.

On the other hand, life expectancy gain is an important and absolute outcome measure of the effectiveness of medical interventions and personal decisions. The gain in life expectancy from a particular decision or intervention is calculated on an additive scale, which may be better understood by patients, healthcare providers, and others. Due to the growing public awareness of the negative health effect of smoking and improved medical screening and treatment techniques, the future burden of cancer is likely to increase with the expected increased life expectancy [189]. Knowing the total remaining life expectancy as a result of different decision about smoking cessation at or after cancer diagnosis is important to patients, their families, as well as healthcare providers and the general public. Therefore, to extend and complete the analyses of impact of post-diagnosis smoking on cancer survivors, estimation for the life expectancy of cancer

survivors who quit smoking and cancer survivors who continue smoking is constructive for better understanding of the topic and for clinical practice as well.

1.4.1. Simulation models of smoking behavior

Simulation models of smoking behaviors were initiated about 30 years ago [190]. In the 90's, a dynamic forecasting model successfully projected that the smoking prevalence would continue to decline in the late 90's [191]; another econometric model estimated the health and economic outcomes associated with tobacco use [192]. Generally, models for tobacco smoking were built to integrate new evidence from empirical studies, incorporate new published information, test the effectiveness of new tobacco control polices, and evaluate surveillance and policy systems to predict trends of smoking prevalence [193, 194] and to project the cost-effectiveness of tobacco policies [180, 195].

Two most frequently applied smoking models developed in the past decade are capable of estimating smoking related mortality rates and change in quality of life. SimSmoke, built on a population model that incorporates birth and death, was created in 2000 [196]. This forecasting model started with numbers of never smokers, former smokers, and current smokers at each age and projected these populations forward. The major objective of constructing the SimSmoke model was to test the impact of a series of tobacco policies and smoking cessation interventions on the trend of smoking prevalence and the mortality rate in different populations defined by age groups in the U.S. and in other countries [196-202]. For example, the SimSmoke model suggested that the impact of a combination of policies can result in lowering the smoking prevalence to 12% to meet the Healthy People 2010 goals in the foreseeable future [200]. The SimSmoke model showed that simulation models provided a useful tool for evaluating complex scenarios in which

policies were implemented simultaneously, and for which there were limited published

data [203].

Another model, the Tobacco Policy Model, was developed to monitor the

dynamic flow of smoking prevalence to assess the relative magnitude of health gains of

quality-adjusted life year (QALY) in association with tobacco policies [204-207]. The

calibrated model divided an initial simulated U.S. population by smoking status. By using

secondary survey data on tobacco use and the probability of live birth and mortality, the

model simulated the impact of behavioral changes in smoking, including initiation,

cessation, and relapse on public health outcomes, measured by the QALYs. Series

applications of the Tobacco Policy Model found that reduction in the initiation of

smoking [207], mandatory reduction of nicotine in cigarettes [205], safer cigarettes [204], or

intensive school-based anti-tobacco educational effort [206] may cause smoking prevalence

to decline and cause cumulative gains in QALYs for the simulated population.

1.4.2. Markov model in medical decision making

In 1983, Beck and Pauker introduced the use of Markov models for determining

prognosis in medical applications [208]. A Markov model used in medical decision making

is defined as a set of mutually exclusive, collectively exhaustive health states that

describe the various clinical events that can occur in the history of a disease [209].

Markov models are useful when a decision problem involves risk that is

continuous over time, when the timing of events is important, and when important events

may happen more than once [209, 210]. For decision analyses involving cancer prevention

and treatment, Markov models are used in clinical settings to simulate the natural course

of cancer outcomes or estimate the prognostic consequences of a disease management strategy.

1.4.3. Life expectancy estimates using simulation modeling

Simulation models are usually designed to capture the natural history and course of chronic disease. One of the major applications of modeling in the field of public health is to estimate the influence of alternative medical decisions on chronic disease management on the life expectancy for the simulated cohort. Questions of interest are how patients with chronic diseases can be affected by types of prevention strategies, including upstream prevention of disease onset, and downstream prevention of disease complications [211].

Decision analyses have been performed to examine the effects of screening and preventive strategies, medical interventions, and treatments options for prostate, colorectal, breast, cervical, and lung cancer. A Markov simulation showed that radical prostatectomy had better life expectancy than watchful waiting for younger prostate cancer patients [212]. Screening techniques for colorectal cancer and HPV-based cervical cancer can extend the life expectancy for patients [213, 214]. For breast cancer, model estimation suggested tumor growth rate was age dependent for patients to undertake screening strategies [215]. Breast cancer mortality may be reduced substantially by ensuring that Black women receive equal adjuvant treatment and screening as White women [216]. Medical interventions offer substantial gains of life expectancy for young women with *BRCA*-associated early-stage breast cancer [217-219].

In addition, with advancements in molecular biology, more studies have applied Markov analysis to evaluate the important role of genetic biomarkers in cancer etiology

and in early cancer detecting techniques. One model suggested that genes in specific regions may play a major role in the process of carcinogenesis of the lung [220]; another one showed that observation of an increased serum marker level was strongly associated with a worse prognosis for small cell lung cancer [221].

1.4.4. The benefits and limitations of modeling the life expectancy gain for cancer survivors

Simulation models are capable of evaluating multiple associations and pathways simultaneously in the complex and comprehensive scenario of cancer survivorship by providing a framework to address nonlinear dynamic issues, synthesize information based on diverse fields, and project the future impact of a medical preventive behavior [194]. Moreover, estimations of gain in life expectancy derived from different simulated cohorts are useful and meaningful for patients to get a richer understanding of lifesaving strategies. Patients can evaluate whether the benefits of a decision may outweigh its harm, with the integration of personal preference. The gain in life expectancy estimates helps healthcare providers to pass on the message about anticipated outcomes of a decision and to communicate and inform patients and families at- or after- diagnosis of cancer. It also helps insurance companies and pharmaceutical companies to decide whether an intervention or a drug for smoking cessation is sufficiently cost-effective [222].

There are a few challenges associated with the simulation of life expectancy. The accuracy of estimates generated from a simulation is strongly dependent on the quality of the inputs and evidence derived from different sources. Slight differences in results from data sources may cause great variations in life expectancy estimates. In addition, strong simplifying assumptions on a parameter will need to be made sometimes, which may

result in the projections of the models being conditioned on certain circumstances. Moreover, the *interpretation* of projected gains in life expectancy needs to be addressed carefully with regard to patients and to the general public. For example, the life expectancy gain from smoking cessation is a *probabilistic* gain throughout the remainder of life for a cohort of cancer survivors, rather than a certain gain at the end of life for an individual patient [223].

2.1. Shanghai Cohort Study

2.1.1. Study population and cancer case ascertainment

Between January 1st, 1986 and September 30th, 1989, all eligible male residents of four small, geographically defined communities scattered over a wide area of the city of Shanghai, China were invited to participate in a prospective epidemiological study of diet and cancer [224]. These four regions were chosen to cover a broad geographic cross section of the city but were comparable in terms of social class, including education and family income. The eligibility criteria were ages 45 to 64 years and no history of cancer. In addition to providing biospecimen samples of urine and blood, each subject was interviewed in person using a structured questionnaire that included level of education, usual occupation, current height and weight, current diet, smoking behavior, and medical history. Interviews were administered by retired nurses who had been specially trained. During the 3-year recruitment period, 18,244 men (about 80% of eligible subjects) enrolled in the study [225].

Identification of incident cancer cases among cohort participants has been accomplished via linkage analysis of the cohort database with the population-based Shanghai Cancer Registry. Hospitals in Shanghai where cancer was diagnosed or treated were required by governmental regulations to report cases to the Registry. Case-ascertainment by the Registry through the hospital system was estimated to be 85% complete. Most remaining cancer cases were identified by the Registry through death certificates. Incident cancer cases among cohort members were identified through manual screening of case reports, based on name, date of birth, and address of residency. The

other way for the identification of incident cancer cases among cohort members to reduce losses to follow-up was to re-contact each surviving cohort member annually. Retired nurses employed by the Shanghai Cancer Institute visit the last known address of each living cohort member and recorded details of the interim health history [224, 225]. For subjects who had moved, the new address was sought from neighbors, former employers, or local police department. As of July 2010, the cutoff date for case ascertainment of this dissertation, 1,042 (5.7%) original cohort participants were lost to our annual follow-up. in total, 3,310 participants of the Shanghai Cohort Study who were free of cancer at enrollment were diagnosed with cancer.

Deaths among cohort participants were ascertained via linkage of the cohort database with the Shanghai Municipal Vital Statistics Office databases. Copies of death certificates, which include cause of death, for residents of the districts targeted for the cohort study were routinely obtained and matched against the cohort master file. Because the vital status was known for more than 99% of the participants, follow-up in terms of mortality was essentially complete.

2.1.2. Assessment of smoking status

At the baseline in-person interview, the nurse interviewer asked each study participant about whether he had ever smoked one or more cigarettes per day for 6 months or longer in his lifetime. If the answer was yes, then the age at smoking initiation, current smoking status, number of cigarettes smoked per day, and number of years of smoking was obtained. For those who already quit smoking at baseline, age at quitting smoking and the number of years since quitting smoking were documented. Besides information of smoking status, intensity and duration collected at baseline, trained

interviewers asked all surviving cohort members for their smoking status and number of cigarettes smoked per day during the 6 months prior to a given interview date in all annual in-person follow-up interviews. Total number of pack-years of cigarettes smoked before the date of cancer diagnosis was defined as the cumulative years of smoking multiplied by the average numbers of packs (20 cigarettes per pack) smoked per day prior to cancer diagnosis.

2.2. The Iowa Women's Health Study (IWHS)

2.2.1. Study population and cancer case ascertainment

In January 1986, a mailed questionnaire was sent and completed by 41,836 (42.7%) of 98,030 randomly selected women between age of 55 and 69 years who had a valid Iowa driver's license in 1985. Compared with non-respondents, respondents were slightly older and had lower body mass index [226]. The baseline questionnaire included standard questions on educational level, past and current smoking status and amount, usual alcohol intake during the past year, history of hormone replacement therapy, medical history, exercise pattern, and reproductive history. A food frequency questionnaire was used to assess dietary intake. Prevalent heart disease was ascertained through self-reports of physician-diagnosed myocardial infarction, angina, or other heart disease. Prevalent hypertension and diabetes were similarly assessed [227].

Information on the vital status of the cohort was collected by several methods. Participant identifiers (name, address, social security number, birth date, and maiden name) were linked to death certificates at the State Health Registry of Iowa for 1986 through 2008. To identify deaths outside of Iowa and nonfatal, non-cancer end points, mailed follow-ups (response rates) were undertaken in 1987 (91%), 1989 (90%), 1992

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(83%), 1997 (79%), and 2004 (68%); the vital status of non-respondents was identified

by linkage with the National Death Index. For deaths outside of Iowa, the censoring date

was the midpoint between the date of last contact in Iowa and the date of death. Women

known to have moved from Iowa were censored at the date of the move, if known, or at

the midpoint between the date of last contact in Iowa and first known date out of Iowa, or

the end of the follow-up period [227]. It was estimated that 99% of deaths in the cohort have

been identified.

To ascertain prevalent cancer, subjects were asked whether they had ever been

diagnosed by a physician as having any form of cancer other than skin cancer and to

specify the site. Participants were asked whether their mother, maternal or paternal

grandmothers, aunts, sisters, or daughters had cancer diagnosed. After the baseline

enrollment, cancer incidence was ascertained through linkage with the State Health

Registry of Iowa, a National Cancer Institute–supported Surveillance, Epidemiology, and

End Results cancer registry, via an annual computer match of name, maiden name, and

date of birth [226]. Primary site, morphology, grade (well, moderately, poorly, or

undifferentiated), extent of disease (stage 0-IV or unknown), first course of treatment,

and date of diagnosis were obtained for each incident cancer case from 1986 through

2008. Only cases diagnosed within the state of Iowa were identified and included in the

study. Among the total 38,006 eligible women who were free of cancer at enrollment,

between 1986 and 2008, 9,821 women had been diagnosed with cancer.

2.2.2. Assessment of smoking status

In the baseline questionnaire, women were asked for information on smoking

status (never, ever, former, or current), age at smoking initiation, average number of

cigarettes smoked per day, and years of smoking. For those who already quit smoking at baseline, age and the number of years since quitting smoking were documented. Total number of pack-years of cigarettes smoked at baseline was defined as the cumulative years of smoking multiplied by the average numbers of packs (20 cigarettes per pack) smoked per day. After the baseline questionnaire, the information on current smoking status at the time of follow-up was updated for all surviving cohort members in questionnaires mailed in 1992, 1997, and 2004.

CHAPTER 3: IMPACT OF POST-DIAGNOSIS SMOKING ON CANCER SURVIVAL, THE SHANGHAI COHORT STUDY

3.1. Introduction

Cancer is the first leading cause of death for men in China and the second leading cause of death for men in the U.S. [1, 228]. Tobacco use is the most important recognized cause of cancer-related death, accounting for 16% of all deaths worldwide [2]. There is sufficient evidence in support of a causal relationship between tobacco use and the development of many cancers, including cancers of the lung and bladder [5]. Among patients diagnosed with smoking-related cancers, smoking is attributable to 50% of the total mortality for men in China and 70% in the U.S. [4, 229]. Nevertheless, despite the public awareness about harmful health effect of smoking, 53% men in China and 22% men in the U.S. are still current smokers as of 2010 [7, 230].

Strong and consistent evidence is available to support the relationship between smoking and the elevated cancer risk, as well as substantial health benefits derived from smoking cessation [22, 104, 106]. However, the impact of smoking on cancer survivors in the post-diagnosis setting is not well studied. Existing evidence for post-diagnosis smoking understandably focuses on treatment related characteristics of patients with lung or head and neck cancer. Adverse outcomes due to continued smoking following treatment for lung or head and neck cancer patients include treatment complications [127, 158], occurrence of a second cancer [137, 149, 231], and poorer general health [145, 146]. The impact of post-cancer diagnosis smoking on survival is less clear. A few hospital-based studies found improved survival outcomes for early staged lung cancer patients who quit smoking after diagnosis

compared with persistent smokers [110, 132], while other studies did not detect a difference in survival time [136, 146, 149, 150, 158-161].

After the diagnosis of cancer, patient are expected to show great interest and motivation to stop smoking, which opens a window of "teachable" opportunity for healthcare providers to intervene and emphasize the importance of smoking cessation [135, 138, 232]. However, disease diagnosis and treatment imposes physical, psychological, and social barriers on cancer patients in terms of quitting smoking [135, 138]. The barriers for quitting smoking resulted in relatively high proportion of smokers to continue to smoke after cancer diagnosis [13]. Smoking prevalence among cancer survivors is similar to that of the general population without a history of cancer [13].

On the other hand, innovations in medical technology have led to early diagnoses and improved treatment, resulting in increasing numbers of survivors and prolonged life expectancy for cancer survivors. In fact, more than 40% of all people living with cancer have been diagnosed with cancer for at least 10 years [12]. Among cancer survivors, only a fraction of smoking patients receive formal smoking cessation counseling [14]. As a consequence, there is considerable room for improvement with regard to tobacco control in the post diagnosis clinical setting for the growing population of cancer survivors. Healthcare providers, patients and family, and policy makers need solid evidence to be confident about the efficacy of smoking interventions when considering smoking cessation.

To address the critical issue of tobacco control for cancer survivors, we examined the association between smoking cessation after cancer diagnosis and risk of all-cause death and survival of cancer patients from a population-based prospective cohort of

Chinese men after 25 years of follow-up. We hypothesize that post-diagnosis smoking cessation reduces mortality risk and increases survival time of cancer patients among Chinese men who had survived for at least one year after cancer diagnosis. The present study is a companion study of the Iowa Women's Health Study (IWHS), a prospective cohort of majority white women in the U.S.

3.2. Methods

3.2.1. The Shanghai Cohort Study

The Shanghai Cohort Study is a prospective cohort study investigating the association between lifestyle characteristics and risk of cancer development among middle-age or older men in Shanghai, China. Detailed methods for subject recruitment and data collection have been previously published [224, 225]. Briefly, all male residents between the ages of 45 and 64 years and resided in one of four geographically defined communities in Shanghai with no prior history of cancer were invited to participate in the study. Between January 1, 1986 and September 30, 1989, 18,244 men enrolled in the study. At enrollment, each participant completed an in-person interview using a structured questionnaire to obtain demographic information, history of tobacco and alcohol use, information of usual adult diet, and medical history. The study was approved by the internal review boards of the Shanghai Cancer Institute and the University of Minnesota.

Identification of incident cancer cases and deaths among cohort participants has been accomplished via linkage analysis of the cohort database with the population-based Shanghai Cancer Registry and Shanghai Municipal Vital Statistics Office databases. Surviving cohort members have been contacted in-person annually. Study staff visits the

last known address of each surviving cohort member to administer the follow-up questionnaire. Medical histories including treatment received for cancer patients were also updated. As of July 2010, the cutoff date for case ascertainment for the present study, the cumulative losses to follow-up were 1,042 (5.7%) subjects (i.e., the vital status for these subjects was unable to be determined via routine ascertainment methods).

As of July 31, 2010, 3,310 participants of the Shanghai Cohort Study who were free of cancer at enrollment were diagnosed with cancer. Among them, 1,704 (51.5 %) patients died prior to the first annual follow-up interview after cancer diagnosis, and therefore, no information of smoking status after cancer diagnosis was collected. Given that the present study was to examine the effect of post-diagnosis smoking on survival, these patients were excluded from the present analysis.

3.2.2. Assessment of smoking status

At the baseline in-person interview, nurse interviewers asked each study participant about whether he had ever smoked one or more cigarettes per day for 6 months or longer. If the answer was yes, information of age at smoking initiation, current smoking status, number of cigarettes smoked per day, and number of years of smoking over lifetime was obtained. For those who had already quit smoking at the baseline, additional information of age of smoking initiation and quitting was recorded. Besides information of smoking status, smoking intensity and duration were collected at baseline, trained interviewers asked all surviving cohort members for their smoking status and number of cigarettes smoked per day during the 6 months prior to a given interview date in all annual in-person follow-up interviews for up to 25 follow-up years. Total number of pack-years of cigarettes smoked before cancer diagnosis was defined as the cumulative

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year of smoking multiplied by average numbers of packs (20 cigarettes per pack) smoked per day prior to cancer diagnosis.

We classified patients' smoking status after cancer diagnosis based on aggregated information on smoking status during 25 years of follow-up interviews. A ratio (r) was calculated by dividing number of years smoked after cancer diagnosis with the total number of years survived for a given patient after cancer diagnosis (r = (No. of smoking years after diagnosis)/(No. of total survival years)%). Patients who had a ratio of less than 0.5 for smoking years over total survival years were considered as "nonsmokers" after diagnosis ($r < 0.5$), while patients who had been smoking for more than half of the years survived were defined as "smokers" after cancer diagnosis ($r \geq 0.5$). The adoption of this 0.5 cut-off point was based on the distribution of patients by smoking status after diagnosis among those who reported as currently smoking in the follow-up interview immediately before cancer diagnosis (Supplemental Figure 3-1 and Supplemental Table 3-1). Under the definition above, the ratio of smoking years after diagnosis out of total survival years have a bi-modal distribution with two peaks near 0 and 1 respectively, and a mean as well as a median value of 0.5. Choosing 0.5 as the criteria threshold ensured a best balance between statistical power and subjects' distribution. As supporting evidence, a sensitivity analysis for hazard ratios at each one-tenth ratio interval defined above were performed (Supplemental Table 3-1), which demonstrated that the hazard ratio trend is consistent with the understanding of smoking impact to cancer survival that was established by this study in general.

In the present study, current smokers before cancer diagnosis were defined as those who reported smoking in the past 6 months in the follow-up interview immediately

preceding cancer diagnosis. Current smokers who were nonsmoking ($r < 0.5$) after cancer diagnosis were defined as "quitters", and current smokers who continued to smoke ($r \geq 0.5$) after diagnoses were classified as "persistent smokers". Lifelong nonsmokers were defined as patients who never smoked cigarettes at baseline interview and at all annual follow-up interviews before cancer diagnosis, and were nonsmoking after diagnosis ($r < 0.5$). Former smokers were patients who smoked one or more cigarettes per day for 6 months or longer at baseline or in any annual follow-up interviews but were not smoking at the follow-up immediately before cancer diagnosis, and were nonsmoking after the diagnosis ($r < 0.5$). A total of 14 cancer patients who initiated smoking after diagnosis were not included in any analysis. The mean ratio (r) of post-diagnosis smoking was 0.01 for lifelong nonsmokers and former smokers, 0.09 for quitters, and 0.86 for persistent smokers.

3.2.3. Statistical analysis

The present study included 1,592 (48.1% of all 3,310 cancer patients) cancer patients who had survived beyond the first follow-up interview after diagnosis. Among these patients, 898 (56.4%) died from any cause as of July 31, 2010. For each cancer patient, person-years were calculated from the date of cancer diagnosis through the date of death or the cut-off date for those who are alive (07/31/2010), whichever occurred first.

The Kaplan-Meier method and log-rank test were used to compare the difference in survival time among lifelong nonsmokers, former smokers, quitters, and persistent smokers. We also used the Cox proportional hazard regression method to estimate hazard ratios, their corresponding 95% confidence intervals (95% CIs), and P values that

assessed the strength of the associations between the patterns of smoking after cancer diagnosis and risk of death. In addition, we developed a time-dependent variable which measured the current smoking status (yes or no) on a yearly basis after cancer diagnosis in the Cox regression model. The time-dependent variable integrated repeated measures of smoking status over all annual follow-up interviews after cancer diagnosis in the regression models, based on the dynamic change in smoking status for a given patient after cancer diagnosis [233]. All Cox models included the following covariates: age at cancer diagnosis, level of education (less than primary school, middle school, and college or above), cumulative pack-years prior to cancer diagnosis (continuous), and treatment for cancer including surgery (yes/no), radiation (yes/no), and chemotherapy (yes/no).

The association between post-diagnosis smoking and risk of all-cause mortality was examined among all cancer patients combined as well as for patients with specific types of cancers including lung, stomach, and colorectal cancer. We studied cancers that had a statistical power of more than 0.8 for reasonable hypothesis testing.

All statistical analyses were carried out using SAS software version 9.2 (SAS Institute). All P values reported are two-sided, and those that were <0.05 were considered to be statistically significant.

3.3. Results

Of the 1,592 cancer patients who had survived more than 1 year, mean age (± standard deviation) at cancer diagnosis was 68.8 (±7.2) years and the mean years of follow-up was 5.3 (± 4.8) after cancer diagnosis. The median survival time was 5.5 years (Table 3-1). Seventy-four percent of patients received surgical treatment whereas 45.7% and 18.2% had chemotherapy and radiation therapy, respectively. Overall, patients with

esophageal or liver cancer were diagnosed at a younger age, had a shorter survival time, and were less likely to receive surgical treatment compared to patients who had other cancers (Table 3-1).

Of all 1,592 patients, 337 (21.2%) were lifelong nonsmokers, 524 (32.9%) were former smokers, 359 (22.6%) were quitters, and 372 (23.4%) were persistent smokers. The median survival times for never, former, quitters, and persistent smokers were 7.7, 6.1, 6.4, and 2.8 years, respectively (Table 3- 2). Cancer patients who continued smoking after diagnosis experienced a statistically significant 44% (HR = 1.44, 95% CI = 1.14-1.82) increase in risk of death compared with cancer patients who were lifelong nonsmokers after adjustment for age, level of education, cumulative number of pack-years of smoking up to the year before cancer diagnosis, and treatment for cancer. Smoking cessation, before or after cancer diagnosis, caused the risk all-cause mortality close to that of lifelong nonsmokers. The HR (95% CI) was 0.96 (0.78-1.19) for former smokers and 0.96 (0.76-1.22) for quitters, compared with lifelong nonsmokers.

Persistent smokers had statistically significant shorter survival time compared with lifelong nonsmokers and patients who quitted smoking before or after cancer diagnosis (Figure 3- 1) (P $_{\text{log-rank}}$ < 0.01). At 5 years, 42.7%, 33.3%, 43.2 and 29.5% of patients who were lifelong nonsmokers, former smokers, quitters, and persistent smokers, respectively, were alive. The difference in survival time between persistent smokers and all other nonsmokers after cancer diagnosis was statistically significant for patients with lung, stomach, colorectal (Supplemental Figure 3- 2).

Table 3- 3 shows all-cause mortality HRs using the time-dependent smoking status at each year after diagnosis for all patients, as well as for patients with specific cancers after adjustment for potential confounders. Cancer patients who smoked after diagnosis had a 52% increased risk of death (HR =1.52, 95% CI = 1.28-1.80) compared with post-diagnosis nonsmokers. The multivariate-adjusted HRs (95% CI) of death for smokers relative to nonsmokers after cancer diagnosis was 1.72 (1.22-2.43) among lung cancer patients, 1.71 (1.15-2.55) among stomach cancer patients, and 1.81(1.15-2.85) among colorectal cancer patients. Similarly, for all current smokers at cancer diagnosis, persistent smokers experienced 1.61 fold increased risk (95% CI = 1.33-1.94). Among current smokers, the corresponding HR (95% CI) of death due to post-diagnosis smoking was 2.00 (1.34-2.98), 2.30 (1.40-3.76), and 1.71 (1.02-2.87) for lung, stomach, and colorectal cancer patients, respectively, compared with patients who had smoking cessation after diagnosis (Table 3-3).

3.4. Discussion

The present study demonstrates a statistically significantly elevated risk of all-cause mortality and reduced median survival time for cancer survivors who continue smoking after cancer diagnosis. Smoking cessation after cancer diagnosis leads to more than 3 years extension of median survival time. We observe a statistically significant positive impact of post-diagnosis smoking on mortality risk for patients with lung, stomach, and colorectal cancer patients. The findings strongly suggest that post-diagnosis smoking cessation results in better cancer survival prognosis, even though smoking was not a strong etiological factor for the specific cancer site. Findings of the inverse relationship between smoking after cancer diagnosis and survival from our companion

analysis of the Iowa Women's Health Study, a cohort of primarily white women in the U.S., are very similar to the present study. Compared with nonsmokers, women who ever smoked cigarettes after cancer diagnosis had a statistically significant 35% increased mortality risk.

3.4.1. Pathways by which smoking may increase mortality rates for cancer patients

Post-diagnosis smoking affects cancer patients' general health and treatment efficacy. It has been suggested that continued smoking after cancer diagnosis is related to increased risks of unfavorable treatment consequences, including complications from general anesthesia and surgery, severe pulmonary complications, detrimental effects on wound healing, toxicity and side effects of radiation and chemotherapy, immune suppression, infection, and cancer recurrence or occurrence of a second primary cancer [15, 135, 137, 141, 142, 149]. For instance, cigarette smoking had been shown to be an important risk factor for elevated mortality among operable colorectal cancer patients [234]. Lower quality of life, worse performance status, higher level of usual pain, and poorer general health and social functioning were also reported for smokers compared to nonsmokers after diagnosis [144-148]. Favorable general health and better treatment efficacy as a result of smoking cessation after the diagnosis enhance cancer survivors' overall prognosis.

Furthermore, biological mechanisms of etiological carcinogenicity of tobacco smoke support our findings, particularly for smoking-caused cancers. There are 3 major pathways of cigarette smoking-related cancer development and progression: the exposure to cancer-causing substances, the formation of DNA adducts, and accumulation of permanent mutations in critical genes (reviewed in ref. [71]). On the other hand, tobacco compounds also induce dysfunction in coronary and significantly increase cardiovascular

disease-specific death rate [5, 75]. In the present study, 89.8% of patient deaths occurred (95.4%, 86.6%, and 84.5% of all deaths for lung, stomach, and colorectal cancer, respectively) were due to cancer. The association between post-diagnosis smoking and increased mortality risk was stronger for cancer-specific deaths than that for all-cause mortality (Supplemental Table 3- 3). We found no association between smoking and cardiovascular disease-specific deaths and all other causes of death (data not shown). Therefore, we conjecture that post-diagnosis smoking cessation improves cancer survival by slowing down the progression of tumor via carcinogenic pathways.

In addition, smoking cessation after cancer diagnosis results in decreased exposure to other significant risk factors for some cancers. The dietary habits of smokers are usually less healthy than those of nonsmokers [235, 236]. Smoking is also highly correlated with alcohol drinking and less physical activity in both Chinese [237] and Western population [238-241]. It is conceivable that unhealthy lifestyles of smokers exacerbates the harmful effects of smoking exposure on the progression of tumor, given that bad diet, alcohol consumption, lack of physical activity, and other lifestyle factors are substantially inversely related to cancer mortality, especially for colorectal and stomach cancers [242-245].

3.4.2. Public health implications

Smokers who were diagnosed with cancer, especially smoking-related cancers, were expected to have a strong motivation to quit smoking after diagnosis [124, 125]. However, cancer survivors face tremendous physical, psychological, social, spiritual, and financial challenges during cancer diagnosis and treatment [138]. Given smoking as a possible means for stress reduction, it is not surprised that smoking prevalence among

cancer survivors were as high as that of the general population. Smoking prevalence is 20.2% among cancer patients, compared with 23.6% among the general population in the U.S. [13, 126]. Due to lack of evidence in survival benefits, physicians do not emphasize the importance of smoking cessation to cancer patients, especially to patients with smoking-related cancers that are believed it was too late to quit given that the damage had been done [165]. Less than 50% of smokers received formal smoking cessation counseling from healthcare providers at diagnosis, during treatment, or on follow-up visits [14]. Several smoking cessation programs that were designed to help cancer patients to quit smoking had limited success [15, 176, 187]. Therefore, there is considerable room to improve the rate of self-managed or healthcare provider-assisted smoking cessation in the clinical setting for cancer patients.

Findings from our study have important public health implications for survivors, healthcare providers, policy makers, and others. A patient's health perception is one of the most important factors that relate to the adoption of protective actions [246]. The current study provides an important piece of evidence to assist in the development of a cancer survivor's perception toward his long-term survival. The decreased mortality risk as a result of smoking cessation after diagnosis provides a critical rationale for patients to incorporate personal preferences and health perceptions to opt for smoking cessation. Furthermore, the diagnosis of cancer provides a window of "teachable" opportunity [135, 138] for healthcare providers to introduce smoking cessation advice and assistance into comprehensive cancer care at a time when survivors' health and survival is paramount. All healthcare providers, including physicians, oncologists, nurses, and pharmacists should take the opportunity of this teachable moment to convey the message of

substantial survival benefits of post-diagnosis smoking cessation to cancer survivors and their families. Specific smoking cessation interventions are needed to adjust health perception and address updating disease- and treatment- related issues at diagnosis, during treatment, and in follow-up visits. For patients who are intermittent smokers or are not able to quit right after diagnosis, intensified supports are needed to facilitate a personalized intervention at a regular basis. Moreover, our findings grant support to tobacco control programs and policies, and cancer survivorship initiative programs. Findings of the significantly decreased mortality risk caused by post-diagnosis smoking cessation should be included in guidelines and evidence-based clinical practices in the context of cancer care and survivorship. In addition, smoking cessation is considered cost-effective in the general population [177] as well as for lung cancer patients who have had surgery [180]. Insurance and pharmaceutical companies may consider promoting highly effective and sufficiently cancer- tolerable smoking cessation interventions, medications, and disease management strategies for cancer patients.

3.4.3. Strengths and limitations

The present study is the only population-based prospective study which closely followed smoking status after cancer diagnosis for over 20 years to assess the impact of post-diagnosis smoking of all cancers combined as well as many common cancers including lung, stomach, and colorectal cancer for male patients. The major strength of the present study is that smoking status for all subjects in this cohort of men was precisely monitored and documented in the baseline enrollment as well as in annual follow-up questionnaires for a long period of time. The complete information on smoking status enables us to construct a time-dependent variable, which allows for a more

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precisely estimated association between smoking status after diagnosis and risk of death. The time-dependent approach also accurately captures the dynamic variations of smoking behavior over a prolonged period of time of cancer diagnosis. In addition, the large number of cancer survivors with complete follow-up provided sufficient statistical power for unbiased risk estimation.

In spite of the considerable strengths, the present analysis may be subject to potential limitations. One possible limitation is the concern that pre-diagnosis smokers may be diagnosed at a later age [247], with poorly differentiated, and advanced tumors [78, 79]. Unfortunately, in the present analysis, there is no complete documentation on tumor stage and histological subtypes for subjects in the cohort. However, the mean age at diagnosis of current smokers in our study is comparable to that of lifelong nonsmokers and former smokers (68.6, 71.4, and 67.0, for lifelong nonsmokers, former, and current smokers at diagnosis, respectively, p = 0.57, Supplemental Table 3- 4). Our companion study of women in Iowa showed that further classification or adjustment by stage and grade of the tumors did not materially alter the survival estimates associated with smoking. Also, patients with advanced tumors were less likely to receive surgical treatment due to its ineffectiveness. In the present study, 77%, 77%, and 71% of lifelong nonsmokers, former, and current smokers at diagnosis received surgical treatment (p = 0.14). Current smokers were similar in receiving chemotherapy (p = 0.28) but were more likely to have radiation therapy (21% for current smokers vs. 17% for lifelong nonsmokers and 15% for former smokers, p = 0.04) (Supplemental Table 3- 4). Treatment options in Cox regression models were adjusted as a way to incorporate the potential difference in the stage of tumors between smokers and nonsmokers.

An additional concern is the feasibility of generalizing our findings based on a Chinese population to the Western population. Smoking is responsible for a higher proportion of cancer deaths in U.S. men than in Chinese men[4, 229]. Besides stomach cancer, the age-adjusted mortality rate of the other common cancers included in the present study, the lung, and colorectal, are all higher in U.S. men than that in Chinese men [248]. Also, studies have suggested that Caucasians are more susceptible to cancers including lung than Asians given the same smoking intensity and duration [249-251]. In addition, although smoking prevalence was higher in Chinese men than in U.S. men (52.9% in Chinese men vs. 21.5% in U.S. men), higher number of cigarettes per day was consumed among U.S. smokers (mean cigarettes smoked per day 14.2 in China vs. 15.1 in the U.S.) [7, 230]. Further, studies found considerably lower concentrations of tobacco carcinogens in local Chinese cigarette brands relative to the main stream western brands [252]. Therefore it is reasonable to infer that smoking may be more harmful in terms of cancer mortality in a Western population than in an Asian population. Given that quit smoking rate is generally lower among Chinese men compared with U.S. men [13, 253], we would suggest that findings of the present Asian population would only underestimate the impact of post-diagnosis smoking on cancer survival for a Western population.

3.4.4 Excluded cancer patients

Finally, it is worth noting that in the present analysis, we only included patients who had survival one or more years after the date of cancer diagnosis to gather updated smoking status information. Patients who died soon after the diagnosis were excluded. Median survival was less than 4 months for these 1,704 excluded patients. The rationale of eliminating these patients from the current analysis is based on the following reasons.

First, the present study is only interested in the impact of post-diagnosis smoking cessation on cancer survival. Patients without updated post-diagnosis smoking information are considered as ineligible and irrelevant to our study. Moreover, the distribution of patients by smoking status at diagnosis is comparable between the excluded and included populations for lung, stomach, and colorectal cancer patients (Supplemental Table 3- 4). Among stomach and colorectal cancer patients, slightly fewer current smokers and more nonsmokers were excluded than included, whereas a higher percentage of current smokers who were diagnosed with lung cancer died quickly after diagnosis and thus were not included in the paper. Then we went on to assess the effect of smoking cessation on survival for patients who lived a short period of time after diagnosis by comparing HRs of current smokers vs. former smokers. We found that after adjusting for potential confounders, mortality risks were comparable for smokers and former smokers in this population of excluded patients with lung, stomach, or colorectal cancer. A majority (67%) of patients who lived too briefly after diagnosis and were excluded from the studies were patients diagnosed with lung, liver, stomach, and pancreatic cancers. Therefore, we suggest that smoking is not a major factor in causing any difference in mortality risk for cancer patients who were expected to have a very short span of life after diagnosis. The impact of smoking cessation may only affect patients who are able to live long enough to gain survival benefits. Based on our findings, caution is warranted when generalizing conclusions of beneficial survival due to post-diagnosis smoking cessation to cancer patients who anticipate having a short life expectancy after diagnosis. Male cancer patients who survived beyond one year are the target population to gain survival benefits due to post-diagnosis smoking cessation.

In summary, smoking cessation after cancer diagnosis increased median survival time by 3.6 years for male cancer patients. Continued smoking after cancer diagnosis increased risk of death by 52% (95% CI = 28% - 80%). These beneficial health effect derived from smoking cessation after cancer diagnosis were seen among patients who had strong smoking-related cancers (lung and stomach) as well as among patients with less smoking-related cancers (colon-rectum). Such findings of smoking cessation on increased survival time of cancer patients support the idea that smoking cessation could be one of the most cost-effective treatments that extend the life expectancy of a cancer patient. Prominent advice and assistance should be provided to encourage or to enforce smoking cessation at the time of cancer diagnosis, during and after cancer treatment.

Table 3- 1. Selected characteristics of cancer patients, the Shanghai Cohort Study 1986-2010

	No. of Cases*	No. of Deaths (%)	Total Person -years	Average Person -years	Median Survival (year)	Average Age at Diagnosis	Received Surgery (%)	Received Chemotherapy (%)	Received Radiation Therapy (%)
Total Cancer Patients	1592	898 (56.4)	8475	5.3	5.5	68.8	74.2	45.7	18.2
Smoking Related Cancer Patients[†]	835	533 (63.8)	4348	5.2	4.0	68.1	69.1	46.7	21.8
Lung	275	216 (78.6)	1107	4.0	2.3	68.2	49.1	54.2	24.0
Esophageal	51	43 (84.3)	166	3.2	2.0	67.5	62.8	23.5	31.4
Stomach	244	149 (61.1)	1302	5.3	4.0	67.8	86.1	54.9	17.2
Bladder	105	38 (36.2)	772	7.4	15.0	69.2	86.7	49.5	12.4
Others[‡]	160	87 (54.4)	1000	6.2	7.3	67.9	68.1	26.9	28.1
Non-Smoking Related Cancer Patients[†]	757	365 (48.2)	4127	5.5	7.9	69.6	79.8	44.5	14.3
Liver	64	51 (79.7)	218	3.4	2.5	67.6	62.5	46.9	7.8
Colorectal	356	155 (43.5)	2128	6.0	10.9	69.6	92.7	59.0	13.8
Prostate	129	46 (35.7)	576	4.4	8.5	73.3	86.1	18.6	12.4
Others[§]	208	113 (54.3)	1216	5.8	7.4	67.8	66.4	35.1	18.3

* The present study included 1,592 cancer patients who survived for one or more annual follow-ups when smoking status was updated.

† Smoking and non-smoking related cancers were classified according to the 2004 Surgeon's General Report.[1]

‡ Including kidney, laryngeal, oral, pancreatic cancers, or acute myeloid leukemia.

§ Including gall bladder, bone, melanoma, breast, brain, thyroid cancers, lymphoma, or myeloma.

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[1] The Health Consequences of Smoking: A Report of the Surgeon General. Atlanta, GA: Centers for Disease Control and Prevention, Office on Smoking and Health; 2004.

Table 3- 2. Hazard ratio (95% confidence interval) of all-cause death for all cancer patients by smoking status, the Shanghai Cohort Study 1986-2010

Smoking Status †	Average Age at Diagnosis	No. of Cases	No. of Deaths (%)	Median Survival	HR* (95% CI)
Lifelong nonsmokers	68.6	337	167 (50.0)	7.7	1.00 (ref)
Former smokers	71.4	524	254 (48.5)	6.1	0.96 (0.78-1.19)
Quitters	67.6	359	208 (57.9)	6.4	0.96 (0.76-1.22)
Persistent smokers	66.4	372	269 (72.3)	2.8	1.44 (1.14-1.82)

*All hazard ratios were adjusted for age at diagnosis (continuous), level of education (primary school, middle school, or college or above), cumulative number of pack-year smoked up to year prior to diagnosis (continuous), and treatment options (surgery (yes/no), chemotherapy (yes/no), and radiation therapy (yes/no)).

† See method section for definition of lifelong nonsmokers, former smokers, quitters and persistent smokers.

Table 3- 3. Time-dependent hazard ratio (95% confidence interval) of all-cause death for smoking after cancer diagnosis for all cancer patients and for current smokers at cancer diagnosis, The Shanghai Cohort Study 1986-2010

	All patients	Lung Cancer	Stomach Cancer	Colorectal Cancer
Total patients				
No. of cases	1592	275	244	356
No. of deaths (%)	898 (56.4)	216 (78.6)	149 (61.1)	155 (43.5)
Total person-years	8475	1107	1302	2128
Median survival time (year)	5.5	2.3	4.0	10.9
Hazard ratio (95% confidence interval)[*]	1.52 (1.28-1.80)	1.72 (1.22-2.43)	1.71 (1.15-2.55)	1.81 (1.15-2.85)
Limited to current smokers at cancer diagnosis				
No. of cases	731	174	115	248
No. of deaths (%)	477 (65.3)	141 (81.0)	74 (64.4)	112 (45.2)
Total person-years	4046	716	711	1467
Median survival time (year)	4.3	2.1	4.2	8.2
Hazard ratio (95% confidence interval)[*]	1.61 (1.33-1.94)	2.00 (1.34-2.98)	2.30 (1.40-3.76)	1.71 (1.02-2.87)

* Derived from a yearly based time-dependent variable of smoking status (yes versus no) after cancer diagnosis with the adjustment for age at diagnosis (continuous), level of education (primary school, middle school, or college or above), cumulative number of pack-year of smoking prior to diagnosis (continuous), and treatment options of surgery (yes/no), chemotherapy (yes/no), and radiation therapy (yes/no).

Figure 3- 1. Kaplan-Meier survival curves by smoking status for all cancer patients, the Shanghai Cohort Study 1986-2010
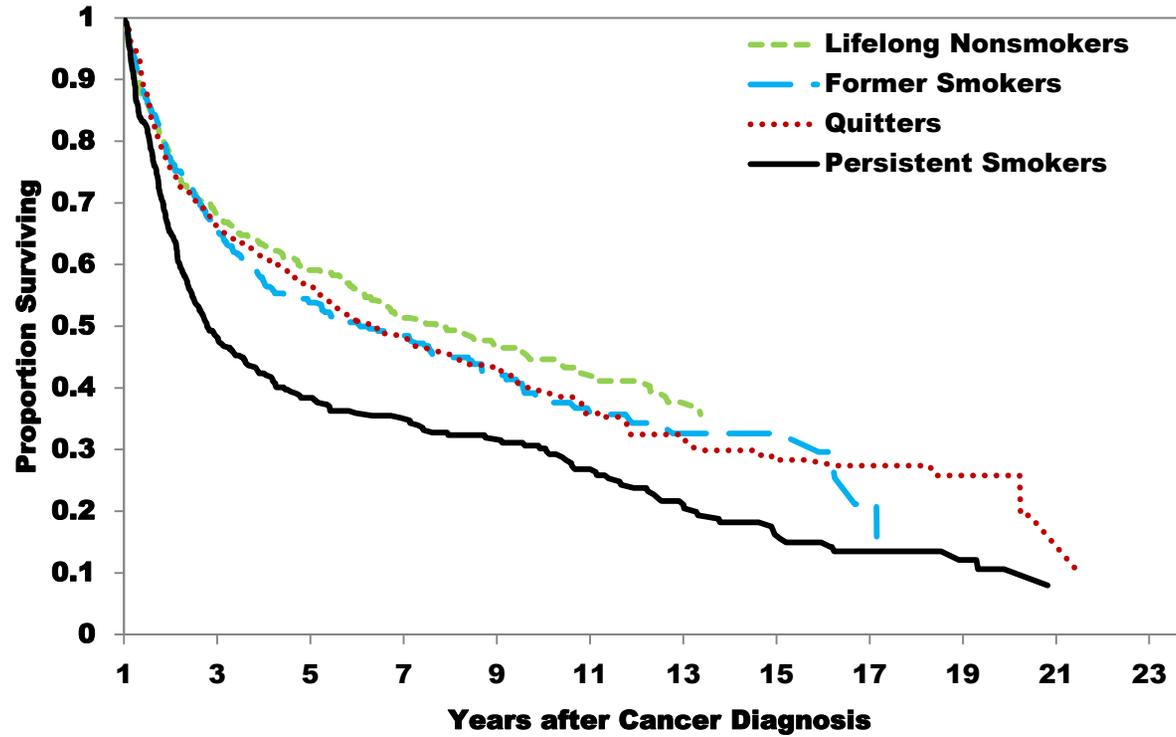
No. at risk

Lifelong nonsmokers	330	141	74	57	0	0
Former smokers	513	171	62	36	3	0
Quitters	354	153	94	63	16	1
Persistent smokers	370	109	74	54	9	0

Supplemental Figure 3- 1. Distribution of patients by different cut-point of ratio of smoking year out of total survival year (r) among current smokers at diagnosis, The Shanghai Cohort Study 1986-2010
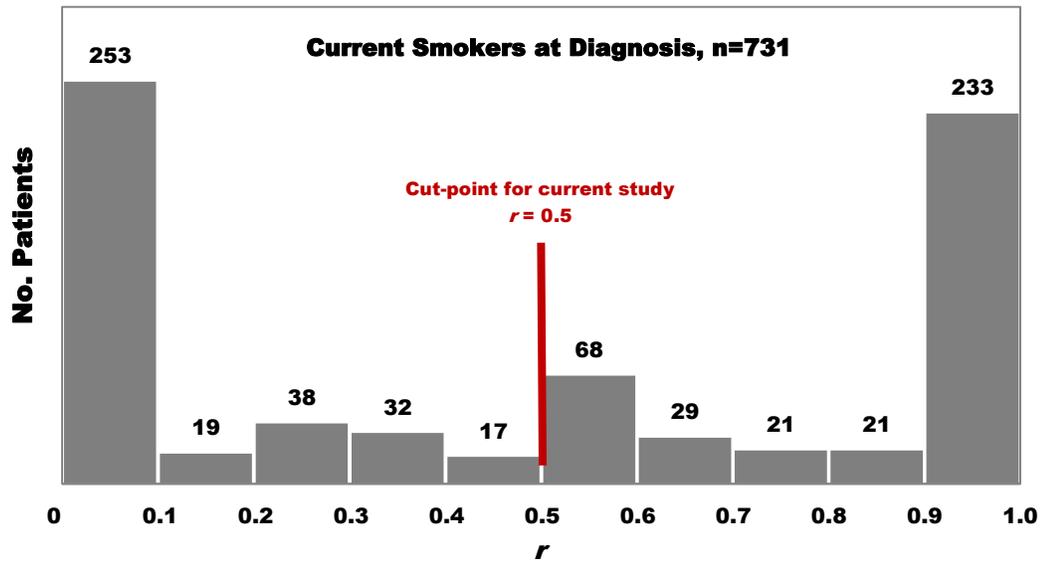
Supplemental Table 3- 1. Sensitivity analysis of variation in ratio of smoking year out of total survival year (r), the Shanghai Cohort Study 1986-2010

	No.	HR[*] (95% CI)
Smoking status by cut-points (r)		
0.1		
Quitters (<0.1)	253	1.00(ref)
Smokers (≥0.1)	478	0.97 (0.79-1.19)
0.2		
Quitters (<0.2)	272	1.00(ref)
Smokers (≥0.2)	459	1.05 (0.86-1.29)
0.3		
Quitters (<0.3)	310	1.00(ref)
Smokers (≥0.3)	421	1.32 (1.09-1.60)
0.4		
Quitters (<0.4)	342	1.00(ref)
Smokers (≥0.4)	389	1.41 (1.17-1.70)
0.5		
Quitters (<0.5)	359	1.00(ref)
Smokers (≥0.5)	372	1.57 (1.31-1.90)
0.6		
Quitters (<0.6)	427	1.00(ref)
Smokers (≥0.6)	304	1.44 (1.20-1.75)
0.7		
Quitters (<0.7)	456	1.00(ref)
Smokers (≥0.7)	275	1.49 (1.23-1.80)
0.8		
Quitters (<0.8)	477	1.00(ref)
Smokers (≥0.8)	254	1.71 (1.42-2.07)
0.9		
Quitters (<0.9)	498	1.00(ref)
Smokers (≥0.9)	233	2.01 (1.66-2.44)
1.0		
Quitters (<1.0)	507	1.00(ref)
Smokers (1.0)	224	2.30 (1.89-2.81)
Quitters (0)	241	1.00(ref)
Smokers (1)	224	1.51 (1.19-1.91)

* r = (No.of smoking years after diagnosis)/(No.of total survival years). All HRs were adjusted for age at diagnosis (continuous), level of education (primary school, middle school, or college or above), number of pack-year smoked up to year prior to diagnosis (continuous), and treatment options (surgery (yes/no), chemotherapy (yes/no), and radiation therapy (yes/no)).

**Supplemental Figure 3- 2. Kaplan-Meier survival curves by smoking status after cancer diagnosis for patients with cancers of the lung, stomach, and colon-rectum, the Shanghai Cohort Study 1986-2010**
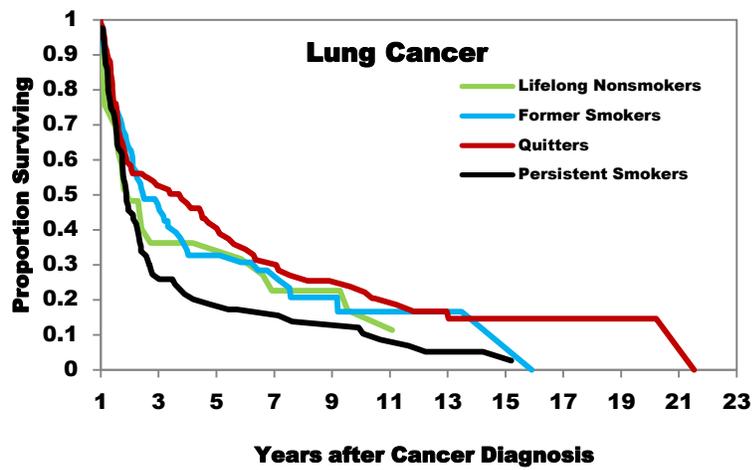
P log-rank < 0.01
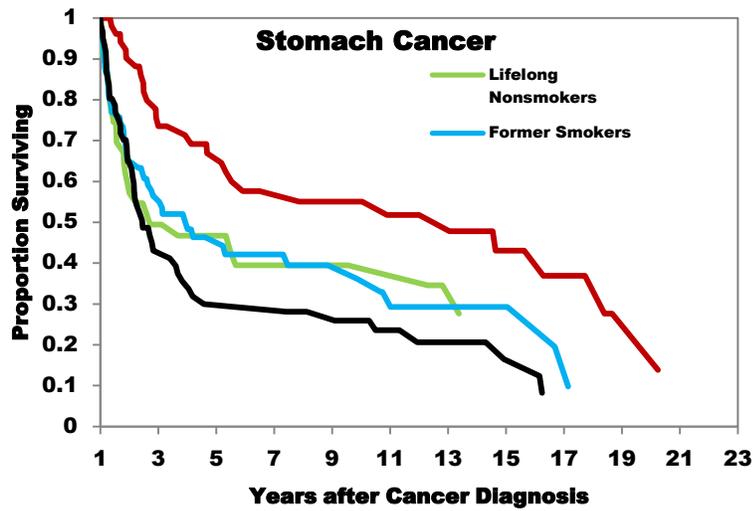
P log-rank < 0.01
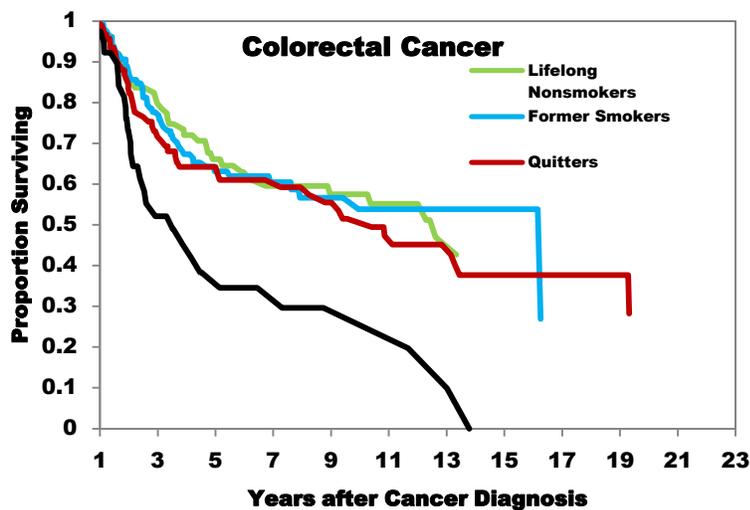
P log-rank < 0.01

Supplemental Table 3- 2. Hazard ratios of cancer specific deaths for continued smoking after cancer diagnosis, the Shanghai Cohort Study 1986-2010

|	All patients	Lung Cancer	Stomach Cancer	Colorectal Cancer
Total patients				
No. of cases	1500	265	224	332
No. of deaths (%)	806 (53.7)	206 (77.7)	129 (57.6)	131 (39.5)
Percentage out of total death (%)	89.8	95.4	86.6	84.5
Total person-years	7846	1050	1108	1943
Median survival time (year)	5.4	2.2	3.6	13.0
Hazard ratio (95% confidence interval)[*]	1.56 (1.31-1.86)	1.80 (1.27-2.56)	1.79 (1.17-2.73)	2.10 (1.29-3.43)
Limited to current smokers at cancer diagnosis				
No. of cases	689	169	103	123
No. of deaths (%)	435 (63.1)	136 (80.5)	62 (60.2)	60 (48.8)
Percentage out of total death (%)	91.2	96.5	83.8	53.6
Total person-years	3714	686	565	683
Median survival time (year)	3.9	2.1	3.6	8.2
Hazard ratio (95% confidence interval)[*]	1.65 (1.35-2.01)	2.12 (1.42-3.17)	2.39 (1.38-4.14)	1.99 (1.13-3.51)

* Derived based on a yearly time-dependent variable of smoking status (yes versus no) after cancer diagnosis with the adjustment for age at diagnosis (continuous), level of education (primary school, middle school, or college or above), number of pack-year of smoking before diagnosis (continuous), and treatment options of surgery (yes/no), chemotherapy (yes/no), and radiation therapy (yes/no).

Supplemental Table 3- 3. Characteristic of the study population by smoking status, the Shanghai Cohort Study 1986-2010

	Total N	No. of death (%)	Median Survival (year)	Average Age at Diagnosis	Lifelong nonsmokers N (%)	Former smokers N (%)	Current smokers N (%)	*P*
Received treatments								
Surgery	1592				337 (100%)	524 (100%)	731 (100%)	0.14
Yes	1181	582 (49.3)	8.2	68.6	258 (76.6)	402 (76.7)	521 (71.3)	
No	364	280 (76.9)	2.3	69.6	69 (20.5)	111 (21.2)	184 (25.2)	
Chemotherapy								0.28
Yes	727	423 (58.2)	5.2	67.8	146 (43.3)	231 (44.1)	350 (48.0)	
No	750	402 (53.6)	6.2	70.0	167 (50.0)	260 (49.6)	323 (44.2)	
Radiation therapy								0.04
Yes	290	194 (66.9)	4.9	65.3	58 (17.2)	78 (14.9)	154 (21.1)	
No	1128	590 (52.3)	5.9	69.9	245 (72.7)	393 (75.0)	490 (67.0)	

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Supplemental Table 3- 4. Distribution of the study population and excluded population by smoking status at cancer diagnosis and hazard ratio (HR) (95% CI) of all-cause mortality of former smokers and current smokers, the Shanghai Cohort Study 1986-2010

	Total N	No. of deaths (%)	% of death within 1 year	Median Survival (year)	Average Age at Diagnosis	Nonsmokers N (%)	Former smokers N (%)	Current smokers N (%)	P	HR (95%CI) *
All cancer patients									0.01	
Current study population	1592	898 (56.4)		5.5	68.8	337 (21.2)	524 (32.9)	731 (45.9)		
Excluded population	1718	1718 (100)	51.9	0.3	70.1	288 (16.7)	602 (35.0)	828 (48.0)		1.26 (1.06-1.49)
Lung cancer patients									0.09	
Current study population	275	216 (78.6)		2.3	68.2	29 (10.6)	72 (26.2)	174 (63.3)		
Excluded population	550	550 (100)	66.7	0.3	70.2	42 (7.6)	180 (32.7)	328 (59.6)		1.11 (0.82-1.50)
Stomach cancer patients									0.74	
Current study population	244	149 (61.1)		4.0	67.8	45 (18.4)	84 (34.4)	115 (47.1)		
Excluded population	251	251 (100)	62.8	0.4	70.0	51 (20.3)	90 (35.9)	110 (43.8)		1.06 (0.68-1.66)
Colorectal cancer patients									0.07	
Current study population	356	155 (43.5)		10.9	69.6	88 (24.7)	134 (37.6)	134 (37.6)		
Excluded population	150	150 (100)	29.6	0.5	72.4	47 (31.3)	62 (41.3)	41 (27.3)		1.83 (0.83-4.06)

* Hazard ratio of current smokers vs. former smokers (reference) among excluded population of the study. All HRs were adjusted for age at diagnosis (continuous), level of education (primary school, middle school, or college or above), number of pack-year of smoking before diagnosis (continuous), and treatment options of surgery (yes/no), chemotherapy (yes/no), and radiation therapy (yes/no).

## CHAPTER 4: IMPACT OF POST-DIAGNOSIS SMOKING ON CANCER SURVIVAL, THE IOWA WOMEN'S HEALTH STUDY

4.1. Introduction

Cancer is a leading cause of death [254]. Tobacco use is the most important recognized cause of cancer-related death, accounting for 30% of all cancer deaths in the U.S. [8]. There are sufficient evidence to infer causal relationships between tobacco use and many types of cancers, including lung, bladder, and stomach cancer [5]. Nevertheless, despite the public awareness of harmful effects of smoking [5], 17.9% women in the U.S. are still current smokers as of 2010 [7].

Smoking cessation reduces the risk of cancer and cancer-related mortality [1, 22, 71, 104, 106]. However, evidence of the impact of post-diagnosis smoking cessation on cancer-related mortality for women patients is limited. Existing evidence about post-diagnosis smoking understandably focused on treatment-related outcomes of early stage, primarily male lung or head and neck cancer patients. For example, continued smoking following the diagnosis is associated with increased risk of occurrence of a secondary tumor, treatment complications, poorer general health, and lower quality of life compared to patients who quitted smoking [127, 142, 145, 146, 158]. Studies focused on women patients suggested that post-diagnosis smoking had important modification effect on the association between radiation therapy and secondary lung cancer risk among breast cancer patients [151-155]. The impact of post-cancer diagnosis smoking on survival is less clear. A few studies found decreased mortality rates associated with smoking cessation after diagnosis or before treatment [110, 132, 147], while most studies didn't find such relationships [136, 140, 146, 150, 158-161, 255]. Reasons for the heterogeneity of findings from these

studies include variations on quality of study design, sample selection biases, and insufficient statistical power in analyses. No study has provided direct evidence for the association of post-diagnosis smoking and cancer-mortality for female cancer survivors.

Following the diagnosis of cancer, patients are expected to have a strong motivation to stop smoking, which opens a window of "teachable" opportunity for healthcare providers to intervene and emphasize the importance of smoking cessation [135, 138, 232]. However, disease diagnosis and treatment imposes physical, psychological, and social barriers on cancer patients in terms of quitting smoking [135, 138]. Compare to men, women cancer patients may have more specific issues when making the decision about quit smoking [256]. The barriers for quitting smoking caused smoking prevalence among cancer survivors to be as high as 20.2% [13]. Smoking prevalence among cancer survivors is similar to that of the general population without a history of cancer [13].

On the other hand, innovations in medical technology have led to early diagnoses and improved treatment, resulting in increasing numbers and prolonged life expectancy for cancer survivors. In fact, more than 40% of all people living with cancer have been diagnosed with cancer for at least 10 years [12]. Among these cancer survivors, only a fraction of smoking patients receive formal smoking cessation counseling from their physicians or healthcare providers at diagnosis, during treatment, or on follow-up visits [14]. As a consequence, there is considerable room for improvement with regard to tobacco control in the post diagnosis clinical setting for the growing population of cancer survivors. Healthcare providers, patients and family, and policy makers need solid evidence to be confident about the efficacy of smoking interventions when considering smoking cessation.

To fill the gap of existing evidence about smoking and cancer mortality in women and to provide data to guide clinical practice for smoking intervention, the present study examines the association between smoking after cancer diagnosis and survival in female cancer patients of the Iowa Women Health Study. We hypothesize that there is an increased mortality risk associated with post-diagnosis smoking. The present analysis in primarily white women in the U.S. is a companion study of our study of the Shanghai Cohort Study, a male-subjects only cohort in China.

4.2. Methods

4.2.1. The Iowa Women's Health Study

The Iowa Women's Health Study (IWHS) is a prospective cohort study to investigate potential risk factors for incident cancer in women in Iowa. Detailed methods for recruitment and data collection of the IWHS were reported previously [257]. Briefly, in 1986, 41,836 women (43%) of the 99,826 randomly selected Iowa women aged 55-69 completed a mailed-in self-administered questionnaire. The baseline questionnaire asked study participants for information on demographic characteristics, history of tobacco and alcohol use, usual adult diet, medical history, and self body measurements. After baseline, all surviving study participants were sent follow-up questionnaires by mail in 1987, 1989, 1992, 1997, and 2004, respectively, for information on their vital status, residence, and some exposure measurements. The study was approved by the institutional review board of the University of Minnesota.

Cancer incidence was ascertained via annual linkage with the State Health Registry of Iowa, a National Cancer Institute–supported Surveillance, Epidemiology, and End Results (SEER) cancer registry. Information on stage, grade, histological codes, and

first course of treatment (surgery, radiation, chemotherapy) were collected and defined using ICD-O codes (International Classification of Diseases for Oncology, 3rd edition) [258]. Deaths of study participants were ascertained through the Iowa death certificates and supplemented by linkage to the National Death Index for non-respondents and emigrants from Iowa.

4.2.2. Assessment of smoking status

In the baseline questionnaire, women were asked for information on smoking status (never, ever, and former, current), age at smoking initiation, and average number of cigarettes smoked per day. For formers smokers at baseline, age at quitting smoking was also collected. The information of current smoking status was updated in follow-up questionnaires mailed in 1992, 1997, and 2004. We classified patients' smoking status based on the aggregated information of smoking status of the baseline and the 3 follow-up interviews during more than 20 years of the cohort study.

Patients who reported ever smoked cigarettes at baseline or at any follow-up questionnaires before cancer diagnosis were defined as ever smokers before diagnosis. Among ever smokers, patients who did not smoke at all follow-up questionnaires after cancer diagnosis were defined as quitters, while patients who reported current smoking at any follow-up questionnaires after diagnosis were defined as persistent smokers. Participating patients who never smoked at baseline and all follow-up questionnaires were defined as lifelong nonsmokers. The pack-years of smoking at baseline (one pack = 20 cigarettes) was defined as years of smoking multiplied by the average numbers of packs smoked per day at the time of baseline interview. For all quitters, we calculated years since quitting smoking until diagnosis. For patients who already quitted smoking at

baseline, age at quitting was documented in the baseline questionnaire; for patients who quitted between baseline and diagnosis, age at quitting was defined as the year of last record that a woman reported current smoking plus 3 years (half of the median length of intervals between two follow-ups (6 years) of the current study). Years since quitting were calculated by subtracting age at quitting smoking from age at diagnosis

As of December 31, 2008, the cutoff date for case ascertainment of the present study, 9,821 out of 38,006 eligible women who were free of cancer at the enrollment of IWHS were diagnosed with cancer. Among them, 5,283 (53.8%) patients, with a median survival time of 2.5 years, did not have valid smoking information on all of the post-diagnosis follow-up questionnaires or had died before the next follow-up interview after diagnosis for updating of their smoking status, and therefore, no information of smoking status after cancer diagnosis was collected. Given that the objective of the present study was to examine the effect of post-diagnosis smoking on survival, these patients were excluded from our analysis.

Of the 4,538 cancer patients who survived at least one follow-up interview following cancer diagnosis to have updated information on post-diagnosis smoking status, 36 patients did not have any records of smoking status before diagnosis, and 12 patients initiated smoking after cancer diagnosis. These 48 patients were not included in any analyses of the present study. Among the remaining 4,490 eligible patients of the current study, 2,906 (64.7%) were lifelong nonsmokers, 1,303 (29.0%) were ever smokers and had quitted smoking before diagnosis (quitters), and 281 (6.3%) were ever smokers before diagnosis and continued to smoke after diagnosis (persistent smokers).

4.2.2. Statistical analysis

For each of 4,490 cancer patients included in the present study, person-years of follow-up were calculated from the date of cancer diagnosis to the date of death or December 31, 2008 (date for last linkage to the Iowa death certificates), whichever occurred first. The Kaplan-Meier method and log-rank test were used to examine the difference in survival time of lifelong nonsmokers, quitters, and persistent smokers for all cancer patients and breast cancer patients.

To adjust for multiple confounders, we used Cox proportional hazard regression method to estimate hazard ratios (HR), their corresponding 95% confidence intervals (95% CIs), and P values to compare the all-cause mortality risk. All Cox regression models included the following covariates: age at cancer diagnosis, level of education (no formal schooling, primary school, junior middle school, senior high school, and college or above), body mass index (BMI, kg/m^2) at baseline, number of pack-years of smoking at baseline, total numbers of tumors, stage (localized, regional/distant or undetermined), and first course of treatment options including surgery (yes/no), radiation (yes/no), and chemotherapy (yes/no). Regression models for analysis of breast cancer patients were additionally adjusted for tumor grade (well, moderately, poorly differentiated, and undetermined, classified specifically for breast cancer based on SEER coding manual [259]) and the status of estrogen/progesterone receptor (both non-null, either null, or unknown). In addition, for the analysis of comparing hazard risk for persistent smokers vs. quitters, we perform the analysis with further adjustment of number of years between quitting and cancer diagnosis in the Cox model to incorporate the time effect of smoking cessation for all ever smokers.

The Kaplan-Meier analysis and the Cox regression model were performed among all cancer patients and patients with cancers of the breast, colon-rectum, lung, or gynecological organs, respectively. All statistical analyses were carried out using SAS software version 9.2 (SAS Institute). All P values reported are two-sided, and those that were <0.05 were considered to be statistically significant.

4.3. Results

Of the 4,490 eligible cancer patients, a total of 51,097 person-years accrued from cancer diagnosis to death or the end of 2008 (Table 4- 1), and 1,769 (39%) patients had died. The mean age (± standard deviation) of patients at cancer diagnosis was 70.6 (±6.3) years. The median survival time was 17.9 years after cancer diagnosis. Eighty-nine percent of all patients received surgery, whereas 19.3% received chemotherapy and 20.8% had radiation therapy. Overall the median survival time was shorter for women patients with lung cancer (median survival = 6.8 years) than their counterparts with breast cancer (median survival = 19.3 years), gynecologic cancer (median survival = 18.3 years), or colorectal cancer (median survival = 19.0) (Table 4- 1).

Persistent smokers had statistically significant shorter survival time compared with lifelong nonsmokers and ever smokers who quitted smoking (Figure 4- 1) ($P_{\text{log-rank}} <$ 0.01). Similarly, breast cancer patients who were quitters and persistent smokers had significant reduced overall survival compared to lifelong nonsmokers ($P_{\text{log-rank}} < 0.01$). At 10 years following diagnosis, 62.7%, 59.2%, and 59.5% of breast cancer patients who were lifelong nonsmokers, quitters, and persistent smokers, respectively, were alive. Lower survival rate associated with smoking after cancer diagnosis was seen for patients with colorectal cancer ($P_{\text{log-rank}} = 0.01$) and lung cancer ($P_{\text{log-rank}} = 0.07$). The overall

survival was comparable between never smokers, quitters, and persistent smokers after diagnosis for patients who had gynecologic cancers ($P_{log-rank}$ = 0.71, Supplemental Figure 4- 1).

The median survival time for persistent smokers was 13.9 years, which was 2.0 years and 5.3 years less than that of quitters and lifelong nonsmokers, respectively (Table 4- 2). Compared with lifelong nonsmokers, persistent smokers had a borderline statistically significant increased risk of all-cause mortality (HR = 1.22, 95% CI = 0.99-1.52). Among breast cancer patients, the all-cause mortality risk was comparable between persistent smokers and lifelong nonsmokers (HR = 1.30, 95% CI = 0.91-1.85). HRs for quitters were similar to that of lifelong nonsmokers (HR = 0.92, 95% CI = 0.79-1.06 for all patients, and HR = 0.98, 95% CI = 0.76-1.26 for breast cancer patients) (Table 4- 2).

Table 4- 3 shows the hazard ratios of all-cause death for persistent smokers vs. quitters among all patients as well as patients with specific cancers. After adjusting for potential confounders, persistent smokers experienced a statistically significant 32% (95% CI = 10% - 60%) increased risk of all-cause mortality compared with quitters. Continue to smoke after cancer diagnosis was associated with substantial adverse survival outcomes for patients with lung (HR = 2.23, 95% CI = 1.17-4.25), colorectal (HR = 1.95, 95% CI = 1.15-3.31), and breast cancer (HR = 1.41, 95% CI = 1.04-1.92). Post-diagnosis smoking had no impact on survival for gynecologic cancer patients (HR = 0.91, 95% CI = 0.47-1.77). After further adjustment for the number of years between quitting smoking and diagnosis, women who smoked after diagnosis had a significant 23% increased mortality risk (95% CI = 0% - 51%). The elevated mortality risk remained statistically significant for lung and colorectal cancer patients (HR = 1.83, 95% CI =

1.10-4.24 and HR = 2.16, 95% CI = 1.02-3.31, respectively), but not for breast cancer patients (HR = 1.09, 95% CI = 0.76-1.57) (Table 4- 3).

4.4. Discussion

The present study of women in Iowa demonstrates that post-diagnosis cigarette-smoking is associated with significantly increased mortality risk and reduced median survival time. After adjusting for confounders, the all-cause mortality risk is ~30% higher for persistent smokers after diagnosis than quitters. The statistically significant increased mortality risk associated with post-diagnosis smoking has been detected among patients with lung and colorectal cancer patients, and possibly among breast cancer patients. Continued smoking after diagnosis has no impact on survival for gynecologic cancer patients. Consistent with findings in the present study, cigarette smoking after cancer diagnosis was associated with a significant 1.6 fold increased mortality risk of male cancer patients in the Shanghai Cohort Study. The impact of smoking on long-term survival was statistically significant for lung, stomach, and colorectal cancer patients in Shanghai, China.

4.4.1 Implications for women cancer survivors

Although the linkage between pre-diagnosis smoking cessation and the reduced cancer-related mortality has been established for decades [1, 22, 71, 104, 106], evidence about post-diagnosis smoking and long-term survival among women cancer patients are scarce. Overall, women are less likely to smoke than men [256]. Most studies about post-diagnosis smoking and cancer mortality have less than 30% female patients of total study samples [110, 132, 136, 140, 146, 150, 159, 160].

On the other hand, the once-wide gender gap in smoking prevalence narrowed until the mid-1980s and has remained constant thereafter [256]. Smoking is currently more popular among younger rather than older women [256], which is an alarming trend that smoking in women may cause future burden with smoking-related mortality and morbidity. In addition, molecular epidemiology research showed the impact of a given amount of smoking on the risk and prognosis of smoking-related cancers, such as lung cancer, may be greater for women than for men [24, 260, 261]. Therefore, given the deficiency of the existing literature and the anticipated increasing burden of cancer caused by smoking for women cancer patients, it is valuable to provide evidence of effects of smoking cessation in the post-diagnosis setting for female cancer patients.

Findings of our study are particularly important for women cancer survivors and their families. First, breast cancer is by far the most commonly diagnosed cancer in women. Survivors with a history of breast cancer represent 22% of all cancer survivors in the U.S. and the five year survival rate of breast cancer is as high as 88% [6, 12]. In the present study, we find that compared to lifelong nonsmokers, smoking cessation does not reduce breast cancer mortality, which is consistent with previous studies reporting no substantial association between smoking or smoking cessation and breast cancer death rate [104, 256, 262]. However, our findings point out the overall survival for persistent smokers is worse than quitters, shown by the Kaplan-Meier curve. Also, compared to ever smokers who have quitted smoking, persistent smokers after diagnosis experienced a statistically significant 41% increased mortality risk. After adjusting for time since quitting, breast cancer patients who continued smoking after diagnosis have a 10% increased non-significant risk. Thus although the time since quitting plays an important

role in smoking-related mortality, we suggest that the impact of post-diagnosis smoking on survival for breast cancer patients is non-negligible. Second, we find that the mortality risk of lung, breast, and colorectal cancer, the top three leading causes of cancer deaths in the U.S., are closely correlated with post-diagnoses smoking among women patients. Deaths from lung, breast, and colorectal cancer account for more than 50% of total cancer deaths among women in the U.S. Implementing smoking cessation interventions after diagnosis may cause a significant overall reduction in cancer mortality for female patients in the U.S. Therefore, in order to obtain beneficial survival outcomes, it is critical for female cancer patients who have ever smoked before diagnosis to stop smoking after diagnosis, even if smoking is not a strong predictor for long-term survival of a specific cancer, such as colorectal and breast cancer.

4.4.2 Public health implications

There is considerable room to improve the rate of self-managed or healthcare provider-assisted smoking cessation in the post-cancer diagnosis clinical setting. Smokers diagnosed with cancer, especially smoking-related cancers, were expected to have a strong motivation to quit after diagnosis [124, 125]. However, cancer survivors face physical, psychological, social, spiritual, and financial issues during diagnosis and treatment [138]. Compared to men, women are less likely to show confidence in the ability to quit smoking, have lower levels of quitting motivation, more easily to feel stressful during the cessation period, and have more tobacco withdrawal symptoms including anxiety, depression, and irritability [263-265]. In addition, physicians may not be motivated to advise cancer patients to quit because of a deficiency of evidence for survival outcomes and a fatalistic belief that it is too late to quit [165]. As of today, only a fraction of smoking

patients received formal smoking cessation counseling from healthcare providers [14, 166]. A few smoking cessation programs tailored to cancer patients were attempted and the efficacy of these programs was not consistent [15].

Results of our study have important implications for patients, healthcare providers, and policy makers. A patient's legitimate health perception is one of the most important reasons related to the adoption of protective actions [246]. The current study provides an important piece of evidence to help cancer survivors to build up perception toward long-term survival. Patients may incorporate personal preferences and their health perceptions after diagnosis to opt for smoking or nonsmoking. Furthermore, healthcare providers can take advantage of the "teachable" moment [135, 138] to accommodate smoking cessation assistance into comprehensive cancer care at a time when survivors' health and survival is paramount. Specific smoking cessation interventions for cancer patients, especially women patients, are necessary to assist patients in adjusting anticipations of health and addressing updating disease- and treatment- related issues. Moreover, our findings grant support to tobacco control programs, policies, and cancer survivorship initiative programs. Findings of the increased mortality risk caused by post-diagnosis smoking should be included in guidelines and evidence-based clinical practices in the context of cancer care and survivorship. In addition, smoking cessation is generally considered as cost-effective [177, 180]. Based on our findings about survival benefits among patients with some types of cancers, insurance and pharmaceutical companies may consider promoting smoking cessation interventions, medications, and disease management strategies for targeted cancer patients.

4.4.3 Strengths and limitations

The present study has certain strengths and limitations. On the strength side, the population-based prospective cohort design enables an unbiased selection of study population of women diagnosed with cancer. The large number and well-identified cancer cases allowed the evaluation of risk associations with adequate statistical power and sufficient length of follow-up for all patients as well as cancer patients of a specific type.

Although our study provides insightful implications, we acknowledge several data-related limitations. One concern is that smokers may be diagnosed at an older age with delayed diagnosis and treatment [247]. However, in our study population, we found that ever smokers were diagnosed at a slightly younger age than nonsmokers. The mean age (±standard deviation) of ever smokers was 69.9 (±6.0), which was 1 year younger than lifelong nonsmokers (71.0 (±6.4)) of the IWHS. Similarly, the mean age at diagnosis was 70.6 (±6.2) and 69.8 (±5.9) for lifelong nonsmoking and ever smoking breast cancer patients, respectively. Another concern is that smokers may have worse prognostic cancers, defined by poorly differentiated or invasive tumors, than their nonsmoking counterparts [78, 79]. On the contrary to that, we found no significant differences in distributions of different clinical- or pathological- factors between smoking groups in our study population of women in Iowa (Supplemental Table 4- 1). The corresponding proportion of breast cancer patients in the lifelong nonsmoker group, quitters group, and persistent smokers group were also comparable in terms of stage and grade of cancer, histological subtypes, and first course of treatment received. Additionally, since the IWHS is linked to the SEER cancer registry, we have good measures of cancer stage,

grade, number of tumors, and treatment options for patients. These measures of tumor characteristics were included as adjustments in Cox regression models when estimating the hazard ratios. Therefore, survival benefit due to smoking cessation detected in the present study is less likely to be biased by prognostic factors which are correlated with pre-diagnosis smoking history.

Another potential limitation is that some quitters have been ex-smokers for a long time at the cancer diagnosis. In response to that, we included the number of years since smoking cessation until diagnosis as a covariate in our analysis to accommodate the effect of quit time. We found that while the strength of the association diminished, a statistically significant relationship between post-diagnosis smoking and increased mortality risk remained among total cancer patients, as well as lung and colorectal patients, but not among breast cancer patients. It is likely that for breast cancer patients, time since smoking cessation is an important independent prognostic predictor. Nonetheless, breast cancer patients are anticipated to survive long after diagnosis (median survival = 19.3 years). Quit smoking after diagnosis may still benefit patients in the long run. This notion is supported by the fact that overall survival is worse with persistent smokers than with quitters since about 8 years after diagnosis, shown on the Kaplan-Meier curve. Under these circumstances, we would definitely recommend post-diagnosis smoking cessation for breast cancer patients in clinical setting. Furthermore, even though quit smoking in people's early rather than later stage of life confers benefits in reducing lung and colorectal cancer risk [22, 62], we denote that smoking cessation after diagnosis for elderly women also leads to a beneficial decrease in mortality risk, specifically among

lung and colorectal cancer patients. Therefore, the message of important survival benefits due to post-diagnosis smoking cessation is inclusive and clear.

Additionally, we notice that the average length of time between cancer diagnosis and the next follow-up measure was 2.9 years for lifelong nonsmokers and 2.8 years for ever smokers. After diagnosis, lifelong nonsmokers, quitters, and persistent smokers all had an equivalent 3 years until the next follow-up among breast cancer patients. However, for lung and colorectal cancer patients, length of time between diagnosis and the next smoking status measurement was shorter for persistent smokers than that for lifelong nonsmokers and quitters (Supplemental Table 4- 1). The difference of time interval may suggest that more enduring smokers than former smokers or lifelong nonsmokers died soon after the diagnosis of lung and colorectal cancer. They did not live until the first follow-up and were excluded from the current study population.

4.4.4 Excluded cancer patients

Finally, it is worth noting that in the present analysis, we only studied patients who had survived beyond one follow-up after the date of cancer diagnosis. Patients who died soon after the diagnosis were excluded. Median survival was 2.5 years for these 5,283 excluded patients. The rationale of eliminating these patients from the current analysis based on the following reasons. First of all, the present study is only interested in the impact of post-diagnosis smoking cessation on cancer survival. Patients without updated post-diagnosis smoking information are considered as ineligible and irrelevant to our study. Moreover, the distribution of patients with different smoking status among the excluded and included colorectal and lung cancer patients is statistically non-significant (Supplemental Table 4- 2). When comparing the distribution of these patients according

to smoking status, we classify smokers as patients who reported currently smoking at the follow-up immediately before cancer diagnosis, quitters as ever smokers at baseline or at any follow-ups but not the one immediately prior to diagnosis, and nonsmokers as patients who had never reported smoking before diagnosis. Among breast and colorectal cancer patients, a similar proportion of smokers were excluded and included, while as projected, a higher percentage of smokers who were diagnosed with lung cancer died quickly after diagnosis and thus were not included in the paper. Then we went on to assess the effect of smoking cessation on survival for patients who lived a short period of time after diagnosis by comparing HRs of smokers vs. quitters (Supplemental Table 4-2). We found that after adjusting for potential confounders, mortality risks were comparable for smokers and quitters of this population of excluded cancer patients, regardless of types of cancer. Therefore, it is conceivable that smoking is not a major factor in causing any difference in mortality risk for cancer patients who expect a short span of life after diagnosis. The impact of smoking cessation may only affect patients who are able to live long enough to gain survival benefits. Based on our findings, caution is warranted when generalizing conclusions of beneficial survival due to post-diagnosis smoking cessation to cancer patients who anticipate having a short life expectancy after diagnosis.

In summary, smoking after cancer diagnosis decrease median survival time by 2 years and substantially increase risk of all-cause death by 30% for female cancer patients. The survival benefits derived from smoking cessation after cancer diagnosis are seen among lung, colorectal, and breast cancer patients. We recommend that prominent advice and assistance should be provided to patients to encourage or to enforce smoking cessation policy at the time of cancer diagnosis and during and after cancer treatment.

Table 4- 1. Distributions of selected characteristics of cancer patients, the Iowa Women Health Study 1986-2008

	No. of Cases	No. of Death (%)	Total Person-years	Average Person-years	Median Survival (yr)	Age at diagnosis	Tumor stage (% localized)	Received Surgery (%)	Received Chemotherapy (%)	Received Radiation Therapy (%)
Total cancer patients	4490	1769 (39.4)	51097	11.4	17.9	70.6	59.6	88.8	19.3	20.8
By cancer sites										
Breast	1918	644 (33.6)	23316	12.2	19.3	70.3	70.3	98.8	20.6	28.0
Colon-rectum	729	256 (35.1)	8427	11.6	19.0	71.2	47.9	98.1	20.6	6.3
Gynecologic organs	613	254 (41.4)	7434	12.1	18.3	69.7	64.4	95.6	9.3	25.1
Lung	153	108 (70.6)	1090	7.1	6.8	70.0	40.5	60.8	20.9	30.1
Bladder	108	51 (47.2)	1135	10.5	14.2	71.4	77.8	93.5	10.2	1.9
Kidney	80	42 (52.5)	867	10.8	13.9	70.9	70.0	96.3	0	0
Others	889	414 (46.6)	8828	9.9	14.5	71.4	42.9	58.5	25.1	16.8

Figure 4- 1. Kaplan-Meier survival curves by smoking for all cancer patients and breast cancer patients, the Iowa Women's Health Study 1986-2008
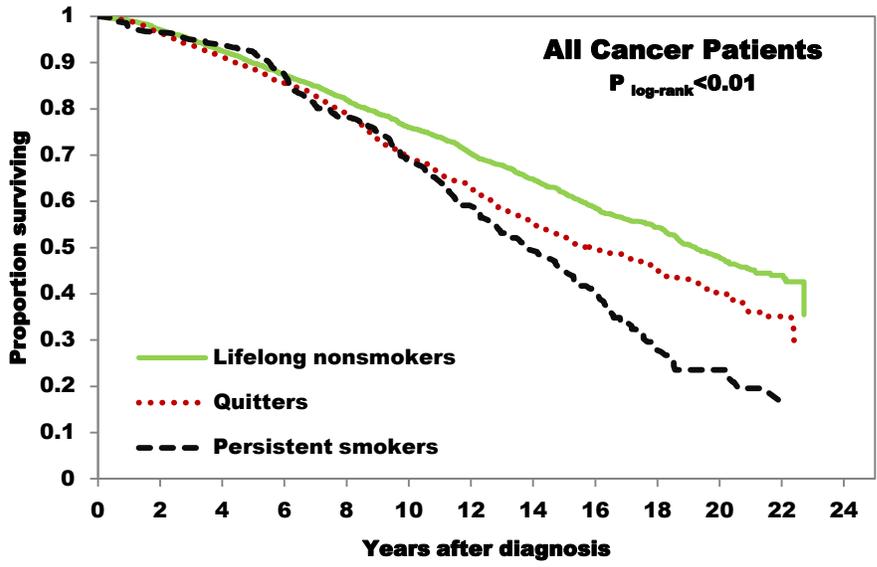
No. at risk
Lifelong nonsmokers	2823	1993	1011	247
Quitters	1258	866	385	77
Persistent smokers	271	194	96	17
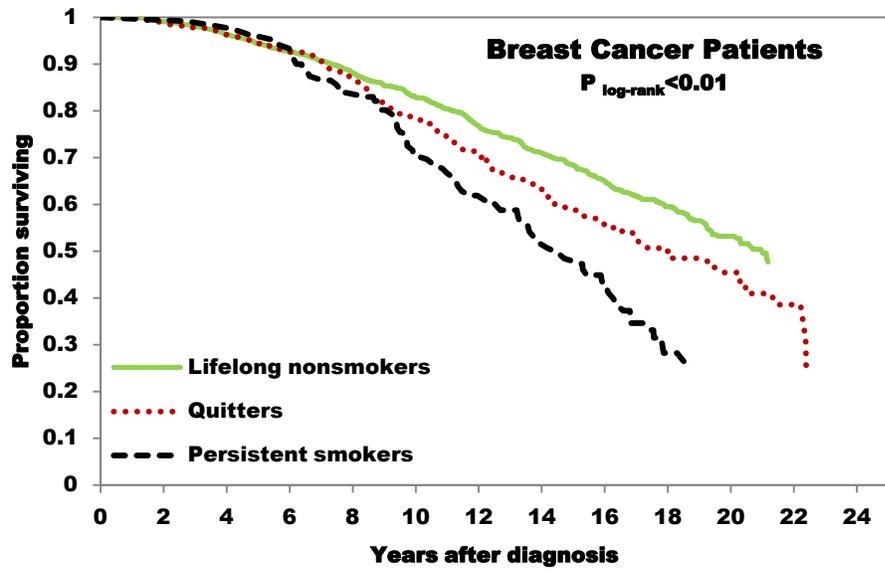
No. at risk
Lifelong nonsmokers	1265	970	497	111
Quitters	513	374	166	32
Persistent smokers	120	92	44	0

Table 4- 2. Hazard ratio of all-cause mortality by smoking status among all cancer patients and breast cancer patients, the Iowa Women Health Study 1986-2008

	No. of Cases	No. of Death (%)	Average Person-years	Median Survival (yr)	HR (95%CI) *
Total cancer patients	4490	1769 (39.4)	11.4	17.9	
Lifelong nonsmokers	2906	1039 (35.8)	11.5	19.2	1.00 (reference)
Quitters	1303	559 (42.9)	11.0	15.9	0.92 (0.79-1.06)
Persistent smokers	281	171 (60.9)	11.6	13.9	1.22 (0.99-1.52)
Breast cancer patients	1918	644 (33.6)	12.2	17.9	
Lifelong nonsmokers	1277	387 (30.3)	12.3	21.0	1.00 (reference)
Quitters	520	187 (36.0)	11.6	18.1	0.98 (0.76-1.26)
Persistent smokers	121	70 (57.9)	12.4	14.5	1.30 (0.92-1.85)

* Hazard ratios (HR) for total subjects were adjusted for age at diagnosis (continuous), BMI at baseline (continuous), level of education, race, number of pack-years smoked at baseline (continuous), type of first course of treatment: chemotherapy (no, yes), surgery (no, yes), and radiation (no, yes), stage (localized, regional/distant, undetermined), and number of total tumors (continuous). HRs for breast cancer patients were further adjusted for estrogen/progesterone receptor (+/+, either null, or unknown) and grade of tumor (well-moderately differentiated, poorly differentiated, or unknown).

Table 4- 3. Hazard ratio (HR) (95% CI) of all-cause mortality of quitters and persistent smokers by cancer sites, the IWHS 1986-2008

	No. of total cases	No. of quitters (median survival)	No. of persistent smokers (median survival)	HR1 (95%CI) *	HR2 (95%CI) †
All cancer patients	4490	1303 (15.9)	281 (13.9)	1.32 (1.10-1.60)	1.23 (1.00-1.51)
Breast	1918	520 (18.1)	121 (14.5)	1.40 (1.03-1.91)	1.09 (0.76-1.57)
Gynecologic organs	613	159 (17.7)	35 (20.2)	0.91 (0.47-1.77)	0.92 (0.45-1.91)
Colon-rectum	729	218 (18.5)	38 (14.1)	1.95 (1.15-3.31)	1.83 (1.02-3.31)
Lung	153	107 (6.7)	16 (5.0)	2.23 (1.17-4.25)	2.16 (1.10-4.24)

* HR1 derived from Cox model to compare all-cause mortality of persistent smokers vs. quitters. For total subjects and all other cancer patients except for breast cancer patients, HRs were adjusted for age at diagnosis (continuous), BMI at baseline (continuous), level of education, race, number of pack-years smoked at baseline (continuous), type of first course of treatment: chemotherapy (no, yes), surgery (no, yes), and radiation (no, yes), stage (localized, regional/distant, undetermined), and number of total tumors (continuous). HRs for breast cancer patients were further adjusted for estrogen/progesterone receptor (+/+, either null, or unknown) and grade of tumor (well-moderately differentiated, poorly differentiated, or unknown).

† HR2 was further adjusted for number of years between smoking cessation and cancer diagnosis in addition to all covariates adjusted for HR1.

Supplemental Figure 4- 1. Kaplan-Meier survival curves by smoking status for patients with cancers of the colon-rectum, lung, and gynecologic organs, the Iowa Women's Health Study 1986-2008
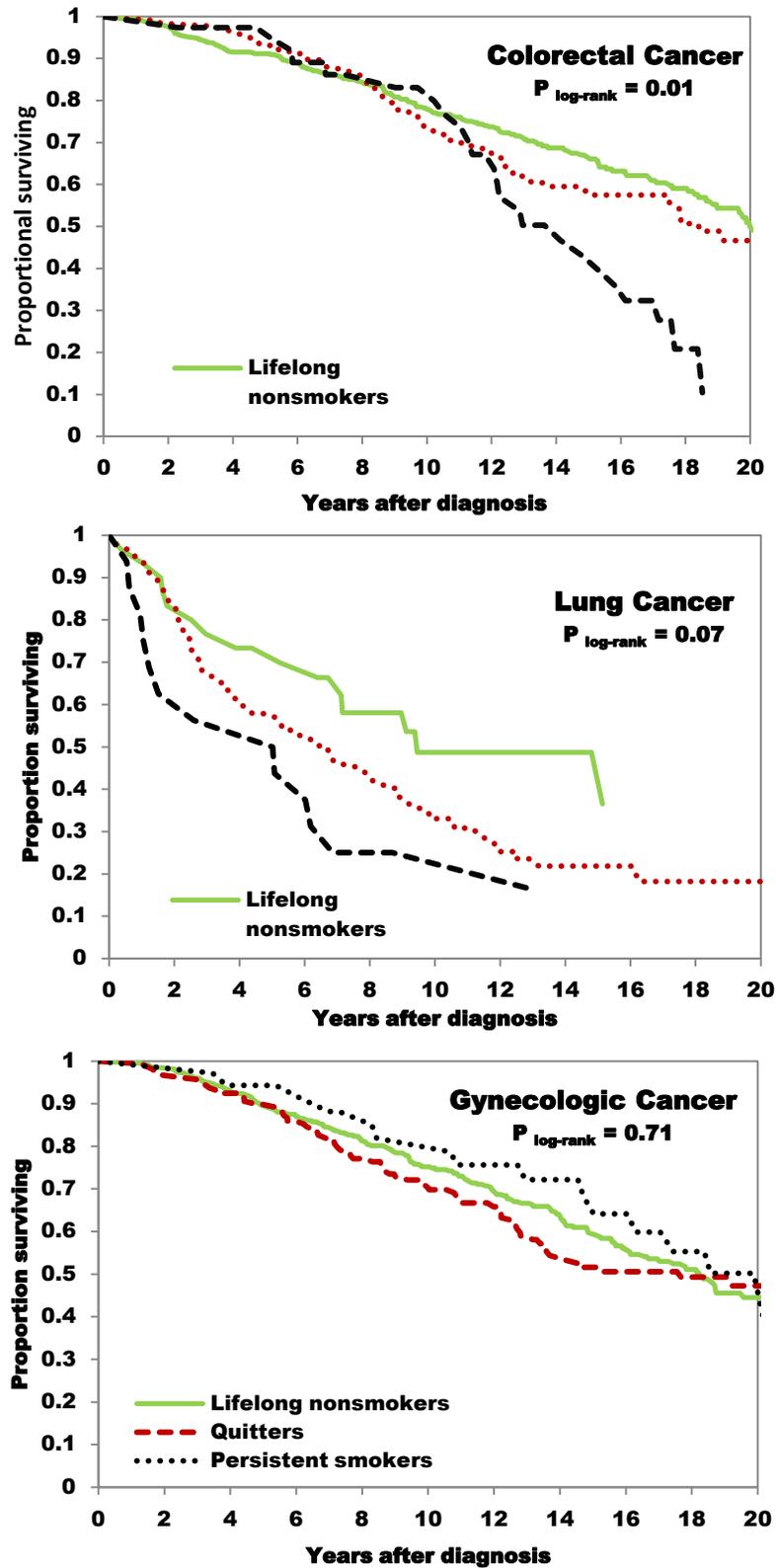
Supplemental Table 4- 1. Characteristic of the study population by smoking status, the IWHS 1986-2008

	Total N (%)	Lifelong Nonsmokers N (%)	Quitters N (%)	Persistent Smokers N (%)	P
All cancer patients	4490	2906	1303	281	
Mean age at diagnosis (yr)	70.6	71.0	70.4	67.9	0.01
By stage					0.33
Localized	2675	1737 (64.9)	774 (28.9)	164 (6.1)	
Regional/Distant	1137	742 (65.3)	332 (29.2)	63 (5.5)	
By treatment					
Surgery					0.09
Yes	3987	2604 (65.3)	1138 (28.5)	245 (6.1)	
No	181	108 (59.7)	56 (30.9)	17 (9.4)	
Chemotherapy					0.88
Yes	868	574 (66.1)	243 (28.0)	51 (5.9)	
No	3581	2306 (64.4)	1047 (29.2)	228 (6.4)	
Radiation therapy					0.10
Yes	933	590 (63.2)	297 (31.8)	46 (4.9)	
No	3532	2301 (65.2)	997 (28.2)	234 (6.6)	
Breast cancer patients	1918	1277	520	121	
Mean age at diagnosis (yr)	70.3	70.6	70.3	67.8	0.01
By stage					0.56
Localized	1348	895 (66.4)	368 (27.3)	85 (6.3)	
Regional/Distant	335	232 (69.3)	86 (25.7)	17 (5.1)	
By treatment					
Surgery					0.36
Yes	1895	1265 (66.8)	512 (27.0)	118 (6.2)	
No	8	3 (37.5)	4 (40.0)	1 (12.5)	
Chemotherapy					0.23
Yes	395	279 (70.6)	98 (24.8)	18 (4.6)	
No	1510	989 (65.5)	418 (27.7)	103 (6.8)	
Radiation therapy					0.07
Yes	536	352 (65.7)	162 (30.2)	22 (4.1)	
No	1378	922 (66.9)	357 (25.9)	99 (7.2)	
By grade					0.09
Well/moderate differentiated	760	496 (65.3)	227 (29.9)	37 (4.9)	
Poor/undifferentiated	490	331 (67.6)	124 (25.3)	35 (7.1)	
By histological subtypes *					0.39
Favorable	386	270 (70.0)	99 (25.7)	17 (4.4)	
Unfavorable	1464	961 (65.6)	403 (27.5)	100 (6.8)	
Others	68	46 (67.7)	18 (26.5)	4 (5.9)	
Interval from diagnosis to 1st post-diagnosis follow-up (yr)					
All cancer patients	2.9	2.9	2.8	2.8	0.04
Lung cancer patients	2.4	2.1	2.5	1.9	0.40
Colorectal cancer patients	2.8	2.9	2.8	2.1	0.03
Breast cancer patients	3.0	3.0	2.9	3.0	0.39

* The classification of favorable, unfavorable, and others histological subtypes of breast cancer was based on Gapstur et.al 1999 [2]. Favorable histological subtypes include ductal carcinoma in situ, favorable invasive papillary carcinoma, papillary adenocarcinoma, etc., unfavorable histological subtypes include invasive ductal and/or lobular carcinoma. See table 1 on pp. 2093 of the Gapstur article.

[2] Gapstur, S. M., Morrow, M., and Sellers, T. A. Hormone replacement therapy and risk of breast cancer with a favorable histology: results of the Iowa Women's Health Study. JAMA : the journal of the American Medical Association, *281:* 2091-7, 1999

Supplemental Table 4- 2. Characteristic of the study population by smoking status[*] at cancer diagnosis, for current study population and the excluded population, the IWHS 1986-2008

	Total N (%)	No. of deaths (%)	% deaths before the next available survey	Age at diagnosis	Nonsmokers at diagnosis N (%)	Ever smokers at diagnosis		P	HR (95%CI) [‡] of smokers vs. quitters
						Quitters N (%)	Smokers N (%)		
All cancer patients									
Current study population	4490	1769 (39.4)		70.6	2723 (65.0)	1011 (24.1)	457 (10.9)		
Excluded population†	5331	3816 (71.6)	62.3	71.5	2557 (58.8)	1136 (26.1)	653 (15.0)	0.01	1.03 (0.88-1.21)
Breast cancer patients									
Current study population	1918	644 (33.6)		70.3	1197 (66.8)	412 (23.0)	182 (10.2)		
Excluded population†	1074	524 (48.8)	37.4	75.8	603 (67.1)	230 (25.6)	66 (7.3)	0.03	1.47 (0.87-2.47)
Lung cancer patients									
Current study population	153	108 (70.6)		70.0	29 (20.1)	58 (40.3)	57 (39.6)		
Excluded population†	864	787 (91.1)	85.0	73.6	112 (16.3)	258 (37.6)	316 (46.1)	0.31	0.95 (0.72-1.26)
Colorectal cancer patients									
Current study population	729	256 (35.1)		71.2	441 (65.7)	174 (25.9)	56 (8.4)		
Excluded population†	874	585 (66.9)	63.1	76.3	485 (68.9)	156 (22.2)	63 (9.0)	0.26	1.15 (0.68-1.97)

* Nonsmokers were patients who had never reported smoking before diagnosis. Smokers were patients who reported currently smoking at the follow-up questionnaire immediately prior to cancer diagnosis. Quitters were nonsmokers at baseline or at any follow-up but not the one immediately prior to cancer diagnosis. A total of 299 patients who were included in the present study, and a total of 937 patients who were excluded from the present study did not have information on smoking status at the follow-up immediately prior to cancer diagnosis, and thus were not included in the Cox regression analysis for estimation of HRs.

† Excluded patients did not have valid smoking information on all of the post-cancer diagnosis follow-up questionnaires or had died before the next follow-up interview after cancer diagnosis for updating of their smoking status.

‡ HR derived from Cox model to compare all-cause mortality of persistent smokers vs. quitters (reference). All HRs were adjusted for age at diagnosis (continuous), BMI at baseline (continuous), level of education, race, number of pack-years smoked at baseline (continuous), years between smoking cessation and diagnosis (continues), type of first course of treatment: chemotherapy (no, yes), surgery (no, yes), and radiation (no, yes), stage (localized, regional/distant, undetermined), and number of total tumors (continuous). HR for breast cancer patients were further adjusted for estrogen/progesterone receptor (+/+, either null, or unknown) and grade of tumor (well-moderately differentiated, poorly differentiated, or unknown).

CHAPTER 5: PROBABILITIES OF DEATH FROM CANCER AND IMPACT OF POST DIAGNOSIS SMOKING ON LIFE EXPECTANCY AMONG CANCER SURVIVORS: A DECISION ANALYSIS

5.1. Introduction

Tobacco use is the most recognized cause of cancer-related death, accounting for 30% of all cancer deaths in the U.S. [4]. There is sufficient evidence suggesting a causal link between tobacco use and the incidence of several types of cancer, including cancers of the lung, bladder, and stomach [5]. Smoking cessation reduces the risk of cancer and cancer-related mortality [1, 22, 71, 104, 106], however, evidence of the impact of post-diagnosis smoking cessation on cancer-related mortality is limited. Adverse outcomes among lung or head and neck cancer patients who continue smoking compared with patients who quit smoking after diagnosis include increased complications and reduced efficacy from treatment, increased probability of tumor recurrence or occurrence of a secondary tumor, lower quality of life, and poorer general health [15, 137, 140-142, 145-149]. A few studies found decreased mortality rates associated with smoking cessation after diagnosis [110, 132, 136], while most studies didn't [140, 146, 150, 159, 160]. Our previous cohort analyses showed that post-diagnosis smoking was associated with reduced long-term survival in both male and female patients. The association was statistically significant for many specific cancers, including lung and colorectal for both male and female, and stomach for male cancer patients.

Decisions regarding cigarette smoking for cancer patients, particularly soon after diagnosis and around the treatment period, are complex. The diagnosis of cancer may be an incentive for patients to stop smoking, which opens a window of "teachable"

opportunity for healthcare providers to intervene and emphasize the importance of smoking cessation [135, 138, 232]. However, disease and treatment impose physical, psychological, and social barriers, such as nicotine dependency, lack of social support, deficiency in knowledge, fatalistic belief, and disease- and treatment- related discomfort and stress for cancer patients to quit smoking [135, 138]. Healthcare providers may also have concerns to implement usual components of smoking cessation interventions, such as exercise regimens, dietary change, and nicotine replacement therapy, to cancer patients given the barriers. Patients and healthcare providers are likely to be uncertain about the efficacy of smoking cessation programs.

Decision analysis is a most helpful tool under circumstances of uncertainty. Projections of survival with and without smoking cessation after cancer diagnosis can provide important information to facilitate decision making between physicians and their patients. Estimates of life expectancy for continued smokers and quitters after cancer diagnosis may be useful for patients to build a perception of life living with cancer, and for healthcare providers to provide data when communicating with patients and families. In the past decade, a few tobacco-related simulation models were applied to assess the impact of tobacco policies on quality-adjusted life years [207, 266] and cost-effectiveness [180, 195]. No decision analyses have been performed to estimate life expectancy for cancer survivors in terms of smoking in the post-diagnosis setting. To address the critical issue of tobacco control for cancer survivors, we developed a decision-analytic model to project the effect of post-diagnosis smoking on life expectancy among patients who have been diagnosed with cancer.

In addition, given the considerable improvements in cancer diagnosis and treatment, cancer survivors are more likely to live longer and die from a cause other than the diagnosed cancer than ever before. The measure of cancer specific probability of death, reflecting the mortality patterns of cancer patients, is useful for healthcare providers to evaluate and balance risks and benefits of clinical options, particularly when patients' risk of comorbidity is increasing with age [267, 268]. Based on the theoretical framework of competing-risk model and analysis of Surveillance, Epidemiology, and End Results (SEER) data, studies showed that the percentage of death from breast cancer increased with advanced tumor stage [268, 269] and declined as age increased because of the increasing risk of death from other causes [267, 270, 271]. However, cancer specific and competing causes of deaths have not been analyzed for other types of cancers by stage and age at diagnosis. Limited available information prompts us to conduct a simulation analysis to calculate the proportion of death that is due to cancer for cancer patients.

The magnitude of potential survival benefits due to smoking cessation and the proportion of patients who died from cancer-specific causes among cancer survivors depends on many factors including age, gender, type of cancer, and the stage of the tumor at diagnosis. Therefore in this decision analysis, we simulate different cohorts of patients defined by both tumor stage and age at diagnosis, and separately for men and women.

5.2. Methods

5.2.1. Markov Model

We develop a Markov state-transition model to provide estimates of proportion of cancer specific death and the life expectancy of smokers and nonsmokers after cancer diagnosis. The simulated cohorts of cancer patients are evaluated annually for all-cause

death. The Markov process for estimating proportion of cancer deaths has three states: alive, dead of cancer and dead of other cause; and the Markov model for simulating post-diagnosis smoking effect has two states: alive and dead. All patients start after cancer diagnoses until death.

5.2.2. Data Source

We used the results of our two companion cohort analyses based on the Shanghai Cohort Study and the Iowa Women's Health Study (IWHS). Details of the two cohorts have been described before [224, 225, 257]. Hazard ratios (HR) that assessed the strength of the associations between post-diagnosis smoking and risk of all-cause death were derived in both studies. The analysis based on the Shanghai Cohort Study included 1,592 male cancer patients (mean diagnosed age 68.8 ($\pm$7.2) years) in Shanghai, China. A time-dependent approach was used to integrate repeated measures and account for dynamic changes of smoking status during more than 20 years of annual follow-up interviews. The companion analysis based on the IWHS included 4,490 primarily Caucasian female cancer patients (mean diagnosed age 70.6 ($\pm$6.3) years) in Iowa, U.S. Information of smoking status was collected in baseline and 3 follow-up questionnaires for up to 20 years after cancer diagnosis. The mortality risk was compared between patients who reported ever smoking and patients who reported nonsmoking after cancer diagnosis. All HRs for both cohort analyses were adjusted for available potential confounders, including age at diagnosis, number of pack years smoked, level of education, tumor characteristics, and treatment options.

The two studies looked at several leading cancers. For men in U.S., prostate, lung, and colorectal cancers are the first three most common cancers; bladder cancer and

stomach cancer are the fourth leading cancer among Whites and Asian Americans, respectively. For women, breast, lung, and colorectal cancers are the three leading cancers in the U.S. [248]. We were not able to get a good HR of post-diagnosis smoking for bladder and prostate cancer patients due to small sample size in the Shanghai Cohort Study. Therefore, in our decision analysis, we simulate cohort of cancer survivors with lung, colorectal, and stomach cancer for male patients, as well as breast, lung, and colorectal cancer for female patients.

The rationale for using HRs from our previous cohort analyses rather than estimates from published data is based on the following reasons. First, existing literature is not equivalent in study design and quality. Among previous studies providing estimates of risk of all-cause mortality in association with post-diagnosis smoking, 4 studies for early stage non-small cell lung cancer patients [110, 146, 159, 160], 2 studies for early stage small cell lung cancer patients [132, 136], and 1 study for superficial transitional cell carcinoma bladder cancer patients [157] are considered as relatively high-quality studies (reviewed in ref.[272] for early staged lung cancer and reviewed in ref. [273] for bladder cancer). These studies have either a hospital- /health center- referral based prospective study design [146, 159] or a retrospective study design [110, 132, 136, 157, 160]. These study designs may be subject to limitations such as recall bias, selection bias of non-equivalent population, small sample sizes, and confounding risk factors. On the other hand, the two cohort analyses we conducted have population-based prospective study design and long-term follow-up which are less likely to have biases in study design than previous studies. Therefore, parameter estimates based on our two cohort analyses provide robust results which are more pertinent to the general cancer survivors relative to clinic- or hospital-

based cancer patients. Second, most published studies were not adjusted for potential confounding factors and were not able to show statistically significant HRs. Only two studies included adjustments such as age, gender, pack-years of smoking, type of operation, and tumor characteristics in the analysis models [110, 132]. The HRs (95% CI) of these two studies were 1.86 (1.33-2.59) and 2.94 (1.15-7.54), respectively, for early stage small cell and non-small cell lung cancer patients. Our estimates of adjusted lung cancer HRs (95% CI), which are 2.00 (1.34-2.98) for men in Shanghai and 2.16 (1.10-4.24) for women in Iowa, fall within the range of estimates from these two studies. Third, evidence is inadequate in terms of HRs for all-cause mortality in relation with post-diagnosis smoking on other types of cancer, besides lung or bladder cancer with a specific histological subtype. Also, none of the previous studies provided estimates for men and women patients separately. Our two cohort analyses for male and female patients have sufficient statistical power to derive HR of all-cause mortality measures of many cancer sites, including colorectal, breast, and stomach cancers, which have not been published before.

We derived the probability of post-diagnosis smoking based on estimates from National Health Interview Survey (NHIS) data (1998-2001) [13]. Besides smoking probability for breast cancer patients, which was directly achieved from the article [13], parameters of post-diagnosis smoking prevalence for male and female lung and colorectal cancer patients separately were derived using the general gender ratio of smoking prevalence of the 1998-2001 period (NHIS 2001, 25.2% and 20.7% current smokers in men and women, respectively) [274], number of female and male patients, and the overall smoking prevalence of lung and colorectal cancer patients based on the article [13]. We

found that smoking prevalence of cancer survivors in the Shanghai Cohort Study is 1.2 and 1.3 times higher than the calculated smoking prevalence of cancer survivors among men in U.S. for lung and colorectal cancer patients, respectively. We also noticed that the post-diagnosis smoking prevalence of women lung, breast, and colorectal cancer survivors in Iowa is 1.5-2.0 times lower than the calculated female smoking prevalence using the national data. To make estimates from this analysis more applicable to general women cancer survivors in the U.S., we choose to use the smoking prevalence derived from the NHIS.

5.2.3. Data Analysis

In this decision analysis, we simulated cohorts of lung and colorectal cancer of both male and female patients, and female breast cancer patients. We studied patients who are diagnosed at age 55, 60, 65, 70, 75, and 80, and with localized, regional, or distant stage of cancer. All analyses were performed by TreeAge (TreeAge Software, Williamstown, MA) software.

Major parameters used in our models are listed in Table 5- 1. Hazard ratios of all-cause mortality for smokers vs. nonsmokers after diagnosis for male or female patients diagnosed with cancers of the lung, breast, stomach, or colon-rectum were based on our previous cohort analyses. Cancer specific annual hazard rates by stage (localized, regional, and distant) (μ_{cancer_stage}) were derived from the 5-year relative survival rates ($S(5)_{cancer\_stage}$) reported by SEER [6]. We assumed rates beyond 5 years are constant:

$$\mu_{cancer\_stage} = - LN (S (5)_{cancer\_stage})/5$$

Using U.S. Life Tables for men and women [275], the age-sex-associated annual mortality hazard rates ($\mu_{as}(age)$) can be estimated as a function of age. We assumed that the risk of death from the specific cancers is negligible in the life tables. All cause mortality rate were calculated by adding the hazard rate of specific cancers by stage and the background mortality for a subgroup of patients:

$$\mu_{all} = \mu_{cancer\_stage} + \mu_{as}(age)$$

We first perform a Markov model to simulate cohorts of cancer patients, defined by types of cancer, stage, and age at diagnosis, to project the percentage of cancer-specific deaths out of total deaths. Probabilities for cancer-specific death and all-cause death were calculated using μ_{cancer_stage} and μ_{all}. A three states Markov model (alive, die of cancer, and die of all other causes) was constructed. We calculated the percentage of the simulated cohort who died from cancer by using the final proportion of the simulated cohort for each state derived from the Treeage software:

Cancer death% = (Proportion of patients died from cancer)/ (Proportion of patients died from cancer + Proportion of patients died from other causes)

To simulate the impact of post-diagnosis smoking, we used all-cause mortality hazard rates (μ_{all}), smoking probability (Pr) after cancer diagnosis by cancer site, and the hazard ratio (HR) to calculate the hazard rate for nonsmoking cancer patients after diagnosis (μ_{nonsmk}):

$$\mu_{nonsmk} = (\mu_{all})/((HR-1)\times Pr+1)$$

The hazard rate for smoking cancer patients (μ_{smk}) after diagnosis was calculated by multiplying the HR and the μ_{nonsmk} :

$$\mu_{smk} = \mu_{nonsmk} \times HR$$

Point estimates of μ_{smk} and μ_{nonsmk} were used to get transition probabilities in the Markov model for smokers and nonsmokers after cancer diagnosis:

$$pDie_{nonsmk} = 1 - \exp(-\mu_{nonsmk})$$

$$pDie_{smk} = 1 - \exp(-\mu_{smk})$$

We further estimated gains of life expectancy due to smoking cessation after diagnosis. Life expectancy gain was defined as the difference of life expectancy between nonsmoking and smoking cancer patients after diagnosis.

5.3. Results

Proportion of cancer deaths out of all deaths varies by gender, cancer types, age, and stage of cancer at diagnosis (Table 5- 2). Overall, percentage of cancer-caused deaths decreases with increased age due to the increasing risk of other causes of death. Among lung and colorectal cancer patients, slightly higher proportion of female patients died of cancer than male patients, given the same age and cancer stage at diagnosis. For patients who have distant metastasis, the majority of patients, ranging from 73% to 99% depending on types of cancer and age at diagnosis, died from cancer. More than 95% of patients who have localized lung cancer and are diagnosed at age 55 died from cancer, while only 51% of deaths are due to cancer when diagnosed at age 90. Proportion of cancer deaths for early stage male stomach cancer patients, ranging from 43% to 94% depending on age, is slightly lower than that of lung cancer patients, but is higher than that of colorectal cancer patients. Among patients who have localized colorectal cancer, 12%-71% male patients and 14%-80% female patients die from cancer, depending on age

at diagnosis. Only 38% of localized breast cancer patients die from cancer if diagnosed at 55, and this percentage declined to 2% when diagnosed at age 90.

Table 5- 3 shows the total remaining life expectancy for male cancer patients after diagnosis. Quitters anticipate longer life expectancy than persistent smokers. Depending on the age at diagnosis, life expectancy ranges from 2.1 to 3.7 years for quitters and 1.1 to 1.9 years for smokers with a localized lung cancer, and about 10 months for quitters and less than 6 months for smokers with more advanced lung cancer. Life expectancy for early stage stomach cancer patients is 2.4-4.8 years for quitters and 1.2-2.2 years for smokers. Stomach cancer patient with a distant tumor have similar life expectancy estimates with patients who have distant lung cancer. Male colorectal cancer patients may live up to 10.0 years for nonsmokers and 7.3 years for continued smokers after diagnosis. Life expectancy for colorectal cancer patients does not exceed 1.2 years for those who quit smoking and 9 months for smokers if diagnosed with a distant tumor. Diagnosis at an older age does not cause the life expectancy to drop substantially among cancer patients diagnosed with regional or distant tumors (Table 5- 3).

The remaining life expectancies for quitters and persistent smokers among female cancer survivors are shown in Table 5- 4. Life expectancy ranges from 2.5 to 4.9 years for patients who quit smoking and 1.3 to 2.4 years for continued smokers diagnosed with a localized lung cancer, depending on age at diagnosis. The life expectancy for more advanced stage of lung cancer patients in female patients is similar to that of male patients. Breast cancer patients have longer life expectancy than female patients with other cancers. For 55-year-old women diagnosed with early stage breast cancer, total remaining life expectancy is 13.5 years for nonsmokers after cancer diagnosis and 13.1

years for those who continue to smoke. Women diagnosed with late stage breast cancer have up to 20 months of life expectancy. The life expectancy ranges from 3.4-10.9 years for nonsmokers to 2.2-7.8 years for smokers diagnosed with early stage colorectal cancer. Life expectancy for colorectal cancer patients does not exceed 15 months for nonsmokers and 9 months for smokers when diagnosed with a distant tumor, regardless of the age of diagnosis (Table 5- 4).

Gains in life expectancy decrease with increasing age at diagnosis because of the decline in remaining natural life expectancy. Similarly, the worse the prognosis of the cancer, the lower the likelihood a patient will survive longer enough to obtain the benefit of smoking cessation after diagnosis (Table 5- 5). Among male patients, the nonsmoking population after diagnosis can expect a gain of 1.8 years in life expectancy for early stage lung cancer patients who are diagnosed at age 55, and 10 months for patients diagnosed at age 85. Gains in life expectancy for regional and distant lung cancer are up to 11 and 5 months respectively. Stomach cancer patients have a similar gain in life expectancy with that of lung cancer patients. For colorectal cancer patients, smoking cessation after cancer diagnosis leads to approximately 3 years of additional life expectancy for early stage patients diagnosed at age 55, and about 1 year for early stage patients diagnosed at age 85. Late stage colorectal cancer patients have up to 6 months more life expectancy by quitting smoking (Table 5- 5). Similarly, female patients can anticipate 1.2-3.2 more years of survival benefits from quitting smoking after the diagnosis of early stage lung or colorectal cancer patients, and about 6 months for late stage cancers.

Sensitivity analysis shows that gains in life expectancy attributable to smoking cessation are sensitive to types of cancer. When cancer mortality rates drops after a

certain years post diagnosis, male and female patients would expect increasing gain in life expectancy due to smoking cessation after lung cancer. Similar trend is expected for male patients after stomach and colorectal cancer, but no change in gains of life expectancy is expected to accompany difference in cancer rate after breast or colorectal cancer in female patients.

Consistent with existing literature, smoking doesn't seem to be as strongly associated with breast cancer as with the other types of cancer. Stage and age at diagnosis seem to have the stronger influence. Gains in life expectancy are consistently lower for women with breast cancer compared with other cancers in female patients. Smoking cessation is associated with no more than 6 months of survival benefits for women with localized breast cancers and only a couple months for patients with advanced stage breast cancer. Both age and stage at diagnosis have a modest effect on the life expectancy gain from smoking cessation for breast cancer patients (Table 5- 5).

The calculated gains in life expectancy due to smoking cessation after cancer diagnosis of all subgroups are plotted by age (Figure 5- 1) and stage of tumor (Figure 5- 2) at cancer diagnosis. In general, at the same age at diagnosis and the same prognostic stage of cancer diagnosed, male cancer survivors have higher gains in life expectance due to smoking cessation than their female counterparts.

5.4. Discussion

Our decision analysis synthesized the proportion of deaths due to cancer and the effect of post-diagnosis cigarette smoking on life expectancies for male and female cancer patients. Percentage of cancer-specific deaths increases with younger age at diagnosis and with more advanced stage of cancer. The majority of patients who have

distant metastasis died from cancer. For early stage cancer patients, 51%-95% lung cancer patients, 12%-80% colorectal cancer patients, and only 2%-38% breast cancer patients die from cancer, depending on gender and age at diagnosis. Post-diagnosis smoking cessation leads to life expectancy gains ranging from a couple of months to more than 3 years, varying by cancer type, gender, age and stage at diagnosis. Relative to persistent smokers, those who quit smoking have considerably increased life expectancy for patients with colorectal cancers. Given the low survival rate, survival benefits are also substantial for lung and stomach cancer patients. In this analysis, we suggest that proportion of cancer specific deaths and gains in life expectancy due to post-diagnosis smoking cessation varied with age at diagnosis and tumor stages, both of which are important prognostic factors of cancer survival. Age does not substantively affect the proportion of cancer death or the impact of smoking cessation once distant metastasis has occurred. Moreover, the magnitude of life expectancy gain is not strongly correlated with the length of remaining life expectancy for specific cancers, especially for female patients. Of all simulated cancer patients, breast cancer patients have the lowest gain in life expectancy but the longest remaining life expectancy for both persistent smokers and quitters. Our model indicates post-diagnosis smoking leads to loss in life expectancy even though smoking was not a strong etiological factor for some cancers, such as colorectal or breast cancer.

Since the development of the competing-risk model [268], a few empirical studies have examined the competing causes of death among women diagnosed with breast cancer using SEER data. Two empirical studies studied breast cancer patients at different ages or who were at different stages of cancer and found the breast cancer specific deaths

accounts for 29%-78% of all deaths in patients diagnosed with breast cancer in age between 50 and 80, regardless of stage [269, 271], and ranged from 29%-84% for localized to distant breast cancers, regardless of age at diagnosis [269]. Another study integrated both age and stage into stratification analyses and suggested that for patients diagnosed at 70 years and older, death from breast cancer accounted for 14%, 34%, and 70% of the total probability of death among white patients with localized, regional, or distant cancer, respectively [267]. These estimates were developed for all elderly patients diagnosed after age of 70. On average, our estimation falls within the range of the empirical studies. Relative to the empirical studies, our analysis provides estimates for the percentage of breast cancer deaths according to both specific stage and age at diagnosis. In addition to breast cancer, we provide estimation for percentage death due to cancer of other sites by age and stage, which have not been shown in the literature before.

For simulation models about tobacco use in the existing literature, the objective was to cast projections on surveillance and policy evaluation systems, trends of smoking prevalence, and economic outcomes [180, 191-193, 195, 196, 200]. A frequently used model, SimSmoke, built on a population model that incorporates birth and death, was developed in 2000 [196]. The SimSmoke model has been applied to different populations in the U.S. as well as other countries and has successfully predicted changes in smoking prevalence and smoking attributable to premature mortality in reaction to certain tobacco policies [196-202]. Another model, the Tobacco Policy Model, was built to monitor the dynamic flow of smoking prevalence to assess the relative magnitude of health gains of quality-adjusted life year (QALY) in association with tobacco policies [204-207]. Series applications of the Tobacco Policy Model found reduction in initiation of smoking [207], reduction in nicotine

contents in cigarettes [205], safer cigarettes [204], or intensive school-based anti-tobacco educational effort [206] could lower smoking prevalence and increase cumulative gains in QALYs for the population.

In this decision analysis, we modeled several common cancers which are the leading causes of cancer death among men and women in the U.S. Our estimates are useful in the wide spectrum of health and healthcare. First, estimates for proportion of cancer-specific deaths may be an optimal measurement of prognosis after a cancer diagnosis [267]. For patients diagnosed with localized tumors, the absolute effect of cancer mortality on survival diminishes with increasing age, thus advanced age may be considered as a contraindication for receiving aggressive treatment of cancer, especially for cancers where the rate of diminishing cancer death with increasing age is high. In fact, elderly patients are more likely to have treatment-associated risks, such as complications after surgery and chemotherapy-associated toxicity [276, 277]. For patients diagnosed with more advanced cancers, cancer deaths remain a substantial concern of mortality even for elderly patients. Our estimates may be particularly relevant in clinical decision making to weigh the harm and benefits of various treatment options for elderly patients. Furthermore, many cancers may not be as strongly perceived as life-threatening diseases now as they used to be, and patients with cancer can survive longer than before. The proportion of cancer patients that died of other diseases, such as heart disease, stroke, respiratory disease, and diabetes, increases with age [278]. The main risk factor for these leading causes of deaths is cigarette smoking, which accounts for 18% of overall death in the U.S. [254]. Based on our estimates, we suggest that for cancer patients who have diminishing cancer-specific death rates with increasing age, prevention of other disease

through adopting a healthy lifestyle, especially smoking cessation, is critically important in cancer survivorship initiatives.

Additionally, our study is the first decision analysis to simulate the impact of cigarette smoking on life expectancy in the post-cancer diagnosis setting. The findings of our model have important public health implications. First, an accurate and clear health perception is one of the most important reasons for a patient to opt for healthy behaviors [246]. Life expectancy estimates derived from our model provide an important piece of evidence to build up a cancer patient's perception toward long-term survival. Patients' attitudes towards smoking are unpredictable and diverse by individual preference. Cancer patients who are smokers at- or before- diagnosis may face tremendous disease- and treatment- related psychological, physical, or social stress when making decisions about smoking cessation after diagnosis or treatment. The present analysis encourages cancer patients to incorporate personal preferences of cigarette smoking and health perceptions into the adoption of healthy lifestyles in order to extend life expectancy. Second, by synthesizing the best available relevant data, life expectancy estimates derived from our decision analysis can serve as meaningful and useful indications to assist physicians, oncologists, and other healthcare providers during communication with patients and their families. Important messages about the anticipated remaining life expectancy of smokers and nonsmokers after diagnosis as well as the gains in life expectancy due to smoking cessation need to be conveyed to patients during physician office or hospital visits for the remaining years that a patient survives cancer. Types of cancer diagnosis may also be a factor to incorporate all preferences when delivering the message. For patients after particular cancers of which the gain in benefits from smoking cessation is not sensitivity

with diminishing cancer specific mortality rates, healthcare providers' advises in the context of smoking control may focus more on patients' general health and comorbidity rather than cancer outcomes. Third, our predictions lend support to tobacco control programs and policies, and cancer survivorship initiative programs. Life expectancy estimates of smokers and nonsmokers should be included in educational materials for specific smoking intervention programs and policies targeting cancer survivors, as well as in evidence-based guidelines for cancer survivorship. Finally, insurance and pharmaceutical companies could reference our estimates to promote highly effective and sufficiently cancer- tolerable smoking cessation interventions, medications, and disease management strategies for cancer patients.

We acknowledge potential limitations of our decision analysis. In the absence of good empirical data, we perform the decision analysis without using HR estimates of established data from published literature. HRs of male cancer patients in this model were calculated based on parameters derived from the cohort analysis of Chinese men. Caution is warranted when generalizing these estimates to the U.S. male population. However, we believe that the hazard ratio estimates of Chinese men are more likely to underestimate the effect of smoking cessation on mortality rate in the U.S. In other words we have made a more conservative estimate of additional life expectancy [reference to the discussion of chapter 3]. Thus gain of life expectancy due to smoking cessation would be greater if hazard ratio estimates from a Western population were used. Moreover, we derived smoking rates after cancer diagnosis for male and female separately from national survey publications due to lack of direct evidence of smoking prevalence among cancer survivors. Our estimates of life expectancy gain underscore the need for further

research on post-diagnosis smoking effects to conduct sensitivity analyses. Studies of cost-effectiveness and other health outcomes associated with post-diagnosis smoking for this population are also warranted.

In summary, the findings of our model indicate the importance of staying cigarette free after cancer diagnosis to amplify cancer survivor's probability in gaining life expectancy. Patients diagnosed at a relatively younger age or with an early stage cancer should be offered strong support with smoking interventions at cancer diagnosis. Prominent advice and assistance should be provided to the general public as well as to the health policy makers to enforce smoking cessation at the time cancer is diagnosed.

Table 5- 1. Cancer specific mortality rates and hazard ratios (HRs) by cancer sites and gender

Cancer sites	Male	Female
Cancer specific mortality rate (μ_{cancer_stage})		
Lung cancer		
Localized	0.15	0.11
Regional	0.30	0.26
Distant	0.70	0.63
Stomach cancer		
Localized	0.11	0.09
Regional	0.26	0.24
Distant	0.66	0.66
Breast cancer		
Localized	N/A	0.003
Regional	N/A	0.04
Distant	N/A	0.29
Colorectal cancer		
Localized	0.02	0.02
Regional	0.07	0.07
Distant	0.44	0.42
HR (95% CI)		
Lung cancer	2.00 (1.34-2.98)	2.16 (1.10-4.24)
Stomach cancer	2.30 (1.40-3.76)	N/A
Breast cancer	N/A	1.09 (0.76-1.57)
Colorectal cancer	1.71 (1.02-2.87)	1.83 (1.02-3.31)
Smoking probability after cancer diagnosis (Pr)		
Lung cancer	0.22	0.18
Stomach cancer	0.19	N/A
Breast cancer	N/A	0.14
Colorectal cancer	0.14	0.11

Table 5- 2. Proportion (%) of deaths due to cancer

	Diagnose at 55	Diagnose at 60	Diagnose at 65	Diagnose at 70	Diagnose at 75	Diagnose at 80	Diagnose at 85	Diagnose at 90
Male cancer patients								
Lung cancer								
Localized	95.2%	93.3%	90.3%	86.3%	79.9%	70.9%	61.0%	50.9%
Regional	97.7%	96.6%	95.2%	93.2%	89.6%	84.1%	77.3%	69.3%
Distant	99.2%	98.8%	98.2%	97.5%	96.2%	93.8%	90.8%	86.7%
Stomach cancer								
Localized	93.7%	91.2%	87.4%	81.9%	73.8%	63.8%	53.1%	42.8%
Regional	97.4%	96.2%	94.6%	92.0%	87.7%	81.8%	74.4%	65.6%
Distant	99.2%	98.8%	98.2%	97.4%	95.8%	93.4%	90.1%	85.8%
Colorectal cancer								
Localized	71.4%	64.5%	54.1%	44.4%	33.3%	23.5%	16.5%	11.6%
Regional	90.7%	86.1%	81.0%	73.9%	64.2%	52.7%	37.7%	31.9%
Distant	98.6%	98.1%	97.0%	95.7%	93.0%	89.4%	84.4%	78.1%
Female cancer patients								
Lung cancer								
Localized	96.3%	94.5%	91.2%	87.4%	80.6%	70.7%	59.4%	47.9%
Regional	98.3%	97.4%	96.6%	94.6%	91.2%	86.1%	79.0%	70.2%
Distant	99.4%	99.2%	98.7%	98.1%	96.9%	94.9%	91.7%	87.5%
Breast cancer								
Localized	37.5%	30.0%	21.4%	15.0%	9.7%	5.9%	3.7%	2.3%
Regional	88.6%	84.8%	78.0%	70.9%	59.1%	45.9%	33.9%	24.4%
Distant	98.4%	98.1%	96.9%	95.1%	92.3%	87.5%	81.0%	72.8%
Colorectal cancer								
Localized	80.0%	74.1%	64.5%	55.6%	41.7%	29.9%	20.6%	13.9%
Regional	94.4%	90.7%	87.2%	81.0%	72.3%	60.7%	48.2%	36.8%
Distant	99.1%	98.6%	98.0%	96.9%	94.8%	91.7%	86.8%	80.5%

Table 5- 3. Life expectancy (years) of nonsmoking and smoking patients after cancer diagnosis for male patients

	Life expectancy of nonsmokers							Life expectancy of smokers						
	Age at diagnose							Age at diagnosis						
	55	60	65	70	75	80	85	55	60	65	70	75	80	85
Lung cancer														
Localized	3.68	3.54	3.35	3.10	2.78	2.42	2.05	1.91	1.85	1.78	1.66	1.51	1.32	1.12
Regional	1.97	1.94	1.89	1.82	1.72	1.58	1.42	1.01	0.99	0.98	0.95	0.90	0.84	0.76
Distant	0.88	0.88	0.87	0.86	0.84	0.81	0.77	0.48	0.48	0.47	0.47	0.46	0.45	0.43
Stomach cancer														
Localized	4.81	4.54	4.22	3.82	3.35	2.85	2.35	2.24	2.15	2.03	1.87	1.65	1.41	1.16
Regional	2.30	2.26	2.19	2.09	1.96	1.78	1.58	1.03	1.01	0.99	0.96	0.90	0.83	0.74
Distant	0.95	0.95	0.94	0.93	0.90	0.87	0.82	0.46	0.45	0.45	0.45	0.44	0.43	0.41
Colorectal cancer														
Localized	9.95	8.69	7.42	6.16	4.95	3.87	2.95	7.30	6.34	5.38	4.41	3.47	2.65	1.98
Regional	5.91	5.46	4.94	4.34	3.69	3.04	2.44	3.78	3.52	3.22	2.85	2.42	1.98	1.57
Distant	1.24	1.23	1.21	1.18	1.14	1.08	0.99	0.75	0.74	0.73	0.72	0.69	0.66	0.61

Table 5- 4. Life expectancy (years) of nonsmoking and smoking patients after cancer diagnosis for female patients

	Life expectancy of nonsmokers							Life expectancy of smokers						
	Age at diagnose							Age at diagnosis						
	55	60	65	70	75	80	85	55	60	65	70	75	80	85
Lung cancer														
Localized	4.88	4.66	4.38	4.01	3.57	3.07	2.54	2.39	2.32	2.22	2.07	1.86	1.61	1.34
Regional	2.27	2.24	2.19	2.11	2.00	1.84	1.65	1.07	1.06	1.05	1.02	0.97	0.91	0.82
Distant	0.97	0.97	0.96	0.95	0.93	0.90	0.86	0.49	0.49	0.48	0.48	0.47	0.46	0.44
Breast cancer														
Localized	13.53	11.55	9.67	7.85	6.18	4.71	3.47	13.13	11.18	9.33	7.55	5.91	4.48	3.29
Regional	8.13	7.37	6.55	5.64	4.69	3.77	2.92	7.67	6.96	6.19	5.34	4.43	3.56	2.75
Distant	1.72	1.70	1.67	1.63	1.55	1.44	1.31	1.58	1.56	1.54	1.50	1.43	1.33	1.21
Colorectal cancer														
Localized	10.94	9.64	8.32	6.98	5.65	4.44	3.36	7.79	6.86	5.90	4.89	3.88	2.97	2.20
Regional	6.23	5.82	5.33	4.75	4.09	3.40	2.72	3.73	3.53	3.28	2.96	2.55	2.12	1.69
Distant	1.30	1.29	1.25	1.21	1.15	1.07	0.97	0.73	0.73	0.71	0.69	0.66	0.62	0.57

Table 5- 5. Life expectancy gain (years) due to smoking cessation after cancer diagnosis

	Life expectancy gain in Male patients								Life expectancy gain in Female patients						
	Age at diagnose									Age at diagnose					
	55	60	65	70	75	80	85		55	60	65	70	75	80	85
Cancer specific mortality rate (μ_{cancer_stage}) drops to 0 after 5 years post diagnosis															
Lung cancer								**Lung cancer**							
Localized	3.79	3.27	2.78	2.29	1.85	1.45	1.12	Localized	4.65	4.05	3.47	2.90	2.36	1.86	1.42
Regional	2.79	2.42	2.05	1.70	1.37	1.08	0.84	Regional	3.60	3.12	2.67	2.22	1.79	1.41	1.08
Distant	0.89	0.80	0.72	0.62	0.54	0.46	0.40	Distant	1.21	1.08	0.96	0.83	0.71	0.61	0.50
Stomach cancer								**Breast cancer**							
Localized	4.61	3.99	3.39	2.81	2.27	1.79	1.37	Localized	0.39	0.37	0.33	0.31	0.34	0.22	0.18
Regional	3.53	3.04	2.58	2.13	1.71	1.35	1.05	Regional	0.50	0.45	0.39	0.34	0.29	0.24	0.18
Distant	1.12	1.01	0.89	0.78	0.67	0.57	0.49	Distant	0.48	0.41	0.35	0.29	0.23	0.18	0.13
Colorectal cancer								**Colorectal cancer**							
Localized	2.72	2.42	2.11	1.82	1.52	1.25	0.99	Localized	3.12	2.84	2.53	2.21	1.88	1.54	1.21
Regional	3.01	2.63	2.25	1.89	1.54	1.22	0.95	Regional	3.75	3.29	2.83	2.39	1.95	1.54	1.17
Distant	1.28	1.21	1.04	0.87	0.72	0.59	0.48	Distant	1.88	1.62	1.38	1.15	0.94	0.74	0.59
Cancer specific mortality rate (µcancer_stage) drops to 0 after 10 years post diagnosis															
Lung cancer								**Lung cancer**							
Localized	2.88	2.49	2.12	1.78	1.46	1.18	0.96	Localized	3.95	3.43	2.92	2.43	1.98	1.58	1.24
Regional	1.45	1.31	1.17	1.04	0.91	0.78	0.67	Regional	1.97	1.76	1.57	1.37	1.18	1.01	0.85
Distant	0.42	0.41	0.41	0.40	0.39	0.36	0.34	Distant	0.52	0.51	0.50	0.49	0.47	0.45	0.42
Stomach cancer								**Breast cancer**							
Localized	3.88	3.34	2.84	2.35	1.92	1.54	1.22	Localized	0.40	0.37	0.34	0.31	0.27	0.23	0.19
Regional	1.98	1.77	1.57	1.37	1.17	1.01	0.86	Regional	0.53	0.47	0.41	0.34	0.29	0.23	0.18
Distant	0.52	0.52	0.51	0.49	0.47	0.44	0.42	Distant	0.25	0.22	0.19	0.17	0.14	0.12	0.11
Colorectal cancer								**Colorectal cancer**							
Localized	2.76	2.43	2.11	1.80	1.51	1.23	0.98	Localized	3.33	2.97	2.60	2.22	1.86	1.50	1.18
Regional	2.85	2.46	2.08	1.72	1.39	1.12	0.88	Regional	3.64	3.14	2.64	2.18	1.75	1.38	1.07
Distant	0.60	0.57	0.54	0.50	0.47	0.42	0.39	Distant	0.74	0.69	0.65	0.60	0.56	0.51	0.46
Cancer specific mortality rate (µcancer_stage) is constant after diagnosis (derived from table 5-3 and 5-4)															
Lung cancer								**Lung cancer**							
Localized	1.77	1.69	1.57	1.44	1.27	1.10	0.93	Localized	2.49	2.34	2.16	1.94	1.71	1.46	1.20
Regional	0.96	0.95	0.91	0.87	0.82	0.74	0.66	Regional	1.20	1.18	1.14	1.09	1.03	0.93	0.83
Distant	0.40	0.40	0.40	0.39	0.38	0.36	0.34	Distant	0.48	0.48	0.48	0.47	0.46	0.44	0.42
Stomach cancer								**Breast cancer**							
Localized	2.57	2.39	2.19	1.95	1.70	1.44	1.19	Localized	0.40	0.37	0.34	0.30	0.27	0.23	0.18
Regional	1.27	1.25	1.20	1.13	1.06	0.95	0.84	Regional	0.46	0.41	0.36	0.30	0.26	0.21	0.17
Distant	0.49	0.50	0.49	0.48	0.46	0.44	0.41	Distant	0.14	0.14	0.13	0.13	0.12	0.11	0.10
Colorectal cancer								**Colorectal cancer**							
Localized	2.65	2.35	2.04	1.75	1.48	1.22	0.97	Localized	3.15	2.78	2.42	2.09	1.77	1.47	1.16
Regional	2.13	1.94	1.72	1.49	1.27	1.06	0.87	Regional	2.50	2.29	2.05	1.79	1.54	1.28	1.03
Distant	0.49	0.49	0.48	0.46	0.45	0.42	0.38	Distant	0.57	0.56	0.54	0.52	0.49	0.45	0.40

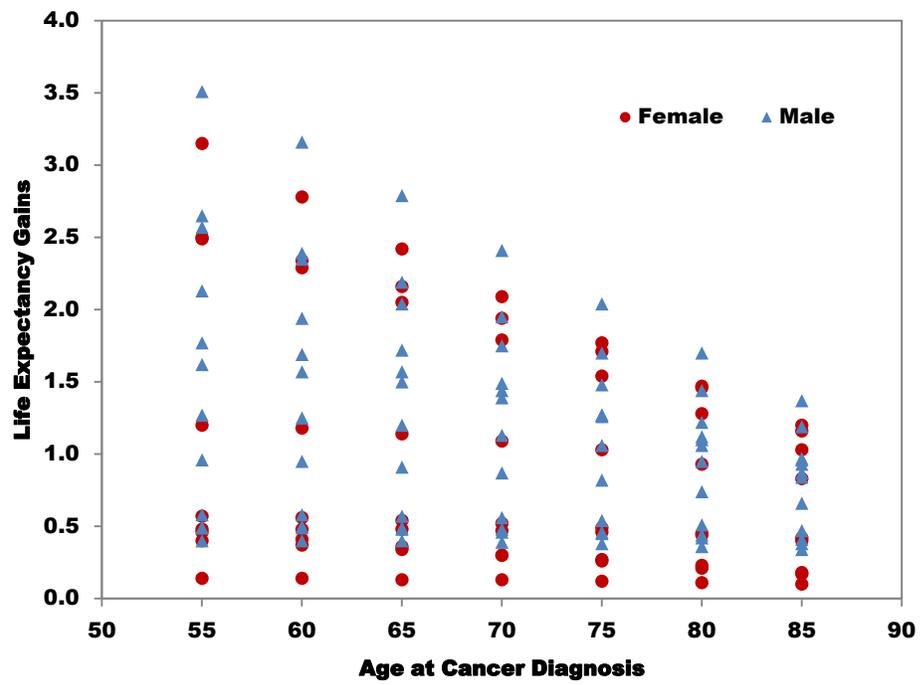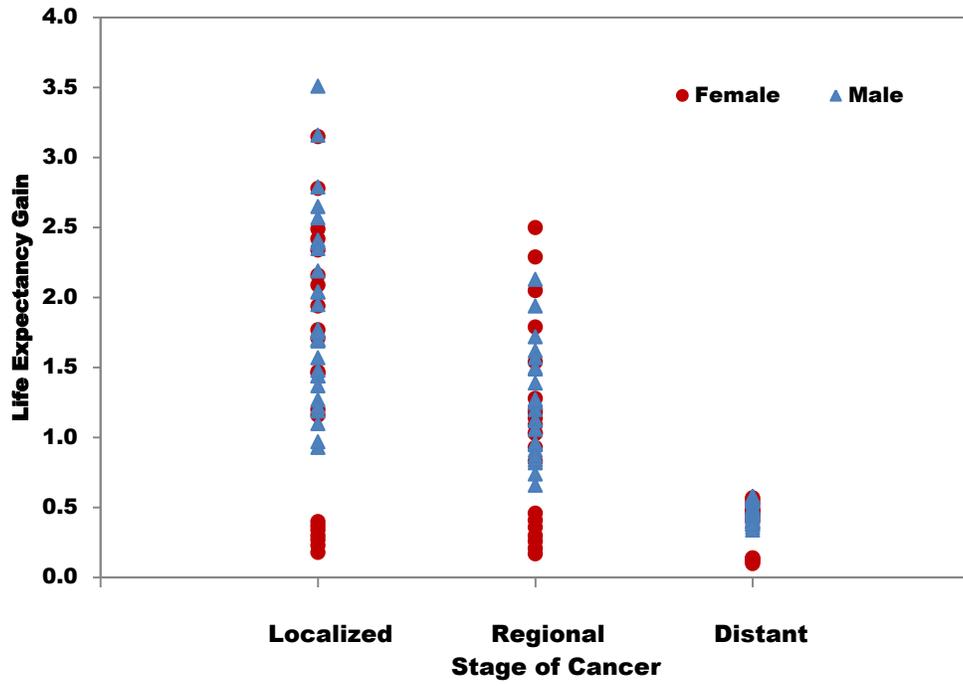**Figure 5- 1. Plot of life expectancy gains due to smoking cessation by age at diagnosis of cancer**

Figure 5- 2. Plot of life expectancy gains due to smoking cessation by stage of cancer at diagnosis

6.1. Major conclusions

In this dissertation, I ask the question of whether smoking cessation after a diagnosis of cancer contributes to an increase in time of survival after diagnosis. Three independent studies were conducted to provide estimates of survival outcomes for persistent smokers and quitters after diagnosis: two cohort analyses for male and female cancer patients separately, followed by a decision analysis. The findings of the three studies in the dissertation complement each other. Major findings of this dissertation are:

FOR ALL CANCER SURVIVORS:

- Smoking after cancer diagnosis substantially reduces the overall survival time and increases mortality risk for both male and female cancer patients, as well as reducing average life expectancy.

- Results varied by cancer type, gender, age and stage at diagnosis.

- At the same age at diagnosis and the same prognostic stage of cancer diagnosed, male cancer survivors have higher gains in life expectance due to smoking cessation than their female counterparts, possibly because men usually start smoking early, and typically smoke more cigarettes per day [279].

FOR MALE CANCER SURVIVORS:

- Smoking cessation after cancer diagnosis increased median survival time by 3.6 years for male cancer patients. Patients were diagnosed with cancer at a mean age of 69 years.

- Persistent smokers after diagnosis had a statistically significant lower survival rate compared with lifelong nonsmokers and patients who quit smoking before or after cancer diagnosis. The decreased survival rate of persistent smokers was statistically significant for all cancer patients as well as patients with lung, stomach, and colorectal cancer.

- Measured on a time-dependent yearly updated smoking status after diagnosis, continue smoking significantly increased the risk of all-cause death by 52% for all cancer patients, 72% for lung cancer patients, 71% for stomach cancer patients, and 81% for colorectal cancer patients.

- Those who were smokers at the time of diagnosis experienced similar significant increase in mortality risk associated with post-diagnosis smoking. The increased risk was 61% for all current smoking cancer patients, 100% for lung cancer patients, 130% for stomach cancer patients, and 171% for colorectal cancer patients.

- For early stage cancer patients, 51%-95% lung cancer patients, 43%-94% stomach cancer patients, and 12%-71% colorectal cancer patients die from cancer, depending on age at diagnosis. The majority of patients who have distant metastasis died from cancer.

- Cancer patients who quit smoking after diagnosis anticipate longer life expectancy than persistent smokers. Among quitters after diagnosis, increased life expectancy ranges from 2 to 3 years for lung and stomach cancer patients, 3-10 years for colorectal cancer patients who have been diagnosed with an early stage cancer, and about 10 months to 1.5 years for patients who have an advanced stage tumor. Total remaining

life expectancy for persistent smokers ranges from 1.1-7.3 years for early stage patients and about 6 months for late stage patients.

- Gains in life expectancy caused due to smoking cessation ranges from 1 year for lung cancer patients to about 3 years for colorectal cancer patients with early stage tumors, and no more than 6 months for cancer patients in advanced stages.

FOR FEMALE CANCER SURVIVORS:

- Smoking cessation after cancer diagnosis increased median survival time by 2 years for female cancer patients. Patients were diagnosed with cancer at a mean age of 71 years.

- Persistent smokers after diagnosis had a statistically significant lower survival rate compared with lifelong nonsmokers and patients who quit smoking. The decreased survival rate of persistent smokers was statistically significant for all cancer patients as well as patients with breast, colorectal cancer, borderline significant for lung cancer patients, and non-significant for gynecologic cancer patients.

- Compared to ever smokers who quit smoking, patients who continued to smoke after cancer diagnosis have a significant 1.23 fold increase in risk of all-cause death. The increased risk of all-cause death for post-diagnosis smokers was 2.16, 1.09, and 1.83 for patients with lung, breast, and colorectal cancer, respectively.

- For early stage cancer patients, 48%-95% lung cancer patients, 2%-38% breast cancer patients, and 14%-80% colorectal cancer patients die from cancer, depending on age at diagnosis. The majority of patients who have distant metastasis died from cancer.

- Cancer patients who quit smoking after diagnosis anticipate longer life expectancy than persistent smokers. Among quitters after diagnosis, life expectancy ranges from 3 to 5 years for lung patients, 3-14 years for breast cancer patients, and 3-11 years for colorectal cancer patients who have been diagnosed with an early stage cancer, and 1-2 years for patients who have an advanced stage tumor. Total remaining life expectancy for persistent smokers ranges from 1 to 3 years for lung patients, 3-14 years for breast cancer patients, and 2-8 years for colorectal cancer patients who have been diagnosed with an early stage cancer, and 6 months to 2 years for patients who have an advanced stage tumor.

- Gains in life expectancy due to post-diagnosis smoking cessation ranges from 1-2 years for lung cancer patients and 1-3 years for colorectal cancer patients, but only a few months for breast cancer patients with an early stage diagnosis, and no more than 6 months for advanced stage patients.

6.2. What this work adds

6.2.1. Survival benefit of post-diagnosis smoking cessation

The major finding of this dissertation---the decreased mortality risk due to post-diagnosis smoking cessation for all as well as specific cancer patients---has added important new information to the literature. Up to now there has been inadequate evidence on the impact of post-diagnosis smoking for long-term cancer survival. Less than 10 studies have assessed the impact of smoking on mortality risk, using all-cause mortality as the endpoint. Early staged lung and head and neck cancer patients are the target study population [110, 132, 136, 146, 160-162]. These studies are subject to study design bias:

most studies (4 out of 7 studies) are retrospective; all studies are hospital-, outpatient clinic-, or physician- based; total follow-up time is less than 10 years; total study sample size is less than 350.

On the other hand, major advantages of the studies conducted for this dissertation include:

- Both Shanghai Cohort Study and the IWHS are well-designed population-based prospective studies which enable precise linkage to death certificates and accurate identification system of cancer incidences. Using cohort data, the two studies in this dissertation have sufficient sample size of patients diagnosed with different types of cancer during more than 20 years of follow-up.

- Multiple common cancers of men and women are examined. Survival outcomes are substantially improved as a result of post-diagnosis smoking cessation for all cancer patients as well as patients with many types of cancer besides lung cancer.

- For all cancer patients and patients with specific types of cancer, analyses in this dissertation have substantially large sample sizes, which would tend to make the statistical findings more robust and the message more reliable.

- The two cohorts have data on any important potential cancer prognostic factors, such as age at diagnosis, treatment received, and stage and grade for women patients. The work in this dissertation included these potential risk factors as covariates in the analyses.

- Estimates of total remaining life expectancy for continued smokers and quitters after cancer diagnosis as well as gains of life expectancy due to post-diagnosis

smoking-cessation are provided. The absolute values of remaining life expectancy and gains in life expectancy not only complement the cohort analyses, but also provide important and easy-understandable estimates for clinical use.

6.2.2. Smoking prevalence among cancer survivors

A few studies looked at the influence of a diagnosis of cancer, especially lung cancer, on the behavioral and lifestyle change among adult cancer survivors. These studies reported that the proportion of patients with lung cancer who continue to smoke after diagnosis ranged from 6%-96% [127, 133, 272]. Reasons for this broad range and heterogeneity may be that some studies collected data on smoking status retrospectively. Some hospital- or clinic- based studies have selection bias for the study population, sample size may be small, and some studies measured smoking status once at the time of diagnosis or treatment without follow-up measurements.

Estimates of post-diagnosis smoking rates of a population-based prospective study during long-term follow-up for over 20 years were provided in this dissertation work. I found that the smoking rates for cancer survivors ranged from 18%-27% in Chinese male patients, and 6%-18% in White female patients, depending on cancer sites.

6.2.3. How tobacco smoking causes cancer death

Post-diagnosis smoking cessation produces substantial survival benefits to cancer patients. There are at least two substantive explanations of the reduction of mortality risk and extended life expectancy for quitters. First, smoking cessation may decrease the risk of death due to other smoking related competing causes of death such as cardio-

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respiratory diseases. Second, smoking cessation might decrease the risk of tumor progression and cancer-related death [71]. Findings of this dissertation favors the latter: the major benefit from smoking cessation is conferred by a reduction in cancer specific risk, which is consistent with a previous study [272].

All deaths that occurred in the Shanghai Cohort Study have been ascertained via linkage of the cohort database with the Shanghai Municipal Vital Statistics Office databases so that follow-up in terms of mortality is essentially complete. The majority (87%) of male cancer patients in Shanghai, China died of cancer. The harmful effect of post-diagnosis smoking on cancer-specific mortality risk is even stronger than that on all-cause mortality (Supplemental Table 3-2). On the other hand, in our study for women in Iowa, only 54% of all deaths occurred have a documented cause of death, so that we are only able to study the association between post-diagnosis smoking and disease-specific mortality based on a potentially biased sample. Among these deaths, 63% female cancer patients died of cancer and 21% died of cardiovascular disease. Findings for cancer-specific mortality are very close to results of all cancer patients (data not shown). It is worth mentioning that in both of our cohort analyses, no associations were detected between post-cancer diagnosis smoking and cardiovascular disease-specific mortality.

6.3. Implications

More information is required for the ever-growing population of cancer survivors. Evidence affects not only survivors and their families but also health care providers and the public at large. In this dissertation, I looked at long-term survival effect of cigarette smoking on multiple common cancers for men and women using population-based

prospective data and simulation modeling. Although the study may be subjected to potential limitations when assessing the smoking-survival association, the message is literally robust to be delivered to cancer patients as well as the general public: post-diagnosis smoking cessation gains survival benefits for cancer survivors.

6.3.1. For cancer survivors and their families

The findings of this dissertation fill an important gap in existing knowledge regarding impact of smoking among cancer survivors. It is common that cancer patients who are smokers may face tremendous disease- and treatment- related psychological, physical, or social stress when making decisions about smoking cessation after diagnosis or treatment. Although the harmful effect of smoking in inducing cancer has been known for decades, patients' attitudes toward smoking after the diagnosis are unpredictable and diverse by individual preference, partly due to the barriers and the deficiency in evidence about health effect of post-diagnosis smoking.

Estimates of survival rate and remaining life expectancy for quitters and persistent smokers after cancer diagnosis derived from this dissertation provide an important piece of evidence to assist patients with the development of a perception toward long-term survival after the cancer diagnosis. A legitimate health perception is one of the most important reasons for a patient to opt for healthy behaviors, including smoking cessation [246]. This dissertation encourages cancer patients to incorporate personal preference of cigarette smoking and an appropriate health perception into the adoption of healthy lifestyles in order to lower mortality rate and to expand life expectancy.

6.3.2. For healthcare providers

The diagnosis of cancer provides a "teachable moment" for healthcare providers to intervene and assist with smoking cessation [138]. A motivation, especially the health outcome expectancy, is a strong predictor for successful smoking cessation attempts [280]. The diagnosis of cancer is a strong stressor for patients both mentally and physically, which cause the patient to be very concerned about health and survival outcomes during the surviving years. Patients may have a strong motivation to opt for smoking cessation at the stressful moment of cancer diagnosis. Thus for these patients, high levels of motivation and strong worry about health or survival could promise great possibilities for successful quitting [281, 282]. Physicians and other healthcare providers need to deliver evidence-based intervention programs which can sustain strong incentive for patients to quit smoking.

Findings of this dissertation can serve as meaningful and useful indications to assist general physicians, oncologists, and other healthcare providers during the communication with patients and their families. Effective smoking cessation education aimed at increasing awareness of cancer survivors' expectations for survival should be conducted. At diagnosis, healthcare providers can emphasize the decreased mortality risk and the anticipated life expectancy gain due to smoking cessation. Individual issues in regard of patients' types of cancer, age at diagnosis, gender, and other factors that may impact survival need to be considered when implementing a cessation program. Specific interventions are necessary to assist patients in adjusting anticipations of health and addressing updating disease- and treatment- related issues. For patients who are

intermittent smokers or are not able to quit right after diagnosis, intensified reinforcement is needed to facilitate a personalized intervention at a regular basis.

6.3.3. For public health policy makers

Healthy People 2020 set a goal of reducing the adult smoking prevalence to 12% by 2020 by increasing smoking cessation attempts and success rate [283]. To reduce the smoking rate, cancer reform strategies and tobacco control campaigns call for actions to support cancer survivors [284]. The development of these strategies and policies should be rested on robust and convincing evidence that a cigarette-free lifestyle improves survival and health and that quitting smoking after diagnosis is never too late. Unfortunately, the evidence is limited. Regardless of the public awareness of the fact that tobacco smoke is the major source of human carcinogen that cause remarkable cancer burden, smoking prevalence is still high. Today, very few smokers who had wanted or attempted to quit smoking obtained enhanced well-being from evidence-based treatments [166].

This dissertation grants support to tobacco control programs and policies, and cancer survivorship initiative programs. Health outcomes of smoking cessation should be included in educational materials for specific intervention programs and policies targeting at cancer survivors, as well as in evidence-based guidelines for cancer survivorship initiatives. Specific strategies of smoking cessation intervention, such as "The 5 A's of Tobacco Cessation Support" [285], should be introduced to guidelines of standard cancer care. Tailored and detailed intervention programs should be developed according to specific types of cancer, in regard of progress of disease and cancer treatment.

6.3.4. For others

Insurance and pharmaceutical companies could reference to the estimates to promote effective and sufficiently cancer- tolerable smoking cessation interventions, medications, and disease management strategies to address issues for cancer patients. These issues may include the importance of effective management or medications of health concerns in relate to the discomfort of smoking cessation, appropriate management of cancer care during the process of cessation, ability to maintain adequate cost coverage, adequate post smoking cessation care, and quality-of-life strategies.

Cancer patient's family, friends, or coworkers need to be aware of the survival benefits that smoking cessation can bring to the patient so that they can support the patient to quit smoking. The social supports patients receive from people in the social network have positive effects for cancer patients to cope with the disease [286, 287]. Family, peer, and community support is important in minimizing preventable discomfort and psychosocial distress for cancer patients who are going through smoking cessation.

6.4. Future directions

Future studies are warranted to confirm estimates of this dissertation, especially considering the data-imposed limitations. Additional data sources that are applicable to examine the impact of post-diagnosis smoking cessation may include a male's study with detailed documentation of tumor prognostic factors such as stage and grade, and a female's study with dynamic close updates on smoking status before and after diagnosis in a Western population. Furthermore, both cohorts analyzed in this dissertation lack the measurement of patients' quality of life. An assessment quality adjusted life years of

cancer survival in terms of the impact of post-diagnosis smoking would make it more applicable to cancer survivors. In addition, this dissertation finds that smoking cessation reduces mortality risk predominantly by lowering cancer-specific mortality instead of mortality due to competing causes. Further research is needed to study the association between post-cancer diagnosis smoking and disease specific mortality, such as cardiovascular diseases.

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