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Personal and Family History of Skin Cancer: A Possible Marker for Increased Internal Cancer Risk and Mortality

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A wise man can learn more from a foolish question than a foolish man can learn from a wise answer. –Bruce Lee

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Abstract

A growing body of evidence supports an association between a personal history of skin cancer and increased risk for adverse health outcomes. However, limitations in this evidence remain, such as incomplete control for confounding factors. Further, family history of skin cancer is likely to provide important etiologic clues but has yet to be thoroughly integrated in research to date. To address this gap, this dissertation investigates in a nationally representative cohort both personal and family history of skin cancer in relation to the risk of 1) developing an internal cancer and 2) mortality. Further, we investigate the translational potential of the association between skin cancer and risk for developing an internal cancer by introducing information for a personal history of skin cancer, family history of skin cancer, and relative's age at skin cancer diagnosis into a model for breast cancer risk, the Gail model, to determine if this additional information could improve the model's predictive ability.

We observed that after adjusting for common cancer risk factors, such as smoking and BMI, a personal history of skin cancer was associated with increased risk for developing an internal cancer but not increased risk for mortality. Additionally our work showed that patients with a skin cancer diagnosed before the age of fifty were at increased risk for developing breast cancer. Also, the results for family history of skin cancer from **Aim 3** revealed that age at relative's skin cancer diagnosis may be crucial to studying the association between a family history of skin cancer and increased risk for developing an internal cancer. Finally, calibrating the Gail model for a patient's personal and family history of skin cancer increased model sensitivity at the cost of lower specificity. Ultimately, a personal and family history of skin cancer and its role as a marker for increased risk for developing an internal malignancy makes skin cancer a rich opportunity to investigate the processes common to cancer development at several cancer sites.

Chapter I: Specific aims

Skin cancer and its subtypes, keratinocyte carcinoma (KC) and melanoma, are among the most common cancers in the United States[1–3]. The conservative estimate for KC incidence, 2 million incident cases per year, means that KC has 40% greater incidence than all other cancers combined in the United States [1]. Similarly, melanoma has an estimated 87,000 new cases per year making it the fifth most common cancer tracked by the Surveillance, Epidemiology, and End Results (SEER) program [3]. However, these cancers also have low mortality with an estimated 0.69 and 2.7 deaths per hundred thousand person years for KC and melanoma respectively. A personal history of KC and melanoma has been observed in multiple large cohort studies to be associated with significantly increased risk of 1) developing internal cancer and 2) all-cause mortality [4–7].

These associations between skin cancer, risk of internal cancer, and mortality may result from skin cancer acting as a marker for the presence of an underlying susceptibility. This susceptibility appears to increase a patient's risk for multiple forms of cancer. The existence of genetic disorders associated with increased risk for cancers at multiple sites such as *BRCA* mutations, Li-Fraumeni syndrome, and Lynch syndrome provide a strong rationale to hypothesize that the underlying susceptibility may be genetic.

A natural starting point to test for a genetic risk factor is to examine the role of family history of a disease. A family history of a disease is indicative of shared risk factors between family members; often behavioral, environmental, or genetic. However, when a family history of a disease is significant and combined with other information, such as a young age at diagnosis for cancer, a family history can support the presence of a genetic risk factor. In this dissertation we investigated if a personal history of skin cancer and a family history of skin cancer are both

associated with increased risk of subsequent internal malignancies and mortality. If both a personal and family history of skin cancer is associated with increased risk for developing internal cancer and mortality it would imply a shared causal agent. This shared association could support the current theory that skin cancer acts as a marker of a heritable predisposition to cancer because of the wide breadth of internal cancers associated with a history of skin cancer and the observation that a younger age at skin cancer diagnosis confers greater risk for developing a subsequent internal cancer. Clinically, determining if family history of skin cancer plays an important role in this association will be an important step forward in distinguishing people most susceptible to adverse health outcomes among patients with skin cancer. Furthermore, understanding the role of personal and family history of skin cancer and risk for internal cancers could improve current cancer risk models. Currently, few internal cancer risk models include information for a personal or family history of skin cancer. However, including information for a personal and family history of skin cancer in a risk model for a cancer associated with skin cancer could improve the model's discriminatory ability. Considering the breadth of internal cancers associated with a personal history of skin cancer, including information for a personal and family history of skin cancer could improve many cancer risk models. Thus, the overall goal of our research is to address the question **"Are a personal and family history of skin cancer associated with increased risk for developing an internal cancer and mortality, and could these associations be of clinical value?"**

Guided by strong preliminary data, we will address this gap in the research using nationally representative data to study the effects of a personal and family history of skin cancer in relation to risk of other cancers and mortality. Our study will use existing NHANES Epidemiological Follow-up Study (NHEFS) data with a cohort of 9,012 people with up to 10

years of follow-up (1982-1992) for **Aim 1** and **Aim 2**, and data from the National Health Interview Survey (NHIS), a cross-sectional study, for 34744 women to train and test a calibrated breast cancer risk model.

Aim 1: Determine the association between a personal history of skin cancer, a family history of skin cancer, and risk of developing an internal cancer. Using the NHEFS cohort, we will compare patients with a personal history of skin cancer to those without a personal history of skin cancer to determine risk for developing an internal malignancy. Similarly, we will evaluate a family history of skin cancer to determine if a family history of skin cancer is likewise associated with increased risk for developing an internal malignancy.

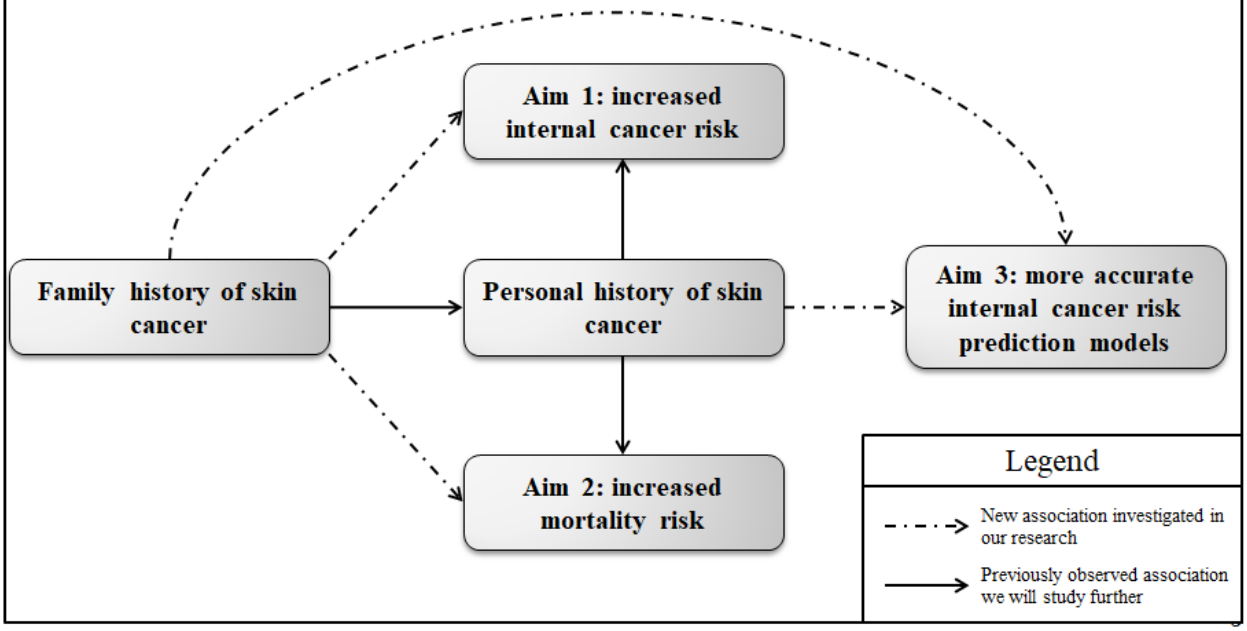
Aim 2: Determine the association between a personal history of skin cancer, a family history of skin cancer, and risk for both cancer-specific and all-cause mortality. Using the NHEFS cohort, we will compare patients with a personal history of skin cancer to those without a personal history of skin cancer to determine risk for both all-cause and cancer-specific mortality. Similarly, we will evaluate a family history of skin cancer to determine if a family history of skin cancer is likewise associated with increased risk for mortality.

Aim 3: Determine the impact of including a personal and family history of skin cancer when measuring a patient's predicted risk for developing an internal cancer. Using the NHIS data our study will train a calibration model to adjust the results of the already existing Gail model to create the Gail with Skin Cancer Modification (SCM) (Gail+SCM) model. The Gail+SCM model will be identical to the Gail model except for calibrating the Gail model's results to account for a person's personal and family history of skin cancer. The models will be compared based on the area under the receiver operating characteristic curve (AUC), sensitivity,

and specificity to determine each model's ability to discriminate between patients who will develop breast cancer and those who will not.

The conceptual model of this research, and the three aims, can be found in **Figure 1.1**.

Figure 1.1: Conceptual model of the relationships between personal and family history of skin cancer with 1) risk of developing internal malignancies, 2)risk of mortality, and 3) internal cancer risk prediction.



Chapter II: Introduction

II.A. Skin cancer and its role as a marker for internal cancer risk and mortality

A large body of consistent evidence demonstrates that a personal history of skin cancer is statistically associated with an increased risk of internal cancers [6,8,9]. The body of evidence for the association between a personal history of skin cancer and mortality outcomes is smaller and more equivocal [10]. The reasons why skin cancer is associated with increased risk for developing an internal cancer and mortality are uncertain but skin cancer may be a marker of an underlying susceptibility factor that increases a person's risk for cancer at multiple sites [4–6]. The underlying susceptibility is potentially genetic in nature due to the wide range of cancers associated with a personal history of skin cancer and the observation that skin cancer diagnosed at an early age, such as before the age of 44, confers greater risk, compared to skin cancer diagnosed later in life [4–6]. The significance of the research questions addressed herein is enhanced by the implications for translation into the clinical setting. If skin cancer acts as a marker for increased risk of developing cancer then patients with a history of both a skin and internal cancer could be used as a model for learning more about the causes of multiple primary cancers, mitigating several of the limitations faced when studying patients with multiple internal cancers. A direct potential translational research implication is that the associations between skin cancer and risk for internal cancer could be used to calibrate existing cancer risk models or to construct completely new models with greater discriminatory ability. This dissertation explores 1) the association between skin cancer and increased risk for developing an internal cancer and mortality; 2) the possibility that family history of skin cancer may shed light on a potential heritable component contributing to the association between skin cancer, internal cancer risk, and

mortality; and 3) the impact of using information for a personal and family history of skin cancer to improve the discriminatory ability of a cancer risk model.

II.B. Descriptive epidemiology of skin cancer

A brief review of the epidemiology of skin cancer is necessary to provide understanding and context for the rest of our work. Skin cancer is the malignant growth of cells in the skin most often appearing on the trunk, arms, and face [11]. Worldwide the highest rates of skin cancer occur in the United States and Australia [11]. Skin cancer can arise from any of the cell types found in human skin, with the characteristics and epidemiology of skin cancer changing based on the originating cell type. There are two major subtypes of skin cancer: melanoma and keratinocyte carcinoma (KC). The latter malignancy KC can be further broken down into its two main subtypes basal cell carcinoma (BCC), and squamous cell carcinoma (SCC). KC and melanoma are both biologically and epidemiologically distinct as shown in **Table 2.1**.

Table 2.1: Comparing Incidence and Mortality Rates of Melanoma and KC

	Melanoma	**Keratinocyte carcinoma**	**Rate Ratio of KC/melanoma**
Originating Cells	Melanocytes	basal and squamous cells	
Percent of All Skin Cancer	~4%	~96%	
Incidence Rate (per 100,000 people)	23.6	6075	257
Mortality Rate (per 100,000 people)	2.7	0.69	.12

II.B.1. Melanoma skin cancer

Melanoma skin cancer originates in melanocytes, which produce the pigment melanin. Melanoma is rarer than BCC or SCC but has a much higher mortality rate.

II.B.1.a. Melanoma incidence

Like most forms of skin cancer melanoma is most prevalent in Australia, and the United States [11]. These countries have experienced similar trends in melanoma incidence [11]. Overall melanoma is the 4th most diagnosed cancer in Australia constituting 10.1% of all new cancer

cases excluding KC. In 2009, the age adjusted incidence rate for melanoma in Australia was 49.8 cases per 100,000 people [12]. This incidence rate is the highest in the world and increased by 86% from the 1982 the rate of 26.8 cases per 100,000 people. Melanoma is the fifth most common form of cancer tracked by the Surveillance, Epidemiology, and End Results (SEER) program in the United States. In 2010 SEER reported melanoma had an incidence rate of 23.6 new cases per 100,000 people per year [3]. This incidence rate is triple what is was in 1975 though how much of this increased incidence is genuine versus due to improved surveillance methods remains unclear [3]. The melanoma incidence rate for Caucasians is roughly 20 times greater compared to African Americans [3]. Men have an incidence rate roughly 70% greater than women in the United States [3].

II.B.1.b. Melanoma mortality

In addition to having the highest incidence rates for melanoma, Australia and the United States have the highest mortality rate for melanoma. The age-adjusted mortality rate in Australia has increased, from 4.7 deaths in 1982 to 5.9 deaths per 100,000 people in 2010 [12]. The mortality rate for the United States has increased, from 2.1 to 2.7 deaths per 100,000 people per year between 1975 to 2010 [3]. As with incidence rates, the overall number of deaths for Caucasians is greater than it is for African Americans, though for mortality it is roughly a two-fold difference [3]. It is important to note, though more Caucasians die from melanoma in the United States, melanoma diagnoses are more likely to be lethal in African Americans [13]. Comparatively the mortality rate for melanoma has grown slower than the incidence rate, ~29% compared to the ~300% increase in incidence [3]. Given the improvement in treatment over the past three decades the increase in melanoma mortality is likely due to improved surveillance as

opposed to a genuine increase. Had the increased mortality rate been genuine then the trends between incidence and mortality should mirror each other.

Sex also influences mortality with 3 and 2 fold increases in melanoma mortality rates for men in Australia and the United States compared to their female counterparts[3,12]. This increased rate is due to both the higher incidence and worse prognosis experienced by men. When cases are adjusted for patient and tumor characteristics such as age and stage, women experience overall better prognosis for survival with women experiencing a hazard ratio (HR) for death of 0.62 (95% CI: 0.56-0.70) and lower risk of progression, HR: 0.68 (95% CI: 0.62–0.75) compared to men [14,15].

II.B.2. Keratinocyte carcinoma

KC is the aggregate of all skin cancers that develop from keratinocyte cells with subtypes determined by which layer of the skin the cancer originates from, most commonly the squamous and basal cell layers. First we will discuss KC as a whole and then move on to its subtypes, SCC and BCC. The following estimates for KC and it's subtypes are less accurate overall than those available for melanoma as most cancer registries, including the SEER database, do not track KC [2]. Due to this lack of accurate tracking any statistics regarding KC are often based on estimations from random samples and cohorts rather than from population based cancer registries. Regardless, when comparing KC and melanoma there are significant differences in their incidence and mortality.

II.B.2.a. Keratinocyte carcinoma incidence

KC is the single most common class of cancer with an estimated 2 to 3.5 million new cases each year in the United States [1]. Using the conservative estimate, 2 million cases, would make KC incidence roughly 33% greater than the incidence of all other cancers combined for the

United States as tracked by the SEER database for 2010 [3]. In 2008, the Australian Institute of Health and Welfare (AIHW) reported the incidence of KC was four times greater than all other cancers combined with 434,000 new cases of KC [11,12,16]. Men experience roughly a two fold increase in overall KC incidence [17,18]. Fair skinned people also experience the greatest incidence for KC though the rate increase is difficult to estimate. The World Health Organization in 2006 estimated roughly 98% of all KC cases occur in patients with Fitzpatrick skin types I, II, III [19].

II.B.2.b. Keratinocyte carcinoma mortality

The mortality rate for KC is 0.69 deaths per 100,000 people per year [11,20], roughly 12% the mortality rate of melanoma [3,11,20]. This lower mortality is due to the lower rate of metastasis for KC.

II.B.3. Keratinocyte carcinoma subtypes

Though BCC and SCC are often grouped together for research purposes the two histologies are clinically and epidemiologically distinct as shown in **Table 2.2**.

Table 2.2: Clinical and Epidemiological Characteristics of BCC and SCC

	BCC	**SCC**
Originating Cells	basal cells	squamous cells
Pre malignant forms	NA	bowen's disease, actinic keratosis
Percent of KC	65-80%	~20%
Incidence Rate Women	165.5	32.4
Incidence Rate Men	309.9	97.2
Metastatic rate	0.0028-0.55%	~3.0%
Risk Factors	ultra violet radiation exposure fitzpatrick skin type sex immunosuppression organ transplant xeroderma pigmentosum epidermodysplasia verruciformis HIV HPV age	ultra violet radiation exposure fitzpatrick skin type sex immunosuppression organ transplant xeroderma pigmentosum epidermodysplasia verruciformis smoking HIV HPV age

II.B.3.a. Basal cell carcinoma

BCCs are carcinomas that originate in the basal skin cells, the outermost layer of the epidermis and generally appear as open sores, red patches, or pink growths. BCC has four major sub-types: superficial, nodular ulcerative, pigmented, and morpheaform [21]. BCC is much more common than SCC, constituting between 65% and 80% of all incident cases of KC in the United States [22]. In Australia, BCC incidence has also increased by 33% from 1985 to 2002 [12,16,21]. If left untreated BCC can invade surrounding tissue and bone. Despite its ability to invade surrounding tissue, BCC is less likely to metastasize than SCC [21]. Between 1894 when the first case was documented and 2011, fewer than 400 cases of metastatic BCC have been

documented [23]. This low number of documented cases makes any estimate of metastasis or mortality very difficult, but the current estimated rate of metastasis is 0.0028% to 0.55% [23]. BCC thus has a lower risk of invasion than SCC with much lower risk of mortality [11].

II.B.3.b. Squamous cell carcinoma

SCCs are carcinomas that originate in the squamous skin cells, which compose the upper layers of the epidermis. SCC appears as scaly red patches, open sores, elevated growths with a central depression, or warts and they may crust or bleed. Invasive SCC may develop de novo, but SCC also has two premalignant forms [11,24]. Bowen's Disease(BD) is the non-invasive stage of SCC and shows similar histological characteristics with SCC with cellular atypia present in the full thickness of the epidermis, but is contained to just the epidermis [21]. Approximately 3-5% of BD patients progress to full SCC [11,24]. The other common premalignant stage is actinic keratosis (AK). AK has been defined as a rough, scaly patch on the epidermis often due to over exposure of ultraviolet radiation (UVR). SCC most often occurs on sun exposed skin with 70-80% of all SCCs occur on the head or neck. It is theorized that up to 20% of untreated AKs progress to SCC [11]. SCC is the second most common form of skin cancer after BCC with an estimated 700,000 new cases annually in the United States and accounts for 20% of all KC cases [21]. The incidence of the SCC in Australia has increased by 133% from 1985 to 2002 suggesting its incidence is increasing at a faster rate than BCC [12,16]. SCC has much greater metastatic potential than BCC with estimates that 2-3% of all SCC metastasize, compared to .0028-.55% for BCC [11,21].

II.B.4. The primary cause of skin cancer: ultraviolet radiation

The predominant risk factor for skin cancer is UVR. UVR has been attributed as the primary cause of up to 90% of all skin cancer tumors [19]. The primary source of UVR comes from sun exposure, though tanning beds have become an increasingly prevalent form of exposure [25]. UVR in sustained doses damages the skin and activates chromophores that in turn create reactive oxygen species. These reactive oxygen species can cause the DNA mutations needed to progress along the pathway to carcinogenesis [18]. The amount of damage done however is dependent upon several factors, most importantly the skin type.

II.B.4.a. The interaction between ultraviolet radiation and skin type

Lighter complexions with less melanin are more susceptible to UVR and consequently suffer greater damage for equivalent doses compared to darker skin types [2,11,24]. Thus the combination of a lighter skin type and UVR exposure is the most important determinant for skin cancer risk. This significant interaction appears at the population level and is the prevalent theory behind why Australia, the United States, and Western Europe have the highest skin cancer incidence rates in the world while predominantly dark skinned populations such as those in Africa have the lowest despite receiving similar doses of UVR [3,11,12]. In the United States the incidence rate for Caucasian men is ~30 greater than it is among African American men, similarly the incidence rate among Caucasian women is ~20 times greater compared to their African American peers [3].

The Fitzpatrick skin type scale categorizes skin phenotypes into categories for more consistently comparing skin cancer risk and ranks from skin type VI which is lighter and more likely to burn down to skin type I which almost never burns. When adjusted for UVR exposure all of the lighter skin types, III, II, and I, showed roughly 40% greater risk for developing

BCC(95% CI: 1.04-1.8, 1.11-1.92, 1.00-1.95), and skin type I showed increased risk for SCC (OR 2.19, 95% CI: 1.02, 4.69) [24].

Having a lighter skin type alone does not cause the development of skin cancer. Lighter skin types are more susceptible to damage, but without exposure to UVR patients with lighter skin types are not more likely to develop the mutations necessary for skin cancer development compared to a darker skinned person [11,16,24]. Thus between UVR and skin type there is an synergistic effect in which patients with lighter skin types suffer progressively greater risk due to UVR exposure compared to darker skinned patients.

II.C.1 The relevance of this research to the study of multiple primary cancers

A focus of oncology and cancer epidemiology has been the study of cancer's causal agents and how to prevent or manage them [26]. This task has proven difficult as cancer is not a single disease but instead the result of unique combinations of genetic mutations, modifications of the cell cycle, and external risk factors such as cigarette smoking [26]. Even at the same cancer site, tumors can present with different clinical and biological characteristics such as some breast cancers being dependent upon estrogen for growth while others are able to grow regardless of the presence of estrogen [26]. However, despite the heterogeneity of tumors, there may be common germline mutations or regulatory abnormalities that cause similar cancer phenotypes across different anatomical sites [26,27]. Identifying common lifestyle and behavioral risk factors, such as smoking, for cancer phenotypes at multiple sites is one approach to identifying shared causes across cancer types. For example, cigarette smoking is linked to 14 different types of cancer [26]. However, to understand underlying shared heritable susceptibilities a different methodologic approach may be needed. One of the most useful indications of a heritable shared risk of two cancers is patients who develop multiple primary

cancers [26,27]. Using *BRCA* mutations as an example, the occurrence of breast cancer and ovarian cancer within a single patient is a strong indicator that the patient carries a *BRCA* mutation [27–29]. A patient is considered to have multiple primary cancers if the patient developed two or more primary malignancies arising in different sites and these malignancies may be either "synchronous", occurring within three months of each other, or "metachronous" by being spread out over a greater period of time [27,29]. Patients with either synchronous or metachronous multiple primary cancers may possess risk factors that increase their risk for developing cancer at multiple sites and would likely present these risk factors more often than the general cancer patient population [27]. However, despite the research opportunity presented by patients with multiple primary cancers, these patients can be difficult to study due to several methodological challenges.

Studying patients with multiple primary cancers poses several challenges. Patients who develop multiple primary cancers, excluding keratinocyte carcinoma, represent 12%-20% of cancer patient population making it difficult to gather sufficient patients for study [29]. Additionally, the lethal nature of cancer introduces survivorship bias when following cancer survivors, especially if they have survived two malignancies before the start of study. Also, for patients who underwent chemo or radiation therapy there is concern that the subsequent cancer was not caused by a heritable risk factor but instead by treatment for the original cancer. For example, if a woman with a prior history of breast cancer treated with tamoxifen were to later develop ovarian cancer it would be difficult to determine if the ovarian cancer developed due to a heritable risk factor or the previous tamoxifen treatment [27,29]. However these challenges can be mitigated if researchers studied patients with a history of skin cancer and an internal cancer as opposed to patients with multiple internal cancers.

Skin cancer is the most common form of cancer with an estimated 2 to 3.5 million annual incident cases, creating a large pool of potential study participants [1,2]. Also, Skin cancer's low mortality rate reduces the potential for survivorship bias compared to internal cancers [3,11]. Additionally, 95% of all melanomas and KCs are treated through excision without chemotherapy or radiation treatments reducing concerns that subsequent cancers may have been caused by treating the original malignancy [13,21]. Thus studying patients with a personal history of both skin cancer and an internal cancer could alleviate several of the issues posed by studying patients with multiple primary cancers. However, there is uncertainty regarding the association between a personal history of skin cancer and increased risk for developing an internal malignancy. Though several registry and cohort studies have observed increase risk for developing an internal cancer among skin cancer patients, critics have noted that registry studies often are unable to adjust for common cancer risk factors and cohorts may not be generalizable to the public [6,8,9]. This dissertation addresses these concerns by investigating the association between a personal history of skin cancer and increased internal cancer risk in a nationally representative cohort with individual level information for common cancer risk factors. By adding strong evidence of an association between skin cancer and internal cancer risk to the existing literature, this dissertation will strengthen the argument that patients with a personal history of both skin and internal cancer may be due to an unknown etiological link between skin cancer and internal cancer risk which can be studied. In turn, this research may encourage future studies to include patients with a personal history of both skin cancer and an internal cancer when studying multiple primary cancers, alleviating several of the methodological issues involved in studying patients with multiple primary cancers which in turn may lead to more studies on the causes and characteristics of multiple primary cancers.

II.C.2. Skin cancer and its potential to improve internal cancer risk models

If skin cancer is associated with increased risk for developing internal cancer, then skin cancer could potentially improve predictive models for cancer risk. In particular, these associations could be used to refine existing risk assessment models as these models rely on clinical information to estimate a patient's risk for developing a specific form of cancer. For example, the Gail model for breast cancer risk uses a woman's age, age at first live birth, age at menarche, family history of breast cancer, and biopsy history to determine a woman's risk for developing breast cancer [30]. These models are commonly used to determine if further testing is required for a patient. One of the most common uses of the Gail model is determining if further screening or genetic testing is necessary for the patient. Since these models lack information from other diagnostic tests, such as genetic testing or a mammography in the case of breast cancer, there is some concern about the models' overall predictive ability. The Gail model regularly reports an area under the receiver operating characteristic curve (AUC) ranging from ~0.55 to ~0.65 [31–35]. In this case an AUC can be interpreted as the probability that the predictive model will assign a higher risk of developing breast cancer to a randomly selected breast cancer patient compared to a randomly selected person without breast cancer. For predictive testing an AUC of 0.5 is considered uninformative, the test performs no better than flipping a coin, while an AUC of 0.75 or greater is desirable. Adding further risk factor information to the Gail model could improve its predictive accuracy and thereby detecting more people at high risk for cancer and decreasing the number of unnecessary screenings and treatments. In this dissertation, we modified the Gail model to determine if calibrating the model with information for a personal and family history of skin cancer could improve the Gail model's predictive ability. If the Gail model could be improved by incorporating such information,

perhaps other risk assessments models would also benefit from incorporating information for a personal and family history of skin cancer.

II.C.2.a. A brief summary of the Gail model

The Gail model is a breast cancer risk model originally created in 1989 by Dr. Mitchel H. Gail [30], developed using information from the Breast Cancer Detection Demonstration Project (BCDDP). The BCDDP was a joint venture between the NCI and the American Cancer Society which provided 2,852 Caucasian women with breast cancer as cases and 3,146 Caucasian women as controls for the study [30]. The Gail model uses readily known patient information and population derived incidence rates to determine a patient's risk of developing breast cancer over a specified period of time. While the Gail model is not the most accurate breast cancer risk model for determining which women will develop breast cancer, it has gained prominence in breast cancer diagnosis and research due to its ease of use. The Gail model requires only information for a patient's age, age at menarche, age at first live birth, first degree relative breast cancer history, and biopsy history to determine a patient's risk of developing breast cancer. As this information is often readily known by a patient the Gail model has become a preferred tool for initial risk assessment. If a woman were to walk into their doctor's office and inquired as to their risk for developing breast cancer the doctor could ask the woman eleven questions, enter them into one of several online Gail model risk tools, and produce a risk estimate for their patient in less than ten minutes. Not only is the Gail model easy to use, but it is also accurate enough that the FDA uses Gail model predicted 5-year breast cancer risk as guideline for referring a patient to pre-emptive tamoxifen or raloxifene risk reduction treatment [36,37]. The simplicity of the model and its ubiquity as an initial risk assessment tool has led to multiple studies modifying the model to better predict risk. While originally built for use with Caucasian women, several

version of the Gail model have been created for use among other ethnic groups such as Asians, Pacific Islanders, and African American women [38,39]. Together the Gail model and its variants form the Breast Cancer Risk Assessment tool (BCRA) on the National Cancer Institute's website [40]. If including a personal and family history of skin cancer improved the predictive ability of such a commonly used into cancer risk assessment model, this would be significant for further benefitting patients in the clinical setting.

II.D. Association between skin cancer and other forms of cancer

Though skin cancer offers many methodological solutions to studying patients with multiple primary cancers and a possible avenue for improving cancer risk models, these applications would be meaningless if skin cancer were not associated with risk of cancer at other sites. However, a growing body of evidence has shown that patients with a history of skin cancer reported increased risk for developing internal cancers. One of the first studies was in 1984 by Sandström and their colleagues, they investigated the link between BCC and increased cancer risk [41]. The Sandström study found no deviation in cancer incidence from what would have been expected, but it did inspire further studies on skin cancer and increased cancer risk [41]. Since Sandström's study there have been numerous studies on the subject with varying results [41]. These studies ranged from large registry studies to smaller cohort studies and have produced varying results while exploring the association between skin cancer and its association with increased internal cancer risk [4–8,42–45].

II.D.1. Registry studies

Large cohort and registry studies have mostly come from Europe, where the presence of thorough cancer and health registries provide much of the needed data to researchers. One of the largest studies, Ong et al. 2014, utilized the England record-linked hospital and mortality

databases to prospectively follow 502,490 KC patients and 8,787,513 patients without a history of KC [4]. Ong et al. observed that patients with a history of KC were 1.27 (95% confidence interval (CI), 1.26–1.28) times more likely to develop a non-cutaneous cancer compared to patients with no history of KC [4]. Likewise the study found increased risk for 26 of the 28 different cancers they investigated with particularly strong findings for salivary gland (relative risk (RR): 5.78, 95% CI: 5.29–6.32), bone (RR: 2.93, 95% CI: 2.66–3.23), and upper gastrointestinal tract (RR: 2.36, 95% CI: 2.25–2.48) cancers. There were also increased risks for all of the "big four" cancers after a personal history of KC: breast (RR: 1.24, 95% CI: 1.21-1.28), colon (RR: 1.16, 95% CI: 1.13-1.19), lung (RR: 1.31, 95% CI: 1.28-1.33), and prostate (RR: 1.12, 95% CI: 1.10-1.14) [4]. Assuming the results followed a binomial distribution with a success rate of 50%, the likelihood of having 26 or more successes out of 29 trials is 1.08E-5 [46]. Another registry study used the Alberta Cancer Registry and observed that patients with a personal history of KC were 30-60% more likely to develop a non-cutaneous cancer and were at greater risk for 30 specific cancers with particularly strong results for bone (RR: 2.2, 95% CI:1.4-3.6), eye(RR: 4.0, 95% CI: 1.7-9.5), and salivary glands (RR: 1.9, 95% CI: 1.3-2.8) as well as for the big four cancers [5]. This registry study also observed that patients with a history of melanoma were at increased risk for developing non-skin cancers (RR: 1.3, 95% CI: 1.2-1.4) and at statistically significant increased risk for developing cancer at 12 other cancer sites including prostate cancer (RR: 1.2, 95% CI: 1.0-1.5) and colon cancer (RR: 1.4, 95% CI: 1.1-1.9) [5]. A systematic review of registry studies by Wheless et al. investigated the results of twelve registry studies and observed an association for increased cancer risk after a diagnosis of KC (Summary random effects RR(SRR): 1.12, 95% CI 1.07-1.17), SCC (SRR 1.17, 95% CI 1.12-1.23, n=7), or BCC (SRR 1.09, 95% CI 1.01-1.17, n=7) [6]. Another meta-analysis by Caini

et al. studied the association between melanoma and risk for other cancers, finding overall increased risk for developing cancer other than melanoma though the finding was not statistically significant (SRR: 1.26, 95% CI:0.66-2.40) though their study did find increased risk for cancer at 8 internal sites [8].

Registry studies tend to show increased risk after a skin cancer diagnosis; however these results have a few limitations. While registries offer a vast number of patients for analysis and capture all cancer cases within a population, most registries cannot collect more than basic information about the patient's other risk factors. For example the Ong et al. study mentioned earlier adjusted for a patient's age, gender, home region, and socio-economic status but no other potentially significant covariates such as smoking history and body mass index (BMI) [4]. Some covariates such as smoking contribute to risk for skin cancer and other cancers allowing for them to act as confounders, influencing or creating the impression of an association if not controlled for. Thus while registry studies are useful they do not fully describe the relationship between skin cancer and increased cancer risk. To help solve this issue, smaller studies with detailed individual level data are necessary.

II.D.2. Cohort studies with individual level data

While registry studies provide powerful evidence of the association between a personal history of skin cancer and increased cancer risk, smaller studies are needed as well. Though smaller than registry studies, cohort studies are often more thorough in handling potential confounders. Studies such as Rees et al. 2014 and Song et al. 2013 were able to adjust their results for several potential confounders, chiefly a history of smoking [7,42,43,47–49]. Unfortunately these studies tend to show less agreement in their results compared to registry studies. The association between skin cancer and increased risk for cancer ranges from not

significant to almost two-fold risk for developing an internal cancer (RR: 1.98, 95% CI: 1.69-2.31) [42,43,50]. Despite this variability there is an overall agreement among these studies that a history of KC and melanoma increases a patient's risk for non-cutaneous cancers.

While cohort studies have been invaluable in controlling for possible confounders, they also allowed researchers to determine if the increased cancer risk following a KC diagnosis was evenly distributed across the KC subtypes and across gender. KC is not a single type of cancer but instead constitutes several subtypes. Of these subtypes SCC and BCC account for roughly 99% of all KC cases [11]. Despite research often grouping these two subtypes together, SCC and BCC have morphological and epidemiological differences which could influence overall cancer risk. Of particular interest is the question if the association observed for KC and internal cancer risk is driven by one of these subtypes. These smaller studies have investigated this question by recruiting their own cohorts and collecting skin cancer diagnosis in greater detail than most registry studies. Robsahm et al. found greater risk (RR: 2.30, 95% CI 2.22-2.37) due to a history of SCC, while others such as Rees et al. found no significant results for SCC (RR: 1.01, 95% CI 0.81-1.27) but found significant results for BCC (RR: 1.24, 95% CI 1.01-1.54) [42,43]. The general trend is that SCC is considered the more dangerous of the two KC subtypes with a statistical review finding SCC carried a SRR of 1.17 with a 95% CI 1.12-1.23 [6]. Investigations into BCC and it's association have occasionally found null results, but the majority of studies still find it to be harmful (SRR: 1.09, 95% CI 1.01-1.17, n=7) [6].

II.D.3. Preliminary data, the SCAN study

Our study's focus on the potentially important role of family history of skin cancer was stimulated by a small-scale intramural pilot study. In a clinic-based case-control study of Caucasians, three groups of 50 patients each were matched by sex and age: 1) KC + other cancer,

2) KC only, and 3) no history of KC or other cancers. Compared to those with no family history of any type of cancer, patients with a positive family history of both KC plus another cancer had an almost 10-fold elevated risk of having a personal history of both KC plus another cancer (**OR 9.8; 95% CI: 1.7-57.0**); further, a family history of only KC was associated with having a personal history of KC plus another type of cancer (**OR 6.9; 95% CI 0.9-55.4**). These striking findings stimulated our interest in the importance of considering family history of KC when measuring a family history of cancer and thus in further pursuing this question in our dissertation [51].

II.D.4. Summary of the relationship between skin cancer and mortality

Prior to the discovery that skin cancer may be associated with increased risk for developing internal malignancies, there had been reports regarding the loss of life and productivity explicitly due to skin cancer associated death [52]. However, there is a growing field of research suggesting that KC may be related to mortality. Since 1998, 12 reports have investigated the association between a personal history of KC and mortality among the general population and cancer patients [10]. These reports have been largely derived from Scandinavian data, of which information was abstracted from the Gerda Frentz Cohort, Danish Cancer Registry, and Swedish Cancer Registry [22,53–60], in addition to North American data, including the Cancer Prevention Study II, New Hampshire Skin Care Study, New Hampshire State Cancer Registry, and Manitoba Cancer Registry [43,61,62]. Together these reports analyzed over 185,000 cases of KC to estimate the relationship with mortality after adjusting for numerous potential confounding factors such as smoking and comorbidities.

Overall, the results of these studies point toward a personal history of KC being associated with increased risk for mortality. Results of reports that did not stratify KC by

histologic subtype reflected a combination of mortality risk estimates of both BCC and SCC, with a RR of 1.03 (95% CI 1.00-1.06) for males and 1.04 (95% CI 1.00-1.09) for females [61]. These associations become stronger when the data was stratified by histologic subtype. Compared to those of the general population with no personal history of any type of KC, patients with a history of SCC were consistently associated with increased all-cause mortality, with relative risk (RR) estimates ranging from 1.11 (95% confidence interval (CI) 1.07-1.15) to 1.54 (95% CI 1.41-1.68) [56,62]. The Jensen 2008 study investigated specific non-cancer causes of death stratified by histological skin cancer type. Jensen's study found an association between SCC and increased risk for mortality due to chronic obstructive pulmonary disease (COPD) (standardized mortality ratio (SMR) 1.21; 95% CI: 1.08–1.35), ischemic heart disease (SMR 1.15; 95% CI 1.10–1.21), and infectious disease (SMR: 1.94; 95% CI: 1.39–2.65) [57]. However, those with a history of BCC were consistently associated with a slight decrease in all-cause mortality, with relative risk estimates ranging from 0.89 (95% CI 0.83-0.95) to 0.97 (95% CI 0.96-0.98) [4, 5]. In the Jensen 2008 study, patients with a history of BCC were at increased risk for suicide (SMR 1.16; 95% CI: 1.02-1.31), but were at decreased risk for COPD (SMR 0.87; 95% CI: 0.83-0.92), ischemic heart disease (SMR 0.93; 95% CI: 0.91–0.95) and diabetes mellitus (SMR 0.78; 0.70–0.86) [57]. The reasons for the perceived decreased mortality for patients with BCC are unknown due to the similar results that were produced when potential confounding factors, such as comorbidity and socioeconomic status, were controlled for [56].

In addition to mortality from all causes, the relation between KC and cancer-specific mortality has been investigated in three reports. Similar to the pattern seen with all-cause mortality, a stronger association with mortality from malignancy was seen in patients with SCC (RRs of 2.17 and 1.63) than those with BCC (RRs of 1.15 and 1.01) [55,57]. However, the

increase was only significant for both subtypes in one report in which melanoma was included as a malignancy [57]. In a study in which KC was not stratified by subtype, increased relative risk of cancer-specific mortality was observed for both males (RR 1.27; 95% CI 1.20-1.33) and females (RR 1.24; 95% CI 1.15-1.33) [61].

Additional studies evaluated the prognosis of cancer patients with a history of KC compared to cancer patients with no history of KC for multiple types of malignancies. Those most commonly studied include Non-Hodgkin's Lymphoma (NHL) and the chronic lymphocytic leukemia (CLL) subtype. The most recent studies with the greatest number of adjustments for confounders, such as smoking, yielded relative mortality risk estimates for patients with a history of SCC and CLL (RR 1.86; 95% CI 1.46-2.36) [59], all types of NHL (RR 1.09; 95% CI 0.81-1.47) [7]. Associations with colon (RR 1.13, 95% CI 0.92-1.40), lung (RR 1.23; 95% CI 1.05-1.43), breast (RR 1.09; 95% CI 0.82-1.43), and prostate cancer (RR 0.97; 95% CI 0.81-1.15) have also been investigated [22]. There are two comparable studies for BCC, and they provided evidence of increased risk for death from NHL/CLL(RR 1.51, 95% CI 1.15-1.99), Colon (RR 1.24, 1.10-1.40), and lung (RR 1.11, 95% CI 1.01-1.22) cancers [54,62]. The relatively small number of studies providing evidence for the association of KC and survival in cancer patients hinders the ability to make any concrete conclusions; however, the general impression is cancer patients with a history of KC are at increased risk for dying of cancer.

Clearly, the increased risk for all-cause mortality does not appear to be driven solely by increased risk for developing cancer. SCC and BCC are both associated with other causes of death ranging from heart disease, pulmonary disease, infections, and suicide [56–58]. This suggests that the association between KC, particularly SCC, and risk of other cancers may

instead be an association with lethal disease in general including pulmonary and infectious disease.

This literature review demonstrates a paucity of research on the topic of skin cancer and risk for mortality. The current research is conflicting in some areas, and needs greater depth in others. While KC is associated with increased risk of cancer-specific mortality, its links to other causes of death needs to be further explored. Additionally the association between a prior KC and poor prognosis for cancer needs to be further explored and expanded to other cancer sites; particularly for the most common cancers (colon, prostate, breast, and lung). There is a dearth of information regarding the association between a prior history of melanoma and risk for mortality from other causes. Further, research is needed to better understand the possible etiologic pathways that might link skin cancer to mortality.

II.D.5. The plausibility of a heritable component to an underlying susceptibility for cancer

Given the low mortality and generally low health risk skin cancer poses for a patient it is unlikely that skin cancer itself increases a patient's risk for a subsequent internal cancer. Instead, skin cancer likely acts as a sentinel disease warning of the presence of another risk factor that increases a patient's risk for developing both skin cancer and internal cancer. The question then becomes, what sort of risk factor or exposure could increase a patient's risk for over 20 forms of cancer [4,5,8]. A heritable risk factor seems plausible based on prior research. The work of Ong et al. and Jung et al. showed that a skin cancer diagnosed earlier in life increased a patients risk for developing a subsequent internal malignancy more than a skin cancer diagnosed later in life, an early age of diagnosis for one or more cancers is a common trait of heritable cancers [4,5,27]. Additionally two separate genetic studies have found results indicative of mutations in DNA repair pathways among patients with a history of KC, possibly increasing their risk for

developing cancer at other sites though the results were not conclusive [63,64]. Also the breadth of internal cancers associated with a history of skin cancer, 26 to 30 different sites, would be difficult to explain through an environmental or behavioral risk factor [4,5]. Also, the work of studies such as Song et al., Rees et al., and Caini et al. adjusted for common cancer risk factors and observed that participants with a personal history of skin cancer were still at increased risk for developing an internal cancer compared to those without a personal history of skin cancer [7,43,44]. The existence of genetic syndromes responsible for increased risk at multiple cancer sites and shared mutations between separate cancer sites lends further credence to the theory that the underlying susceptibility could be hereditary in nature [63–65]. A family history of a disease often acts as a marker for a shared risk factor such as a genetic mutation, behavior, or environment. The association between a personal history of skin cancer and risk for developing an internal cancer behaves like it is due to a hereditary abnormality and there are genetic pathways that could explain the association. Possible pathways include a mutation in a common DNA repair pathway would increase the accrual rate of mutations necessary for tumorigenesis, alternatively a mutation in an inflammatory pathway could lead to increased low grade inflammation at multiple sites which would also increase cancer risk [26,27,29]. Thus, an association between a family history of skin cancer and increased risk for internal cancer would provide evidence that the underlying susceptibility is heritable [4,5,63,64].

II.E. Significance and Innovation

II.E.1. Observing the association between a personal history of skin cancer, internal cancer risk, and mortality in a nationally representative cohort

Our dissertation will capitalize on the NHANES Epidemiological Follow-up Study (NHEFS) for the first time to thoroughly measure the associations between a personal history of skin cancer, risk of incident internal cancer, and mortality. The NHEFS is a nationally representative study

and thus should be generalizable to the at least the American population. Additionally the NHEFS has thorough information available for common cancer covariates, enabling our study to adjust for smoking, BMI, level of education, and other possible confounders. Thus, the observations made in our dissertation will enrich the existing literature on the role of a personal history of skin cancer and its long term effects. Also, if a personal history of skin cancer is associated with increased risk for developing an internal cancer, it would provide evidence that patients with a personal history of both skin cancer and an internal cancer could be used to study risk for developing multiple primary cancers.

II.E.2. Potential Significance of Family History of Skin Cancer

A major innovation of this dissertation research is the thorough integration of family history of skin cancer in addition to personal history of skin cancer in studying these associations. Patients with a family history of a specific cancer are usually at increased risk for that specific cancer and other cancers associated with that specific cancer [27]. Thus, as a personal history of skin cancer is associated with increased risk for at least 26 forms of cancer, a family history of skin cancer could similarly be associated increased risk for at least 20 forms of cancer, a greater variety of internal cancers than cigarette smoking [4–6]. Such an association between a family history of skin cancer and increased risk would provide evidence that the association between a personal history of skin cancer and internal cancer is due to a heritable predisposition. If so, this would imply that patients with a personal and family history of skin cancers may be at compounded risk for internal malignancies.

However, despite the possible research implications of a family history of skin cancer, patients are often only questioned about a family history of non-skin cancers or about a family history of specifically melanoma. Given the cross-cutting nature of the increased risk associated

with a personal history of KC and melanoma, significant associations between a family history of skin cancer and risk for developing internal cancer would emphasize the importance of recording a family history of skin cancer as a part of standard oncological practice.

II.E.3. Improving cancer risk prediction models

Additionally, understanding the association between skin cancer and internal cancer could have a clinical impact by providing an easily measured marker for increased risk for at least twenty forms of internal cancer and mortality. Due to the wide range of cancers associated with skin cancer this information could improve existing models to detect a significant portion of the expected 1.6 million incident cancers in the United States every year. Despite the potential gain of including this information, currently only skin cancer incidence models utilize a patient's personal and family history of skin cancer. Our study proposes to show the potential benefits of including this information by modifying an existing cancer incidence model and calibrating it for the skin cancer history of the patient. For this purpose the Gail model was selected.

II.E.4. Summing up the potential significance of our research

Understanding the association between skin cancer and increased risk for internal cancers and mortality could prove beneficial for several reasons. Skin cancer's high incidence makes the potential impact of a personal and family history of skin cancer on internal cancer risk and excess mortality a question with public health significance. For example, using the conservative estimate for skin cancer incidence, understanding this association between skin cancer and increased internal cancer risk would help identify two million people at increased risk for developing an internal cancer per year [1,2]. Additionally if skin cancer is associated with internal cancer risk then it would increase the number of patients available for studying multiple primary cancers. Further, this line of inquiry could lead to changes in the best practices for

measuring a family history of cancer in both the research and clinical setting to specifically include skin cancer. The research question holds promise for advancing the understanding of why skin cancer is associated with risk of other cancers and increased mortality rates. For example, if family history of skin cancer contributes to the increased risks of other cancers and death experienced by those with a personal history of skin cancer, it would support the hypothesis that there may be an underlying heritable predisposition that plays a role and provide support for future research into the genetic underpinnings of this association. And finally including information for a personal and family history of skin cancer in cancer risk models could improve those models' ability to detect high risk patients and enroll those patients in screening programs.

II.E.5. Innovation

Our study's innovation is the important and novel scientific question addressed "**Are a personal and family history of skin cancer associated with increased risk for developing an internal cancer and mortality, and could these associations be of clinical value?**" This question addresses two concepts 1) the integration of family history of skin cancer into research investigating the adverse health outcomes (cancer, mortality) associated with a personal history of skin cancer, 2) The use of a measure of family history of cancer that distinguishes between family histories of skin cancer versus other cancers. In the context of the existing body of evidence on the association between skin cancer and risk of other cancers and increased mortality, this is uncharted territory, as few studies have addressed these topics. To our knowledge only one study has used a family history of skin cancer as a covariate when evaluating the association between a personal history of skin cancer and increased risk for developing an internal cancer.

Second, the NHEFS and NHIS are robust data resources with the advantage of assessing the study questions within the context of a nationally representative US cohort and a nationally representative survey, respectively. Compared to prior studies on the association between skin cancer and cancer risk and mortality, our study will be unique by including individual-level data embedded within a nationally representative cohort.

Third, our study will be among the first studies to evaluate the impact of including information regarding a history of skin cancer on measuring a patient's predicted internal cancer risk. By comparing models with and without a history of skin cancer this study will show how risk estimation improves by including such information. If the modified cancer risk model shows improvement over the original risk model then our study will generate evidence that could lead to improvements in detecting high risk cancer patients.

Chapter III: First Aim Manuscript

A cohort study of personal and family history of skin cancer in relation to future cancer risk

III.A. Introduction

Keratinocyte carcinoma (KC) and melanoma are two of the most common forms of cancer in the United States with an estimated 2 million and 87,000 new cases annually and account for ~99% of all skin cancers [1–3,11,24], but these diseases are rarely fatal with an estimated 0.69 and 2.7 deaths per hundred thousand person years (PY) for KC and melanoma, respectively [3,20]. The low mortality rates suggest skin cancer poses little direct threat to the patient. However, there is a growing debate in the literature as to the long term implications of a skin cancer diagnosis.

A body of evidence has observed that a prior diagnosis of skin cancer is associated with subsequent increased risk for developing non-cutaneous cancers [4–6,43,50]. This association is not specific to a single tumor site but to a broad spectrum of malignancies. For example, in a large British cohort participants with a personal history of KC had significantly greater risk for developing 26 of the 29 types of internal cancer investigated [4]. Similarly, melanoma has been associated with overall increased internal cancer risk and is associated with increased risk at 12 other cancer sites [5,8]. Additionally, prior studies of genetic variants in DNA repair pathways have yielded results suggesting a potential link between KC and risk of developing an internal cancer [63,64]. This evidence supports the presence of an underlying susceptibility factor, such as a genetic mutation, that increases a patient's risk for developing both skin cancer and other malignancies. Under this paradigm, skin cancer is not the cause but the marker for an underlying predisposition.

A separate set of literature posits that a personal history of skin cancer is indicative of decreased risk for mortality [9,66–68]. The "vitamin D hypothesis" states that vitamin D is protective against developing several forms of cancer [69]. Since 90% of melanoma cases and the vast majority KC cases are attributable to ultraviolet radiation (UVR), the vitamin D hypothesis posits that patients who have developed a skin cancer have also synthesized more vitamin D and therefore are at decreased risk for developing an internal malignancy. This hypothesis has been supported by data from several ecological studies and randomized control trials that administered oral vitamin D supplements to their participants [9,68–71].

The purpose of our study is to address this gap in the research by examining the association between a personal history of skin cancer and risk of developing an internal malignancy in a nationally representative cohort. Additionally, in our study we take a more global approach to testing the theory regarding an underlying genetic risk factor by determining if a personal history of skin cancer and a family history of skin cancer are similarly associated with increased risk for developing an internal cancer.

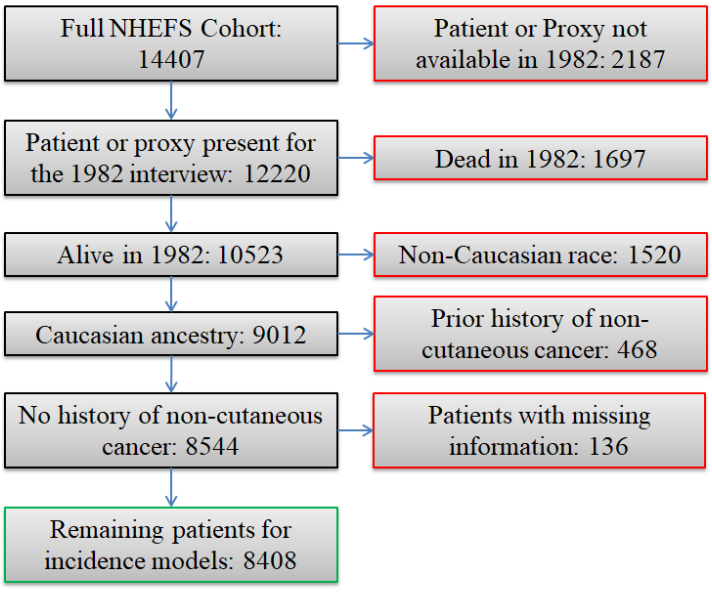
III.B. Methods

III.B.1. Study Population

The source population of our study is the NHANES Epidemiological Follow-up Study (NHEFS). This ten year prospective cohort followed participants from 1982 to 1992. The NHEFS is a nationally representative cohort with a complex survey design. The NHEFS is well suited to address this research topic because the questionnaires for personal and family history of cancer include questions for a history of skin cancer. The sources of data are the initial interview and medical examination in 1982, the follow up interviews for the entire cohort in 1987 and 1992, and the mortality data set linked to the National Death Index.

The NHEFS cohort was composed of persons between the ages of 25 and 74 in 1982 who completed the medical examination during NHANES I study (N=14,407). For the present study additional inclusion criteria were: 1) participant or a proxy (i.e. a spouse or sibling) was present for the 1982 medical examination and interview, 2) participant was alive in 1982, 3) Caucasian ancestry, 4) free of non-cutaneous cancers prior to 1982, 5) not have missing information for personal or family diagnoses of cancer. Participants with a prior internal cancer diagnosis were excluded due to the role of prior cancer diagnoses and treatments in influencing a patient's risk of developing another malignancy. As for race, the differences in skin cancer epidemiology between races, such as a 25 fold difference in melanoma incidence and a 3 fold difference in mortality [3], would introduce heterogeneity that would necessitate a sub-group analysis. However of the 1,520 non-Caucasian participants 1,407 were African Americans, and of those African Americans only 9 had a family history of skin cancer which was too few for a sub group analysis. After applying these inclusion criteria 8,408 cohort numbers were included in the present study study (**Figure 3.1)**.

Figure 3.1: Patient Inclusion and Exclusion from the NHEFS Cohort



III.B.2. Measurement

Due to data collection practices at different time points, our study was not able to differentiate between skin cancer subtypes. At the 1982 interview all cancer related questions had a single categorization for skin cancer: “Skin Including Melanoma”. Later interviews used separate categorizations for melanoma, KC, and miscellaneous skin cancers. However; family history of cancer was only collected at the beginning and end of the cohort, thus for the 1,579 participants that died during follow-up it was not possible to conclusively determine if they had a family history of specifically KC. In order to keep measurement consistent across the cohort and allow use of the full cohort, measurement of personal and family history of skin cancer was limited to the 1982 interview designation of “skin cancer including melanoma.”

Personal history of cancer was determined from the 1982, 1987, and 1992 time points. A positive response to having a personal diagnosis of melanoma, KC, or unidentified skin cancer from the self-reported cancer or dermatological questionnaires resulted in a positive report for a personal history of skin cancer. Similarly, a positive report at the 1987 or 1992 interviews for a specific internal cancer resulted in the patient being recorded as having a personal history of internal cancer. For example a report of breast cancer would result in a positive personal history of internal cancer while a report of unknown cancer would result in an unknown value for the patient. Additionally, if a participant’s cause of death was listed as a specific internal cancer then they were flagged as having developed an internal cancer over the course of the cohort.

Family history of cancer was ascertained for up to five first degree relatives in 1982 and up to nine first degree relatives in 1992. Participants who reported ≥1 first-degree relatives were diagnosed with any type of skin cancer (KC, melanoma, or other skin cancer) at either time point were classified as being positive for family history of skin cancer. Similarly, a report of ≥1 first-

degree relatives with a specific cancer other than KC, melanoma, or “other skin cancer” at either time point resulted in the participant being record as having a positive family history of internal cancer. For example, if a participant reported their father had a diagnosis of “skin cancer including melanoma” at the 1982 interview or a diagnosis of “melanoma”, “non-melanoma”, or “unspecified skin” at the 1992 interview then they would be recorded as having a family history of skin cancer. The Distribution of all common cancer risk factors and measures for a patient’s personal and family history of skin cancer can be found in **Table 3.1**.

Table 3.1: Cancer history and risk factor distribution in the full NHEFS cohort and subdivided by personal and family history of skin cancer							
	Entire cohort	**Personal history of skin cancer**		**P-value**	**Family history of skin cancer**		**P-value**
		No, N (%)	**Yes, N (%)**		**No, N (%)**	**Yes, N (%)**	
Number of participants	8408	7110	1298		7811	597	
Mean age (standard deviation)	56.5 (14.8)	55.4 (14.7)	62.6 (13.7)	<0.01	56.8 (14.8)	52.3 (14.2)	<0.01
Mean time of follow-up (standard deviation)	8.2 (2.4)	8.3 (2.4)	8.1 (2.4)	<0.01	8.2 (2.4)	8.7 (1.8)	<0.01
Gender				<0.01			<0.01
Men	3223	2627 (37.0)	596 (45.9)		3024 (40.0)	181 (30.3)	
Women	5185	4483 (63.0)	702 (54.1)		4769 (61.1)	416 (69.7)	
BMI				0.39			0.02
Underweight	213	179 (2.5)	34 (2.6)		193 (2.5)	20 (3.4)	
Normal weight	3715	3150 (44.3)	565 (43.5)		3417 (43.8)	298 (49.9)	
Over weight	3013	2512 (35.3)	501 (38.6)		2840 (36.4)	173 (30.0)	
Obese	1467	1296 (17.9)	198 (15.3)		1361 (17.4)	106 (17.8)	
Smoking behavior				0.06			0.06
Never smoked	3825	3246 (45.6)	579 (44.6)		3530 (45.2)	295 (49.4)	
Former smoker	2347	1909 (26.9)	438 (33.7)		2191 (28.1)	156 (26.1)	
Current smoker	2236	1955 (27.5)	281 (21.7)		2090 (26.8)	146 (24.5)	
How many years since patient quit smoking?				<0.01			0.07
Less than 5	837	710 (37.2)	127 (29.0)		792 (36.2)	45 (28.8)	
More than 5	1510	1199 (62.8)	311 (71.0)		1399 (63.9)	111 (71.2)	
Regular aspirin use				0.74			0.38
No	6282	5317 (74.8)	965 (74.3)		5845 (74.8)	437 (73.2)	
Yes	2126	1793 (25.2)	333 (25.7)		1966 (25.2)	160 (26.8)	
Highest completed level of education				0.84			<0.01
Less than high school	2981	2500 (35.2)	481 (37.1)		2833 (36.3)	148 (24.8)	
High school graduate	3198	2751 (38.7)	447 (34.4)		2963 (37.9)	235 (39.4)	
More than high school	2229	1859 (26.1)	370 (28.5)		2015 (25.8)	214 (35.9)	

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Table 3.1: Cancer history and risk factor distribution in the full NHEFS cohort and subdivided by personal and family history of skin cancer (continued)							
	Entire cohort	**Personal history of skin cancer**		**P-value**	**Family history of skin cancer**		**P-value**
		No, N (%)	**Yes, N (%)**		**No, N (%)**	**Yes, N (%)**	
Number of participants	8408	7110	1298		7811	597	
Personal history of skin cancer				NA			<0.01
No	7110	7110 (100.0)	0 (0.0)		6638 (85.0)	472 (79.1)	
Yes	1298	0 (0.0)	1298 (100.0)		1173 (15.0)	125 (20.9)	
Family history of skin cancer				<0.01			NA
No	7811	6638 (93.4)	1173 (90.4)		7811 (100.0)	0 (0.0)	
Yes	597	472 (6.6)	125 (9.6)		0 (0.0)	597 (100.0)	
Family history of internal cancer				<0.01			<0.01
No	4408	3807 (53.5)	601 (46.3)		4132 (53.0)	276 (46.2)	
Yes	4000	3303 (46.5)	697 (53.7)		3679 (47.1)	321 (53.8)	

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III.B.3. Statistical Analyses

Cox proportional hazards models were fit to measure the associations between personal history of skin cancer, family history of skin cancer, and family history of internal cancer with risk of developing an internal malignancy during the follow-up period. Cox-proportional hazards were chosen over logistic regression due to the time to event data available from the NHEFS cohort. To evaluate the possibility of interactions between the personal and family history of skin cancer and common cancer risk factors several models were fit: unadjusted models, age adjusted models, and fully adjusted models. Fully adjusted models accounted for age, gender, smoking history, regular aspirin use, and highest completed level of education, personal history of cancer, and family history of cancer. These variables were selected a priori for their associations with overall cancer risk or associations with cancer at multiple sites. Additionally t-tests and Cochran-Mantel-Haenszel tests were used to explore the distribution of common cancer risk factors among patients with a personal history of skin cancer and a family history of skin cancer. The models were analyzed accounting for the complex survey design used in the NHEFS cohort. All analyses were performed in SAS 9.4.

III.C. Results

Of the 8,408 participants, 748 developed an internal cancer during the follow-up period. The average follow-up was 8.2 years. Patients with a personal history of skin cancer were on average more likely to be male, be older, have a family history of skin cancer, and have a family history of internal cancer compared to patients without a personal history of skin cancer (**Table 3.1**). Compared to those with no family history of skin cancer, participants with a family history of skin cancer at baseline were less likely to smoke cigarettes, on average younger, more likely to be female, and be of normal weight. Participants with a family history of skin cancer were

more likely to have a family history of internal cancer, and have a personal history of skin cancer (**Table 3.1**). The incidence of internal cancer was similar between participants with and without a family history of skin cancer, 7.7% and 9.0% respectively (**Table 3.2**).

Table 3.2: Number of incident internal cancers in 10-year NHEFS cohort subdivided by personal and family history of skin cancer

	Entire cohort	**Personal history of skin cancer**		**P-value**
		No, N (%)	**No, N (%)**	
Number of participants	8408	7110	1298	
Developed cancer				<0.01
No	7660	6539 (92.0)	1121 (86.4)	
Yes	748	571 (8.0)	177 (13.6)	
	Entire cohort	**Family history of skin cancer**		**P-value**
		No, N (%)	**Yes, N (%)**	
Number of participants	8408	7811	597	
Developed cancer				0.29
No	7660	7109 (91.0)	551 (92.3)	
Yes	748	702 (9.0)	46 (7.7)	

A personal history of skin cancer was significantly associated with increased risk for internal cancer in the unadjusted model (hazard ratio (HR): 1.72, 95% confidence interval (CI): 1.43-2.07) (**Table 3.3**). This increased risk was attenuated after adjusting for age (HR: 1.31. 95% CI: 1.07-1.60) and did not change significantly in the presence of other covariates (HR 1.33; 95% CI: 1.09-1.61) (**Table 3.3**).

The associations between family history of skin cancer and risk of internal cancers showed a possibly inverse or a null association; the unadjusted association was statistically significant (HR: 0.69, 95% CI: 0.51-0.95) but this association was attenuated and no longer statistically significant after adjusting for age (HR: 0.83, 95% CI: 0.61-1.13) and additional covariates (HR 0.80; 95% CI: 0.58-1.11) (**Table 3.3**). Interactions with family history of skin cancer were tested for age, gender, personal history of skin cancer, and family history of internal cancer but were not found to be significant.

Table 3.3: Hazards ratios (HRs) and 95% confidence intervals (CIs) for developing an internal cancer during 10-year follow-up of the NHEFS cohort, N=8408				
Variable	**Unadjusted[1] Results HR (95% CI)**	**Age Adjusted[2] Results HR (95% CI)**	**Fully Adjusted[3] Results HR (95% CI)**	**Fully Adjusted[3] P-value**
Age at 1982 interview	1.05 (1.05-1.06)	1.05 (1.05-1.06)	1.05 (1.04-1.06)	<0.01
Gender				
Men (N=3223)	1.00 (ref)	1.00 (ref)	1.00 (ref)	
Women (N=5185)	1.05 (0.88-1.26)	0.93 (0.78-1.11)	1.02 (0.83-1.26)	0.86
Smoking habit in 82				
Never Smoked (N=3825)	1.00 (ref)	1.00 (ref)	1.00 (ref)	
Previous Smoker (N=2347)	1.25 (0.99-1.56)	1.35 (1.08-1.69)	1.34 (1.04-1.72)	0.02
Current Smoker (N=2236)	1.14 (0.90-1.45)	1.65 (1.29-2.11)	1.63 (1.27-2.09)	<0.01
Regular aspirin use				
No (N=6282)	1.00 (ref)	1.00 (ref)	1.00 (ref)	
Yes (N=2126)	1.50 (1.24-1.82)	1.36 (1.12-1.64)	1.36 (1.12-1.66)	<0.01
Highest completed level of education				
Less than high school (N=2981)	1.00 (ref)	1.00 (ref)	1.00 (ref)	
High school graduate (N=3198)	0.60 (0.49-0.73)	0.86 (0.70-1.06)	0.86 (0.70-1.06)	0.16
More than high school (N=2229)	0.51 (0.41-0.64)	0.77 (0.62-0.97)	0.77 (0.62-0.96)	0.02
Personal History of Skin Cancer				
No (N=7110)	1.00 (ref)	1.00 (ref)	1.00 (ref)	
Yes (N=1298)	1.72 (1.43-2.07)	1.31 (1.07-1.60)	1.33 (1.09-1.61)	<0.01
Family history of skin cancer				
No (N=7811)	1.00 (ref)	1.00 (ref)	1.00 (ref)	
Yes (N=597)	0.69 (0.51-0.95)	0.83 (0.60-1.13)	0.80 (0.58-1.11)	0.18
Family history of internal cancer				
No (N=4408)	1.00 (ref)	1.00 (ref)	1.00 (ref)	
Yes (N=4000)	1.29 (1.10-1.52)	1.19 (1.00-1.40)	1.18 (0.99-1.40)	0.06

1- Results are not adjusted for any other covariate
2- Results are adjusted for age
3- Results are adjusted for age, gender, BMI, smoking habit, regular aspirin use, highest completed level of education, personal history of skin cancer, family history of skin cancer, and family history of internal cancer.

III.D. Discussion

In our study, a personal history of skin cancer was associated with increased risk for developing an internal cancer. This finding is consistent with prior research on this topic and further deepens the overall body of evidence documenting this association with data from a nationally representative prospective cohort [4–6,43]. Conversely, the results of our study provided no evidence that a family history of skin cancer was associated with increased risk of internal malignancies.

Two arguments made against a personal history of skin cancer being associated with increased internal cancer risk are 1) some prior studies not adjusting for common cancer covariates, such as smoking history, and 2) the study population was not representative of the general population [9]. Our results support a personal history of skin cancer as a marker for increased internal cancer risk, and we observed that association after adjusting for common cancer risk factors in a nationally representative cohort. Additionally we observed that patients with a personal history of skin cancer were more likely to report a family history of internal cancer implying a greater burden of internal cancer on both the personal and familial level compared to participants without a personal history of skin cancer. Furthermore, associations were in the expected direction for many other variables, suggesting the internal validity of the study was strong. For example, compared with never smokers, risk for developing an internal cancer was elevated in former smokers and further elevated in current smokers (**Table 3.3**). The exception among the associations was aspirin use which has previously been associated with decreased risk for colorectal and other internal cancers; further study will be needed to understand why in our study aspirin was associated with increased internal cancer risk [72,73].

Overall, our study supports the association between skin cancer and increased risk for internal cancer.

Compared to the results for a personal history of skin cancer, a family history of skin cancer produced unexpected results. In our study, participants with a family history of skin cancer were more likely to be younger, better educated, less likely to smoke, and have a healthy BMI according to CDC guidelines. These traits are generally recognized to reduce overall cancer risk [26]. Participants with a family history of skin cancer also experienced similar internal cancer incidence as the participants without a family history of skin cancer and developed cancer at a slightly younger age, 64.6 versus 67.8 years. These findings would imply that a family history of skin cancer would be indicative of increased risk, juxtaposing lower risk profiles with an equal burden of personal cancer and an increased burden of familial cancer. However, patients with a family history of skin cancer were not at increased risk. In the unadjusted time to event analyses, participants with a family history of skin cancer were at statistically significant decreased risk for developing an internal cancer. This association attenuated after adjusting for age to a HR of 0.80 that was not statistically significant.

Adjusting for age changed the results for personal history of skin cancer (HR: 1.72 vs. 1.31) and family history of skin cancer (HR: 0.69 vs. 0.83). Age is highly associated with both risk for developing a skin cancer and risk for developing an internal cancer, and is not on the causal pathway between skin and internal cancer. Thus age is possibly a confounder for the association between personal and family history of skin cancer and risk for developing an internal cancer[3,11,27]. Additionally we investigated the possibility of an interaction effect between age and our skin cancer variables but it was not significant.

The novelty of the present study lies in its focus on the potential role of family history of skin cancer; thus, there is a paucity of prior evidence to compare the findings to. In one prior study, there was a lack of a statistically significant association between a family history of KC and risk for developing an internal cancer, but family history of KC was not a focus of the study and no measure of association was reported [43]. A second study, a clinic-based case-control study, provided possible evidence in support of an association between a family history of skin cancer and increased risk for developing cancer. This case-control study observed three matched groups: KC plus another type of cancer (n=50), KC only (n=50), and cancer-free controls (n=50) [51]. Compared to the control group with no history of any type of cancer, patients with a family history of both KC and internal cancer were at increased risk for developing both KC and another type of cancer (OR: 9.8, 95% CI: 1.7-57.0) [51]. However, a similar association for family history was observed for the comparison of the group with KC only compared with the cancer-free controls (OR: 9.9, 95% CI: 1.7-59.7) [51], suggesting the observed associations may be more relevant to developing KC rather than KC plus another type of cancer. The paucity of prior research on this topic, along with our own findings, highlights the need for further research on this topic.

Our study directly relates to the theory that skin cancer can be used as a marker for decreased cancer risk. There have been several studies suggesting that UVR derived Vitamin D may possess anti-tumorigenic properties [68,74,75]. However, difficulty in directly measuring UVR exposure has led some studies to use skin cancer diagnosis as a proxy for UVR exposure [9]. These studies argue that patients with a personal history of skin cancer have greater UVR exposure and therefore more UVR derived vitamin D, culminating in lower risk for developing internal cancer [9]. In our study, a family history of skin cancer was indicative of decreased risk

and could be interpreted as a measure of shared UVR exposure between family members, arguably supporting the vitamin D hypothesis. However, our study has a more direct measure of personal UVR exposure, a personal history of skin cancer, and it was significantly associated with increased risk. Thus our study does not support the theory that skin cancer is a useful marker for decreased risk of developing an internal malignancy through UVR derived vitamin D.

The current study has limitations related to measurement and classification of skin cancer among participants. Firstly, our study relied on self-reported data instead of pathologic confirmation for personal history of skin cancer and other cancers. With respect to self-reported KC history, studies have reported sensitivity ranging from 69-94% and specificity ranging from 87-99% [76,77]. Furthermore, self-reported family history could be expected to be less accurate than personal history and impacted by socio-economic status. For reference, overall the sensitivity of self-reported cancer ranges from 79-93% with a specificity of 99% [78,79]. The error from self-reported histories of KC and other cancers is anticipated to result in under-ascertainment and be non-differential, and therefore likely resulting in bias towards the null that would increase the likelihood to observe a non-significant association. Secondly, our study did not distinguish between skin cancer subtypes. However, both KC and melanoma have been associated with overall increased risk for internal cancer and collectively make up roughly 99% of all skin cancers [3–5,19]. While mixing of effects from different subtypes occurred, all of those effects would be anticipated to be in the direction of increased risk. Finally, the study did not have access to age at skin cancer diagnosis for relatives. This information could have been useful for determining which relatives developed skin cancer due to a hereditary condition and which relatives developed it due to age and accumulated UVR exposure [27,29]. Without age at diagnosis for relatives, our study could be biased towards the null.

Despite these weaknesses, the study also has notable strengths. The NHEFS cohort is nationally representative of the U.S. adult population. Additionally, our study is one of the first to focus upon a family history of skin cancer as a possible risk factor for developing an internal malignancy. The results of our study can be used to guide the further research needed to better elucidate the role a family history of skin cancer plays in determining a patient's risk for developing an internal cancer.

To summarize, a personal history of skin cancer was associated with increased risk for developing internal cancers, and a family history of skin cancer was not associated with risk for developing an internal cancer. As a family history of skin cancer was our marker for inherited risk factors, these results imply that the excess cancer risk among those with a personal history of skin cancer is more likely to be due to acquired rather than inherited characteristics. Future research focusing upon regulatory pathways external to the tumor sites, such as immune system dysregulation, could prove useful in understanding and explaining the association between skin cancer and risk for internal malignancies.

Chapter IV: Second Aim Manuscript

A cohort study of personal and family history of skin cancer in relation to all-cause and cancer-specific mortality

IV.A. Introduction

Skin cancer is the most common form of cancer in the United States with its two most common subtypes, keratinocyte carcinoma (KC) and melanoma, accounting for, respectively, 2 million and 87,000 incident cases every year [1–3]. This high incidence is paired with a low mortality rate of 0.69 and 2.7 deaths per 100,000 person years for KC and melanoma, respectively, often leading to skin cancer being considered a minor risk to the patient [3,20]. However; the evidence is uncertain over whether this typically non-lethal disease can be used as a marker for increased risk for mortality [4–6,9,22,50,56,62,66,80,81].

Previous research has observed multiple associations between skin cancer and risk for mortality, both overall and specifically from cancer. Some research has implied the association with all-cause mortality is driven by the stronger association with cancer specific mortality, i.e. ~3% increased for all cause-mortality but ~25% increased risk for cancer mortality [61]. Other research has associated skin cancer and its subtypes with other causes of death such as cardiac disease and infectious disease [53,56,59]. Finally, some research has used skin cancer as a marker for decreased mortality risk due to ultraviolet radiation (UVR) causing both skin cancer and potentially protective vitamin D [56,66,82,83]. Central to this rift in the literature is the debate over the existence of an underlying susceptibility factor that would explain the observed association between skin cancer and increased risk for mortality.

Proponents of using a personal history of skin cancer as a marker for increased risk for mortality theorize that if a patient had a malfunction in a common immune response or DNA repair pathway, the patient would be more likely to develop skin cancer and less capable of

resisting other diseases. Due to skin cancer's high prevalence and low mortality this underlying susceptibility would cause skin cancer to develop before the lethal disease manifests, creating the observed association between skin cancer and risk for mortality. The greatest weakness of this theory is the current lack of information about the nature of the underlying susceptibility. One of the leading theories is that the susceptibility factor is genetic in nature which would allow for the varied associations observed between a personal history of skin cancer and several causes of death [4,80]. While other studies have focused upon finding a specific mutation [63,64], our study takes a broader approach to determining the presence of a genetic risk factor by investigating a personal and family history of skin cancer within a nationally representative cohort. If a personal history of skin cancer and a family history of skin cancer share similar associations with all-cause and cancer-specific mortality, that similarity would support the existence of an underlying genetic predisposition [4,5,10].

The purpose of this study is to further investigate the association between a personal history of skin cancer and risk for mortality as well as investigate the presence of a genetic component to this association by determining if a family history of skin cancer is similarly associated with increased risk for mortality.

IV.B. Methods

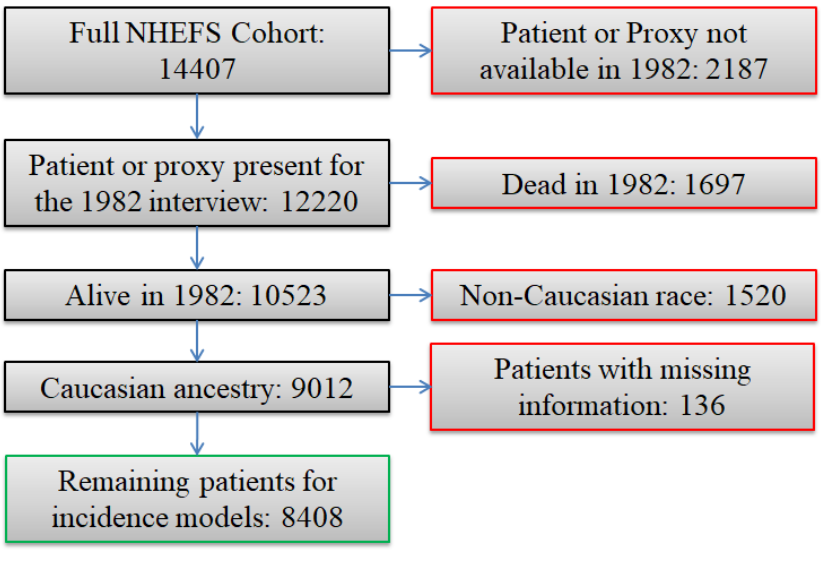
IV.B.1. Study Population, the NHANES I Epidemiological Follow-up Study

The source population of this study is the National Health and Nutrition Examination Survey I (NHANES I) Epidemiological Follow-up Study (NHEFS), a nationally representative prospective cohort. Specifically, the data sources are the initial interview and medical examination from 1982, the follow up interviews conducted in 1987 and 1992, and the vital status and mortality data sets. The NHEFS cohort is well suited to studying the association

between skin cancer and mortality because of the thorough questionnaires for a subject's personal history of cancer and dermatological history from all three interviews, the availability of data for a family history of cancer from the 1982 and 1992 interviews, and accurate mortality information linked to the National Death Index (NDI).

The NHEFS cohort is comprised of persons between the ages of 25 and 74 who completed the medical examination during NHANES I study (N=14407). For the present study additional inclusion criteria were: 1) participant or proxy (i.e. a spouse or sibling) had to be present for the 1982 medical examination and interview, 2) participant was alive in 1982, 3) Caucasian ancestry, 4) must have completed the personal and family history of cancer questionnaires, 5) must have no missing information for study outcomes or model independent variables. Of the 390 participants excluded for missing information 233 were due to being lost to follow-up. After applying these inclusion criteria, the present study included 8622 participants from the NHEFS cohort (**Figure 4.1**).

Figure 4.1: Patient Inclusion and Exclusion from the NHEFS Cohort



Only Caucasians were included in this study due to the differences in skin cancer epidemiology between races. For example, between Caucasians and African Americans there is a 25 fold difference in melanoma incidence and 3 fold difference in mortality [3]. These differences in incidence and mortality would necessitate a sub-group analysis. However; of the 1520 non-Caucasian participants 1407 were African Americans, of which only 9 had a family history of skin cancer. With only 9 participants possessing the exposure of interest there was not enough data to perform a subgroup analysis. Thus, despite the importance of the study question to other racial groups this study was required to exclude non-Caucasians.

IV.B.2. Measurement

At the 1982 interview all cancer related questions had a single categorization for skin cancer: "Skin Including Melanoma". Later interviews in 1987 and 1992 used separate categories for melanoma, KC, and miscellaneous skin cancers. However, family history of cancer was only collected at the beginning and end of the cohort, thus for the 1775 participants that died during follow-up it was not possible to conclusively determine if they had a family history of specifically KC or melanoma. In order to keep measurement consistent across the cohort and use the participants that had died, family and personal history of skin cancer was limited to the designation "any type of skin cancer".

Family history of cancer in first-degree relatives was ascertained for up to five relatives in 1982 and up to nine relatives in 1992. A participant reporting one or more relatives diagnosed with any type of skin cancer (KC, melanoma, or "other skin cancer") was classified as being positive for a family history of skin cancer. Similarly, a participant reporting one or more relatives with a specific cancer diagnosis other than KC, melanoma, or "other skin cancer" at

either interview would be counted as having a family history of internal cancer. If the cancer type was unknown then the cancer was ignored for determining family history of cancer.

Personal history of cancer was collected at the 1982, 1987, and 1992 interviews. A participant that reported a diagnosis of skin cancer during the personal cancer history or dermatological questionnaires at any of the three interviews was counted as having a personal history of skin cancer. A positive report at the 1982 interview for a specific internal cancer diagnosis resulted in the participant being recorded as having a personal history of internal cancer. Cancer diagnosis dates were also ascertained from the 1987 and 1992 interviews to capture any cancers prior to the start of the cohort that a participant may have failed to report at the 1982 interview. This variable does not collect information for internal cancers diagnosed after the 1982 interview due to the overwhelming effect of incident cancers during follow-up on predicting a participant's risk for mortality.

IV.B.3. Statistical Analyses

Means and proportions were calculated for all independent variables used in this study. Additionally means and proportions were calculated for participants without a family history of skin cancer, and participants with a family history of skin cancer in order to compare the distribution of common mortality risk factors between the two groups. T-tests were used to detect differences in continuous variables between participants with and without a personal history of skin cancer and a family history of skin cancer and Cochran-Mantel-Haenzel tests were used to determine the presence of a non-zero correlation for categorical variables with a personal and family history of skin cancer (**Table 4.1**).

Table 4.1: Cancer history and risk factor distribution in the full NHEFS cohort and subdivided by personal and family history of skin cancer							
	Entire cohort	**Personal history of skin cancer**		**P-value**	**Family history of skin cancer**		**P-value**
		No, N (%)	**Yes, N (%)**		**No, N (%)**	**Yes, N (%)**	
Number of participants	8622	7219	1403		8002	620	
Mean time of follow-up (standard deviation)	8.4 (2.2)	8.3 (2.4)	8.0 (2.4)	<0.01	8.2 (2.3)	8.6 (1.6)	<0.01
Mean age (standard deviation)	57.1 (14.8)	55.9 (17.8)	63.1 (13.6)	<0.01	57.4 (14.8)	52.6 (14.3)	<0.01
Gender				<0.01			<0.01
Men	3282	2641 (36.6)	641 (45.7)		3095 (38.7)	187 (30.2)	
Women	5340	4578 (63.4)	762 (54.1)		4907 (61.3)	433 (69.8)	
BMI				0.08			0.02
Underweight	222	184 (2.6)	38 (2.7)		202 (2.5)	30 (3.2)	
Normal weight	3827	3200 (44.3)	627 (44.7)		3516 (43.9)	311 (50.2)	
Over weight	3076	2543 (35.2)	533 (38.0)		2894 (36.2)	182 (29.4)	
Obese	1497	1292 (17.9)	205 (14.6)		1390 (17.4)	107 (17.3)	
Smoking behavior				0.07			0.07
Never smoked	3935	3305 (45.8)	630 (44.9)		3625 (45.3)	310 (50.0)	
Former smoker	2435	1968 (27.3)	467 (33.3)		2278 (28.5)	157 (25.3)	
Current smoker	2252	1946 (27.0)	306 (21.8)		2099 (26.2)	153 (24.7)	
How many years since patient quit smoking?				<0.01			0.09
Less than 5	865	727 (36.9)	138 (29.6)		819 (36.0)	46 (29.3)	
More than 5	1570	1241 (63.1)	329 (70.4)		1459 (64.0)	111 (70.7)	
Highest completed level of education				0.99			<0.01
Less than high school	3055	2533 (35.1)	522 (37.2)		2896 (36.2)	159 (25.7)	
High school graduate	3278	2794 (38.7)	484 (34.5)		3034 (37.9)	244 (39.4)	
Some higher learning	2289	1892 (26.2)	397 (28.3)		2072 (25.9)	217 (35.0)	

Table 4.1: Cancer history and risk factor distribution in the full NHEFS cohort and subdivided by personal and family history of skin cancer (continued)							
	Entire cohort	**Personal history of skin cancer**		**P-value**	**Family history of skin cancer**		**P-value**
		No, N (%)	**Yes, N (%)**		**No, N (%)**	**Yes, N (%)**	
Number of participants	8622	7219	1403		8002	620	
Hypertension				<0.01			0.03
No	5656	4826 (66.9)	830 (59.2)		5225 (65.3)	431 (69.5)	
Yes	2966	2393 (33.1)	573 (40.8)		2777 (34.7)	189 (30.5)	
Diabetes				0.06			0.25
No	8068	6771 (93.8)	1297 (92.4)		7481 (93.5)	587 (94.7)	
Yes	554	448 (6.2)	106 (7.6)		521 (6.5)	33 (5.3)	
Personal history of skin cancer				NA			<0.01
No	7219	7219 (100.0)	0 (0.0)		6735 (84.2)	484 (78.1)	
Yes	1403	0 (0.0)	1403 (100.0)		1267 (15.8)	136 (21.9)	
Family history of skin cancer				<0.01			NA
No	8002	6735 (93.3)	1267 (90.3)		8002 (100.0)	0 (0.0)	
Yes	620	484 (6.7)	136 (9.7)		0 (0.0)	620 (100.0)	
Personal history of internal cancer up to 1982				<0.01			0.68
No	8246	6944 (96.2)	1302 (92.8)		7651 (95.6)	595 (96.0)	
Yes	376	275 (3.8)	101 (7.2)		351 (4.4)	25 (4.0)	
Family history of internal cancer				<0.01			0.01
No	4451	3814 (52.8)	637 (45.4)		4170 (52.1)	281 (45.3)	
Yes	4171	3405 (47.2)	766 (54.6)		3832 (47.9)	339 (54.7)	

Univariate, age adjusted, and fully adjusted Cox-proportional hazards models were created to measure all-cause and cancer specific mortality. Fully adjusted mortality models accounted for age, gender, smoking history, highest completed level of education, personal history of internal cancer up to 1982, and family history of internal cancer. The fully adjusted all-cause mortality model was further adjusted for history of diabetes, hypertension, and body mass index (BMI) categorized according to CDC guidelines. The NHEFS 282 cause of death re-categorization was used to determine a participant's cause of death, and codes 04600 through 11800 were counted as cancer-specific deaths [84]. All models were adjusted for the complex survey design and weights used in the NHEFS cohort and analyses were performed in SAS 9.4.

IV.C. Results

Of the 8,622 participants in the study, 434 died of cancer and 1,341 deaths were due to other causes for a total of 1,775 deaths (**Table 4.2**). Assessing the distribution of common cancer and mortality risk factors among participants with a personal history of skin cancer were more likely to be older, be male, have a family history of skin cancer, have a personal history of internal cancer prior to the start of the cohort, and more likely to report a family history of internal cancer. Patient's with a family history of skin cancer were more likely to be younger, female, have never smoked, former smokers were abstinent longer, have a healthy BMI (18.5-24.9 kg/m^2), not have hypertension, and be better educated compared to those without a family history of skin cancer. Participants with a family history of skin cancer were also more likely to have a personal history of skin cancer and to have a family history of internal cancer (**Table 4.1**).

Table 4.2: Age at Death and vital Status at the end of the NHEFS cohort, N=8622							
Vital status	**Entire Cohort**	**Personal history of skin cancer mean (standard deviation) or N (%)**		**Cochran–Mantel–Haenszel test**	**Family history of skin cancer mean (standard deviation) or N (%)**		**Cochran–Mantel–Haenszel test**
		No	**Yes**		**No**	**Yes**	
Age at death	77.23 (10.6)	76.7 (10.7)	79.4 (9.8)		77.2 (10.6)	78.2 (10.4)	
Vital status							
Alive	6847	5799 (80.3)	1048 (74.7)	<0.01	6306 (78.8)	541 (87.3)	<0.01
Dead	1775	1420 (19.7)	355 (25.3)		1696 (21.2)	79 (12.7)	
Cancer-specific	434	331 (23.3)	103 (29.0)	0.03	416 (24.5)	18 (22.8)	0.72
Other cause	1341	1089 (76.7)	252 (71.0)		1280 (75.5)	61 (77.2)	

A personal history of skin cancer was associated with increased risk for all-cause mortality in unadjusted models (HR: 1.16, 95% CI: 0.98-1.39), but this association inverted after adjusting for age (HR: 0.75, 95% CI: 0.63-0.88) and other covariates (HR: 0.71, 95% CI: 0.60-0.84) (**Table 4.3**). Increased risk for cancer-specific mortality was observed due to a personal history of skin cancer in unadjusted models (HR: 1.54; 95% CI: 1.19-1.98), but a null association was observed after adjusting for age (HR: 1.05, 95% CI: 0.81-1.36) and other covariates (HR: 0.95, 95% CI: 0.72-1.25) (**Table 4.4**).

Before adjustment, a family history of skin cancer was associated with decreased risk for all-cause mortality (0.65, 95% CI: 0.50-0.85) (**Table 4.3**). However; this association became close to null in the age adjusted model (HR: 0.86, 95% CI: 0.68-1.08) and the fully adjusted model (HR: 0.99, 95% CI: 0.78-1.25). For cancer-specific mortality, familial skin cancer was associated with decreased risk in the unadjusted model (HR: 0.50, 95% CI: 0.27-0.93) but weakened once adjusted for age (HR: 0.64, 95% CI: 0.34-1.19), and the association did not appreciably change upon further adjustment (Full model HR: 0.68, 95% CI: 0.38-1.23) (**Table 4.4**).

Table 4.3: All-cause mortality hazard ratios (HR) and 95% confidence intervals (CI) during 10-year follow-up of the NHEFS cohort with various levels of adjustment, From years 1982 to 1992 N=8622

Variable	Unadjusted[1] Results HR (95% CI)	Age Adjusted[2] Results HR (95% CI)	Fully Adjusted[3] Results HR (95% CI)	Fully Adjusted[3] P-value
Personal history of skin cancer				
No (7219)	1.00 (ref)	1.00 (ref)	1.00 (ref)	
Yes (1403)	1.16 (0.98-1.39)	0.75 (0.63-0.88)	0.71 (0.60-0.84)	<0.01
Family history of skin cancer				
No (8002)	1.00 (ref)	1.00 (ref)	1.00 (ref)	
Yes (620)	0.65 (0.50-0.85)	0.86 (0.68-1.08)	0.99 (0.78-1.25)	0.90

1-Results are not adjusted for any other covariate
2-Results are adjusted for age
3-Results are adjusted for age, gender, BMI, smoking habit, time since former smoker quit, highest completed level of education, hypertension, diabetes, personal history of skin cancer, personal history of internal cancer, family history of skin cancer, and family history of internal cancer

Table 4.4: Cancer-specific mortality hazard ratios (HR) and 95% confidence intervals (CI) during 10-year follow-up of the NHEFS cohort with various levels of adjustment, From years 1982 to 1992 N=8622				
Variable	**Unadjusted[1] Results HR (95% CI)**	**Age Adjusted[2] Results HR (95% CI)**	**Fully Adjusted[3] Results HR (95% CI)**	**Fully Adjusted[3] P-value**
Personal history of skin cancer				
No (7219)	1.00 (ref)	1.00 (ref)	1.00 (ref)	
Yes (1403)	1.54 (1.19-1.98)	1.05 (0.81-1.36)	0.95 (0.72-1.25)	0.72
Family history of skin cancer				
No (8002)	1.00 (ref)	1.00 (ref)	1.00 (ref)	
Yes (620)	0.50 (0.27-0.93)	0.64 (0.34-1.19)	0.68 (0.38-1.23)	0.20

1 Results are not adjusted for any other covariate
2 Results are adjusted for age
3 Results are adjusted for age, gender, smoking habit, time since smoker quit smoking, highest completed level of education, personal history of skin cancer, personal history of internal cancer, family history of skin cancer, and family history of internal cancer

IV.D. Discussion

This study found no evidence that a personal or family history of skin cancer were associated with increased mortality. Participants with a personal history of skin cancer were more likely to be older, have a family history of internal cancer, report a personal history of internal cancer before study baseline, and be hypertensive compared to participants without a personal history of skin cancer (**Table 4.1**). A personal history of skin cancer was also associated with decreased risk for all-cause mortality and was not associated with risk for cancer-specific mortality. Furthermore, participants with a family history of skin cancer were more likely to have an overall lower risk profile, such as being younger, less likely to smoke, less likely to have hypertension, be better educated, and more likely to have a healthy BMI ,indicating they should be at lower risk for mortality (**Table 4.1**). This observation was corroborated by the time to event analyses which showed either a possible inverse association between a family history of skin cancer and risk for all-cause mortality (**Table 4.3**) or a null association with cancer-specific mortality (**Table 4.4**).

Adjusting for age changed the results for personal history of skin cancer (all-cause mortality HR: 1.16 vs. 0.75; cancer-specific mortality HR: 1.54 vs. 1.05) and family history of skin cancer (all-cause mortality HR: 0.65 vs. 0.86; cancer-specific mortality HR: 0.50 vs. 0.64). Age is highly associated with both risk for developing a skin cancer and risk for mortality, and is not on the causal pathway between skin and mortality. Thus age is possibly a confounder for the association between personal and family history of skin cancer and risk for mortality [3,11,27]. Additionally we investigated the possibility of an interaction effect between age and our skin cancer variables but found it was not significant.

The results of this study for a personal history of skin cancer run counter to previous research [10,61,66]. Previously, a personal history of KC and melanoma have been associated with increased risk for developing internal cancer, all-cause mortality, and cancer-specific mortality [4–8,22,53,54,56,61,62,80,85]. However, in this study a personal history of skin cancer was associated with decreased risk for all-cause mortality, implying an overall protective effect (**Table 4.3**). Thus, this study did not observe an association between skin cancer and increased risk for mortality, and consequently no evidence of an underlying susceptibility factor. However, our results conflict with the predominant theory linking skin cancer to decreased mortality. In the literature, the "vitamin D hypothesis" claims that a personal history of skin cancer is indicative of decreased risk for cancer and mortality. This hypothesis asserts that vitamin D is protective against developing several forms of cancer, cardiovascular disease, and infectious diseases [9,66,68,71,83]. Because UVR exposure induces vitamin D synthesis and is the primary cause of skin cancer, a person who develops skin cancer has also synthesized more vitamin D and thus should be at lower risk for cancer, several diseases, and therefor mortality [9,66,68,71,83]. However, this study did not observe a protective effect for cancer-specific mortality, one of the

core suppositions of the vitamin D hypothesis (**Table 4.4**). Overall the results for a personal history of skin cancer show decreased risk for mortality, but conflicts current theories regarding how that protective effect would function.

Additionally, this study did not observe evidence of a heritable association between skin cancer and mortality. Typically, a family history of a risk factor would be expected to mirror the effect of a personal history, i.e. participants with a family history of ovarian cancer and those with a personal history of ovarian cancer are both at increased risk for developing breast cancer [86]. However, in this study a personal history of skin cancer was indicative of decreased all-cause mortality and a family history of skin cancer was not associated with all-cause mortality (**Table 4.3**). Also, a personal history of skin cancer was not associated with cancer-specific mortality, but a family history of skin cancer was suggestive of decreased risk for cancer-specific mortality (**Table 4.4**). The observation that personal history and family history of skin cancer did not have similar associations implies the two variables interact with mortality in different ways rather than sharing one underlying pathway. Alternatively, this study may have needed more information about the relative's skin cancer diagnosis to accurately capture the association between a family history of skin cancer and risk for mortality. For example, some studies have noted that having a relative diagnosed earlier in life indicates greater risk for a patient [87,88]. A similar trend has been observed among KC patients, in which patients who developed their KC before the age of 44 are at greater risk for developing internal cancers compared to those who developed KC later in life [4]. Thus, it may not be the presence of a relative with skin cancer that confers risk, but the presence of one who developed skin cancer earlier in life.

The primary weakness of this study was the inability to distinguish between skin cancer subtypes. Personal histories of KC's subtypes, squamous cell carcinoma (SCC) and basal cell

carcinoma (BCC), have been observed to have different associations with mortality [10]. Patients with a history of SCC typically present increased risk for all-cause mortality, with relative risk (RR) estimates ranging from 1.11 to 1.54 [22,56,62,80]. SCC has also been associated with increased mortality among specific types of cancer patients, most notably leukemia [53,54]. Conversely, BCC has sometimes been observed to have a weak protective effect (RR: 0.89) or a null association (RR: 0.97) with mortality [22,56,62,80]. As this study was unable to differentiate between KC subtypes and ~76% of skin cancers reported at later interviews were KC, it is possible that a higher than expected number of BCCs are present in the study which may have overridden the deleterious effects of SCC. However, a similar previous study found increased risk for mortality in the presence of a personal history of KC without differentiating between KC subtypes [61]. Additionally, there may be some inaccuracy in the self-reported skin cancer information. With respect to self-reported KC history, studies have reported sensitivity ranging from 69-94% and specificity ranging from 87-99% [76,77]. Furthermore, self-reported family history could be expected to be less accurate than personal history and impacted by socio-economic status. For reference, overall the sensitivity of self-reported cancer ranges from 79-93% with a specificity of 99% [78,79]. The error from self-reported histories of KC and other cancers is anticipated to result in under-ascertainment and be non-differential, and therefore likely resulting in bias towards the null that would increase the likelihood to observe a non-significant association.

Despite these weaknesses, our study also has notable strengths. The NHEFS cohort is nationally representative of the entire U.S. adult population, allowing the results of this study to be generalizable to a wide population. In particular this asset is helpful as the covariates support the internal validity of the study as male gender, increased age, smoking at the start of the cohort,

history of hypertension, history of diabetes, were all associated with increased risk for mortality as would be expected. Additionally, all deaths in the cohort were linked to the NDI, ensuring accurate information for both time and cause of death.

Our study explored the association between skin cancer and risk for mortality and found results for a personal history of skin cancer conflicted with the prevailing theories on this association. Additionally, the association between family history of skin cancer and mortality did not mirror the association between a personal history of skin cancer and mortality, implying that the susceptibility factor associated with skin cancer and mortality is not heritable. The disagreement between this study and prior work highlights the importance of further research. More studies with detailed information regarding the skin cancer diagnosis of both patients and relatives are needed to understand the link between skin cancer and mortality, and the challenges presented here call for such studies.

Chapter V: Third Aim Manuscript

History of skin cancer, an overlooked risk factor in cancer risk prediction

V.A. Introduction

Skin cancer is the most common form of cancer in the United States with its subtypes, keratinocyte carcinoma (KC) and melanoma, accounting for an estimated 2 million and 87,000 annual incident cases, respectively [1,2]. Despite these high incidence rates, these skin cancer subtypes are considered to be low-risk malignancies due to mortality rates of 0.69 and 2.7 deaths per hundred thousand person years (PY) for KC and melanoma, respectively [20,89]. However, a growing body of evidence has associated KC and melanoma with overall increased risk for developing an internal cancer and increased risk at specific cancer sites [4–8,50]. For example, an Alberta based cohort study found patients with a history of KC were at increased risk for 30 of the 40 specific types of cancer investigated, and melanoma was associated with increased risk for 12 specific sites [5]. Breast cancer is among the malignancies associated with a history of skin cancer with relative risk (RR) estimates ranging from 1.30 to 1.40 for KC and from 1.14 to 5.13 for melanoma [4–8,50].

A personal history of skin cancer is easily collected information and given skin cancer's associations with multiple forms of internal cancer it could prove useful in improving the predictive ability of several cancer risk models. However, few cancer risk models use information for a personal or family history of skin cancer. Our case-control study sought investigate this gap in the research by modifying an existing cancer risk prediction model and investigate how it could be improved by incorporating patient information regarding skin cancer, specifically the Gail model. In 1989 Dr. Mitchell H. Gail created a risk prediction model incorporating a patient's age, race, age at menarche, age at first live birth, number of first degree

relatives with breast cancer, and biopsy history to estimate the patient's absolute risk for developing breast cancer [30]. Using data from a large nationally representative survey, our study assessed 5-year breast cancer risk for breast cancer cases and controls using the Gail model and a skin cancer calibrated version of the Gail model, the Gail+SCM model. The results of these two models were then examined to determine their ability to differentiate between patients who developed breast cancer and those who did not.

V.B. Materials and methods

V.B.1. The study population, the National Health Interview Survey

All data for our study came from the National Health Interview Survey (NHIS), an annual cross-sectional household interview and survey. The NHIS was chosen due to it differentiating between KC and melanoma skin cancers and containing risk factor information needed for the Gail model. Our study uses data from the Adult Sample Questionnaire and Adult Cancer Questionnaire for the years 2000, 2005, 2010, and 2015. Our study applied three inclusion criteria upon the NHIS participants: female gender, Caucasian ancestry, and an age at interview or breast cancer diagnosis of 40 years or greater.

Though the Gail model is capable of calculating risk for multiple racial groups, our study included only Caucasian participants. As skin cancer is most concentrated among Caucasians, any effect associated with skin cancer would be best observed among Caucasians. Additionally, the epidemiological differences for skin cancer between racial groups would have required subgroup analyses that our study was not powered to perform. Age was also used to restrict participant entry due to our study's methodology. Our study assessed 5-year breast cancer risk predictions and the Gail model is accurate for women who are 35 years old or older. To accommodate this requirement of the Gail model, all participants must be 40 years old or older at

either time of breast cancer diagnosis or their interview so they would be no younger than 35 for the risk evaluation.

After applying these inclusion criteria, there were a total of 34,744 participants including 1,419 cases and 33,325 controls. The distribution of Gail model risk factors and personal and family history of skin cancer are shown in **Table 5.1**. For predictive modeling, three quarters (N=26,058, Cases: 1,071, Controls: 24,987) of the participants were randomly assigned to the training data set and the remaining quarter (N=8,686, Cases: 348, Controls: 8,338) were used for the testing data set.

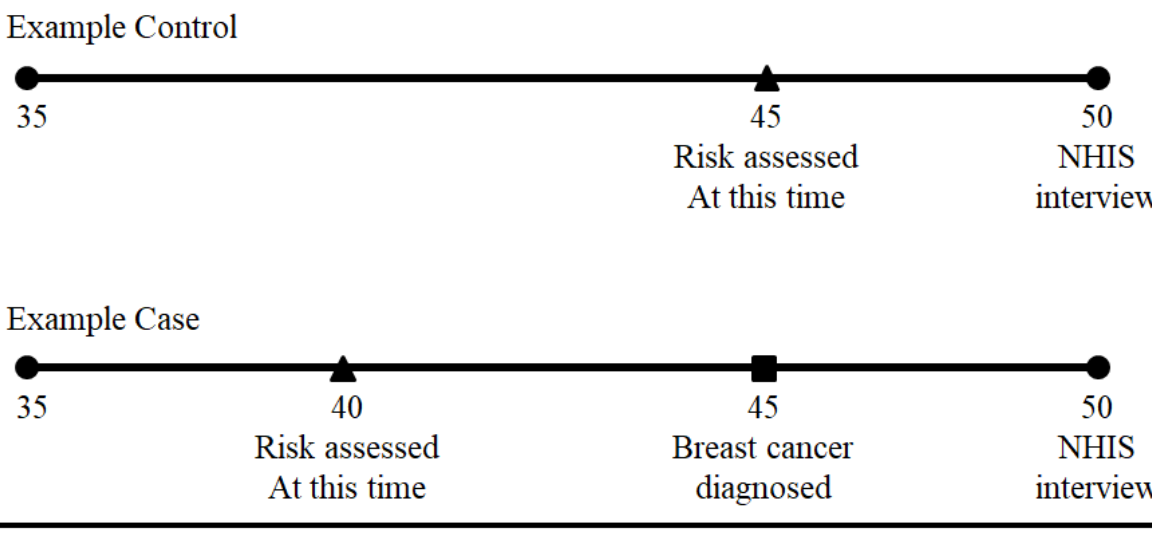
Table 5.1: Frequencies of Gail Model variables and skin cancer related variables among white women in the NHIS study			
Variable	**Entire data set**	**Personal history of breast cancer**	
		No (controls)	**Yes (cases)**
Number of Participants	34744	33325	1419
Age	54.9 (13.26)	55.0 (13.3)	54.6 (11.7)
Age of Menarche			
≤ 14	8419	8078 (24.2%)	341 (24.0%)
12-13	16348	15674 (47.0%)	674 (47.5%)
≤ 11	9977	9573 (28.7%)	404 (28.5%)
Age at first live birth			
Nulliparous	5550	5319 (16.0%)	231 (16.3%)
<20	9228	8885 (26.7%)	343 (24.2%)
20-24	10786	10322 (31.0%)	464 (32.7%)
25-29	5680	5428 (16.3%)	252 (17.8%)
≥30	3500	3371 (10.0%)	129 (9.1%)
Number of Biopsies			
0	29851	29255 (87.8%)	596 (42.0%)
1	3608	3019 (9.1%)	589 (41.5%)
≥2	1285	1051 (3.2%)	234 (16.5%)
Biopsy resulted in hyperplasia			
No	4547	4024 (98.9%)	523 (63.5%)
Yes	346	46 (1.1%)	300 (36.5%)
Number of relatives with breast cancer			
0	30575	29486 (88.5%)	1089 (76.7%)
1	3733	3473 (10.4%)	260 (18.3%)
≥2	436	366 (1.1%)	70 (4.9%)
Personal history of any skin cancer			
No	33189	31877 (95.7%)	1312 (92.5%)
Yes	1555	1448 (4.4%)	107 (7.5%)
Personal history of melanoma			
No	34434	33040 (99.1%)	1394 (98.2%)
Yes	310	285 (0.9%)	25 (1.8%)
Personal history of KC			
No	33864	32499 (97.5%)	1365 (96.7%)
Yes	880	826 (2.5%)	33 (2.3%)
Personal history of unknown skin cancer			
No	34335	32949 (98.9%)	1386 (97.7%)
Yes	409	376 (1.1%)	33 (2.3%)
Relative developed any skin cancer before age of 50			
No	33453	32112 (96.4%)	1341 (94.5%)
Yes	1291	1213 (3.6%)	78 (5.5%)

V.B.2. Breast cancer risk assessment

In our study, a 5-year breast cancer risk assessment was performed for all participants. The risk assessment entailed determining patient risk factors at a time prior to their interview so their predicted risk for breast cancer could be compared to their breast cancer status at a later date. This methodology is possible because most Gail model risk factors are either static variables or markers for an underlying predisposition. For example, if a woman has given birth, her age at first live birth will not change. The static nature of this variable allows for assessing a woman's risk for developing breast cancer prior to her first live birth. Other variables, such as a family history of breast cancer, are indicative of an underlying predisposition for breast cancer present in patients regardless of whether their relative has yet developed breast cancer. Therefore, the variables were easily tracked through a patient's lifetime or were indicative of an underlying risk factor that was always present in the patient. These traits of the Gail model risk factors made it possible to determine a patient's breast cancer risk at a previous point in life.

For cases, the risk assessment was set five years prior to their breast cancer diagnosis and for controls it was set five years prior to their interview. For example, if a patient reported being diagnosed with breast cancer at the age of 45, then they would be assessed according to their risk factors when they were 40 regardless of their age when they were interviewed. Furthermore, if that patient gave birth to their first child at the age of 43, then they would be listed as being nulliparous for the risk assessment as they had yet to give birth at the age of 40. **Figure 5.1** shows a visual example of when a risk assessment would occur for a case and a control.

Figure 5.1: Example of determining age at risk assessment for cases and controls



V.B.3. Calibrating the Gail model

Our study elected to use a method adopted by Gail 2008, Comen et al. 2011, and Mealiffe et al. 2010 to incorporate new risk factor information into the Gail model by building a calibration model to modify a patient's Gail model predicted risk [31,34,35]. The first step of this process was to train a logistic regression model for risk of developing breast cancer due to a personal and family history of skin cancer, the skin cancer modification (SCM) model. This model was trained on three quarters of the NHIS data. Initial logistic regression models were built to assess associations between breast cancer risk and variables for a personal and family history of skin cancer. Variables deemed significant due to either statistical testing or importance in prior research were then placed into a multivariable model for further testing and variable elimination. The final SCM model included risk estimates for a personal history of melanoma, personal history of KC, personal history of unknown type of skin cancer, and if a relative developed any form of skin cancer before the age of 50. To determine if overfitting occurred in the SCM model, we used a bootstrapping procedure to fit our model's risk estimates on 100

bootstrap iterations of the training data set. This methodology provided an estimate for how much overfitting, a.k.a. optimism, was present in the model and allowed us to adjust our risk estimates accordingly [90,91]. The optimism-adjusted risk estimates were then locked and not altered further (**Table 5.2)**.

Table 5.2: Risk estimates for the Skin Calibration Model after adjusting for overfitting

Risk Factor	OR (95% CI)	P-value
Personal history of melanoma (N=225)	1.95 (1.10-3.44)	0.01
Personal history of KC (N=642)	1.39 (0.94-2.06)	0.16
Personal history of unknown skin cancer (N=311)	1.91 (1.17-3.12)	0.02
Relative diagnosed with any skin cancer before age of 50 (N=961)	1.37 (0.98-1.92)	0.07

The next step was to determine the average population risk for developing breast cancer according to the SCM model. As the NHIS data set is a nationally representative survey, the training data was used to determine distributions for personal and familial skin cancer diagnoses in the United States population. The risk estimates from the SCM model and population distributions were then used to calculate an average national odds ratio (OR) for breast cancer risk according to risk factors in the SCM model.

The final step of calibrating the Gail model was to combine the Gail model predicted breast cancer risk, the risk estimates of the SCM model, and the national average risk according to the SCM model. Individual OR for breast cancer risk according to the SCM model (OR_{SCM}) was divided by the national average OR_{SCM} ($OR_{SCM\ pop\ mean}$). By dividing the individual OR_{SCM} by the national average $OR_{SCM\ pop\ mean}$, we could use the resulting ratio to raise or decrease a patient's risk for breast cancer and compensate for the Gail model not previously incorporating a personal and family history of skin cancer. This ratio was then multiplied by the participant's

Gail model predicted absolute 5-year breast cancer risk (ABS $Risk_{Gail}$). The combination of the Gail and SCM models is the Gail+SCM model.

$$(5.1) \qquad Abs\ Risk_{Calibrated} = Abs\ Risk_{Gail} \times \frac{OR_{SCM}}{OR_{SCM\ pop\ mean}}$$

V.B.4. Testing the Gail and Gail+SCM models

For model testing, the Gail model and Gail+SCM model 5-year absolute breast cancer risk were calculated for all participants in the testing data set. Results of the Gail and Gail+SCM models were compared using area under the receiver operating characteristic curve (AUC), sensitivity and specificity, and average 5-year predicted breast cancer risk. Sensitivity and specificity were calculated at several cut points for 5-year breast cancer risk: 1.5%, 1.67%, 2.0%, and 3.0%. These thresholds were chosen because 1.67% absolute predicted risk is an FDA guideline used to determine a patient's eligibility for pharmacological risk reduction [36,37], 1.5% and 2.0% are repeatedly used in the literature [31,34,35], and 3.0% was added in our study to evaluate model performance for very high risk participants.

V.C. Results

Predicting breast cancer risk on the full testing data set, the Gail and Gail+SCM models showed similar results. The Gail model had an AUC of 0.6643 (95% confidence interval (CI): 0.6321-0.6966) and the Gail+SCM model had an AUC of 0.6651 (95% CI: 0.6329-0.6974) (**Table 5.3**). Additionally, the sensitivity and specificity at each risk threshold was similar between the two models with less than a 2% absolute difference between their results, i.e. Gail model sensitivity and specificity at 3% risk: 23.85% and 94.83% vs. Gail+SCM model sensitivity and specificity: 25.57% and 94.30% (**Table 5.4**).

Table 5.3: AUC for 5-year breast cancer risk predictions by model and data used for prediction.		
Data used	**Gail AUC (95% CI)**	**Gail+SCM AUC (95% CI)**
Full training data set (N=8686)	0.6643 (0.6321-0.6966)	0.6651 (0.6329-0.6974)
Personal history of skin cancer only (N=412)	0.7104 (0.6182-0.8026)	0.7128 (0.6218-0.8039)

When predicting risk for only patients with a personal history of any skin cancer, the results of the two models diverged. The difference in AUC between the Gail model and the Gail+SCM model remained similar, Gail AUC: 0.7104 (95% CI: 0.6182-0.8026) vs. Gail+SCM AUC: 0.7128 (95% CI: 0.6218-0.8039) (**Table 5.3**). However, though the AUC was similar between the models, the Gail+SCM model produced higher sensitivity and lower specificity at all risk thresholds (**Table 5.5**). Using the 3% risk threshold as an example, the Gail model had sensitivity and specificity of 37.04% and 91.69% but the Gail+SCM model had a sensitivity and specificity of 66.67% and 68.57% (**Table 5.5**).

Table 5.4: Epidemiological measures for 5-year breast cancer risk at different risk thresholds and using the full testing dataset (N=8686, Cases: 348, Controls: 8338)								
	1.50% Threshold		1.67% Threshold		2.00% Threshold		3.00% Threshold	
Measure	**Gail**	**Gail+SCM**	**Gail**	**Gail+SCM**	**Gail**	**Gail+SCM**	**Gail**	**Gail+SCM**
Sensitivity	51.72%	53.45%	49.14%	49.14%	41.67%	41.67%	23.85%	25.57%
Specificity	68.72%	69.78%	76.47%	76.51%	86.23%	85.36%	94.83%	94.30%

Table 5.5: Epidemiological measures for 5-year breast cancer risk at different risk thresholds among patients with a personal history of skin cancer in the testing dataset (N=412, Cases: 27, Controls: 385)								
	1.50% Threshold		1.67% Threshold		2.00% Threshold		3.00% Threshold	
Measure	**Gail**	**Gail+SCM**	**Gail**	**Gail+SCM**	**Gail**	**Gail+SCM**	**Gail**	**Gail+SCM**
Sensitivity	62.96%	88.89%	62.96%	85.19%	55.56%	77.78%	37.04%	66.67%
Specificity	58.18%	21.30%	63.12%	24.16%	76.62%	35.32%	91.69%	68.57%

Patterns also appeared when the predicted risk for developing breast cancer was stratified by a personal history of skin cancer (**Table 5.6**). Among controls without a personal history of skin cancer, the Gail model produced an average predicted risk of 1.31% for developing breast cancer in five years and the Gail+SCM produced an average predicted risk of 1.27% (**Table 5.6**). However, among controls with a personal history of skin cancer, the Gail model produced an average risk of 1.66%, and the Gail+SCM model produced a predicted risk of 2.73% (**Table 5.6**). For cases without a personal history of skin cancer, the Gail model produced an average risk of 2.27%, and the Gail+SCM model produced an average risk of 2.23%. The difference between the two models was greatest when predicting on cases with a personal history of skin cancer, 2.85% for the Gail model and 4.46% for the Gail+SCM model (**Table 5.6**).

Table 5.6: Mean predicted risk according to the Gail and Gail+SCM models by patient personal history of cancer

	Model	**Mean predicted risk (95% CI)**
Controls without skin cancer (N=7953)	Gail	1.31 (1.29-1.33)
	Gail+SCM	1.27 (1.25-1.29)
Controls with skin cancer (N=385)	Gail	1.66 (1.56-1.75)
	Gail+SCM	2.73 (2.57-2.90)
Cases without skin cancer (N=321)	Gail	2.27 (2.04-2.49)
	Gail+SCM	2.23 (2.01-2.45)
Cases with Skin Cancer (N=27)	Gail	2.85 (1.97-3.71)
	Gail+SCM	4.46 (3.14-5.78)

V.D. Discussion

For patients with a personal history of skin cancer, the Gail+SCM model had higher sensitivity and lower specificity without decreasing overall model predictive ability compared to the Gail model, an intriguing development considering the Gail model's use as an initial risk assessment tool. The Gail+SCM model's higher sensitivity would lead to the identification of more people at high risk for developing breast cancer, a life-saving result as studies have shown that early detection of breast cancer can improve survival rates by 30% to 50% [3,92]. However,

the decrease in specificity increases the Gail+SCM model's false positive rate as well. A false positive in this instance would lead to unnecessary stress for the patient and possibly pre-emptive breast cancer treatment. One such treatment could be tamoxifen, which could increase a patient's risk for developing ovarian cancer, a pertinent consideration as FDA guidelines for prescribing pre-emptive tamoxifen treatment include having a Gail model predicted breast cancer risk above 1.67% [37,93]. Regardless, these results are encouraging; if subsequent versions of the Gail+SCM model can improve sensitivity without decreasing specificity, then the Gail+SCM model would be a clinically useful update to the Gail model.

The Gail+SCM model predicted increased risk for breast cancer among participants with a personal history of skin cancer, curiously so did the Gail model. The Gail model detected increased risk for breast cancer among participants with a personal history of skin cancer; controls with skin cancer had an average predicted risk of 1.66%, and those without skin cancer were at 1.31% absolute risk. Similarly, among cases with a history of skin cancer the average predicted risk was higher compared to those without a personal history of skin cancer, 2.85% vs. 2.27% respectively (**Table 5.6**). The Gail model also showed increased overall predictive ability when predicting breast cancer risk on patients with a personal history of skin cancer compared to predicting risk on the whole testing data set, AUC 0.7104 vs. 0.6643 (**Table 5.3**). This increased risk among skin cancer patients is likely due to an association between a personal history of skin cancer and at least one Gail model risk factor. If a personal or family history of skin cancer is associated with Gail model risk factors then further investigating these associations could improve the accuracy of Gail model risk factors and perhaps reveal interaction effects. Our study did not have sufficient data to accomplish this task but it is a potential avenue for future research.

One of the novel findings of our study is the association between having a 1st degree relative with a skin cancer diagnosis before the age of 50 and risk for developing breast cancer. A younger age at skin cancer diagnosis for a relative conferring greater risk for developing breast cancer mirrors how a relative diagnosed early in life confers greater risk for several other cancers as well. For example, among *BRCA2* carriers having a relative with a younger age of breast cancer diagnosis indicates greater risk than a relative diagnosed later in life [87]. This finding could prove useful as there is a dearth of information on the effects of a family history of skin cancer on internal cancer risk, and may encourage further research on the topic.

The results of our study agree well with previous work. Prior work for modifying the Gail model has found that the addition of risk factors does little to improve the Gail model risk predictions with the AUC seeing less than a 0.05 increase [31,33–35,94–96]. However, much like the work of Comen et al., potentially useful results were found despite little improvement in AUC. Similarities in Gail model AUC also showed validity in our model testing procedures, particularly the results of Dr. Gail's 2008 study when he tested the Gail model on the NHIS year 2000 data set (Gail 2008 AUC: 0.607, our study's AUC: 0.6643) [35]. Additionally; our study's SCM model risk estimates agreed with previous research on the associations between melanoma, KC, and increased risk for breast cancer [4,5,7,8]. It was this high level of agreement with prior results that allowed a personal history of KC to be included in the SCM model despite the variable not being statistically significant at the 0.10 level (Ong 2014: relative risk (RR): 1.24, Jung 2014 RR: 1.4, our study OR: 1.39) [4–6].

Our study has a limitation in the form of survivorship bias. Because the NHIS data was collected after the breast cancer diagnosis had occurred and because breast cancer is potentially lethal, our study is likely influenced by survivorship bias. In retrospective studies, if the exposure

of interest is associated with either incidence or severity of the disease of interest, then exposed and unexposed patients may have different mortality risks. The differential mortality rate among the exposed and unexposed groups will cause only the healthiest among the exposed group to be interviewed, causing the observed association to be weaker than the true association [97,98]. In this instance, as skin cancer is associated with risk for developing breast cancer, it is possible that less healthy skin cancer patients were more likely to die of breast cancer before their interview compared to participants without a personal history of skin cancer [4,5,7,8].

Our study investigated the potential for improvement to the Gail model by including information for a personal and family history of skin cancer. Including this information 1) improved sensitivity and decreased specificity for detecting high risk breast cancer patients with a history of skin cancer, 2) showed that the original Gail model detects increased risk among patients with a personal history of skin cancer and may benefit from a more thorough method of incorporating this information into the Gail model, 3) and presented evidence that a family history of skin cancer may be associated with risk for developing breast cancer. The Gail+SCM model needs further improvement as demonstrated by the model's lower specificity, but if that issue can be solved in subsequent studies and validated against external data sources, then a patient's history of skin cancer could improve detection of women at high risk for breast cancer. Successfully improving the Gail model with information for a history of skin cancer could in turn lead to incorporating this information into risk models for other internal cancer sites associated with skin cancer.

Chapter VI: Discussion and Conclusions

VI.A. Review of the results of the three aims

This project aimed to further investigate the association between skin cancer and risk for developing internal malignancies and mortality. Data from a nationally representative cohort, the NHANES I Epidemiological Follow-up Study (NHEFS), was used to assess the association between a personal and family history of skin cancer with the outcomes of incident internal cancer and mortality. Additionally, the Gail model was calibrated using nationally representative survey data from the National Health Interview Survey (NHIS) with each patient's personal and family history of skin cancer to determine if including this information could improve the Gail model's predictive ability.

Aim 1 explored the association between a personal and family history of skin cancer with a patient's risk for developing an internal cancer in the nationally representative NHEFS cohort. Our first study observed that a personal history of skin cancer was associated with increased risk for developing an internal malignancy (hazard ratio (HR): 1.33, 95% confidence interval (CI): 1.09-1.61) after adjusting for common cancer risk factors such as age, gender, smoking history, and family history of internal cancer. Conversely, a family history of skin cancer was not associated with increased risk for developing an internal cancer (HR: 0.80, 95% CI: 0.58-1.11).

Aim 2 investigated the association between a personal and family history of skin cancer and their association with all-cause mortality and cancer-specific mortality in the nationally representative NHEFS cohort. In our study, a personal history of skin cancer was associated with decreased risk for all-cause mortality (HR: 0.71, 95% CI: 0.60-0.84), but not cancer-specific mortality (HR: 0.95, 95% CI: 0.72-1.25). A family history of skin cancer was not associated with

risk for all-cause mortality (HR: 0.99, 95% CI: 0.78-1.25) or cancer-specific mortality (HR: 0.68, 95% CI: 0.38-1.23).

Aim 3 used information for a personal and family history of skin cancer to calibrate an existing cancer risk model, the Gail model, and detect changes in the Gail model's predictive ability. Testing the Gail and Gail with Skin Cancer Modification (Gail+SCM) models resulted in similar overall predictive ability as determined by area under the receiver operating characteristic curve (AUC) (Gail AUC: 0.6643, Gail+SCM AUC: 0.6651). However, among women with a personal history of skin cancer, the Gail+SCM model had greater sensitivity but lower specificity (i.e. at 3% predicted breast cancer risk Gail model sensitivity and specificity: 37.04% and 91.69%; Gail+SCM model sensitivity and specificity: 66.67% and 68.57%). In addition, our third study observed that patients with a family member who developed skin cancer before the age of 50 were at increased risk for developing breast cancer. We expected the Gail+SCM model to detect increased risk among skin cancer patients, but it was surprising that the Gail model also implicitly detected increased breast cancer risk among those with a personal history of skin cancer. Stratifying the results of the Gail model by personal history of skin cancer also showed that the Gail model predicted higher risk for breast cancer among patients with a personal history of skin cancer (Mean predicted risk: controls without skin cancer 1.31% (1.29%-1.33%), controls with skin cancer 1.66% (1.56%-1.75%), cases without skin cancer 2.27% (2.04%-2.49%), cases with skin cancer 2.85% (1.97%-3.71%)). Additionally when the Gail model predicted risk on only patients with a personal history of skin cancer the Gail model had overall better predictive ability (AUC 0.7104 vs. 0.6643) despite the model not using skin cancer information to predict absolute risk for developing breast cancer.

VI.B. Merging the results the three papers

When the results of our three papers are considered as a unified whole, several inferences can be made regarding the association between personal and family history of skin cancer, risk of internal cancer, and mortality. First, a personal history of skin cancer is associated with increased risk for developing an internal malignancy. Second, a family history of skin cancer may be used as a marker for increased breast cancer risk if a relative's age at diagnosis is accounted for, a finding that may be the impetus for future research. Finally, personal and family history of skin cancer were not associated with increased risk for mortality and require further research to understand why skin cancer would be associated with increased risk for developing cancer but not with increased risk for mortality.

VI.B.1. The association between a personal history of skin cancer and risk for internal malignancies

In our first paper, a personal history of skin cancer was observed to increase a patient's risk for developing an internal cancer. This result was observed after adjustment for common cancer risk factors, such as smoking history and BMI, in a nationally representative cohort. Additionally, the results for a personal history of skin cancer matched risk estimates from other large cohorts, further corroborating our results (**Aim 1** HR: 1.33; Jung et al. 2014 relative risk (RR): 1.4; Ong et al. 2014 RR: 1.36) [4,5]. This observation directly counters the claims that the association between a personal history of skin cancer and increased risk for developing an internal malignancy in previous work was due to uncontrolled confounders or a study population not representative of the general population [4–6,9]. Additionally, these results show that skin cancer may work well as a model for studying multiple primary cancers. Though our first Aim was not powered to detect associations between a personal history of skin cancer and risk for specific internal cancer sites, the results of our third paper included an increased risk for

developing breast cancer after a personal diagnosis of melanoma, KC, or an unknown skin cancer. Though the **Aim 3** results were not adjusted for smoking, our results still occurred in a nationally representative study population and had a high level agreement with prior studies for the association between KC and breast cancer risk (Ong et al. 2014: relative risk (RR): 1.24, Jung et al. 2014 RR: 1.4, our study odds ratio (OR): 1.39) [4–6]. These two papers provide strong evidence corroborated by prior research in support of the theory that a personal history of skin cancer is a marker for increased internal cancer risk. This finding in turn means specifying for a personal history of skin cancer may be useful when studying multiple primary cancers

VI.B.2.b. Family history of skin cancer and risk for developing internal cancer

The reasons for the association between a personal history of skin cancer and increased risk for internal cancer are not understood, but could be due to underlying genetic susceptibility to cancer [4,5]. Our study sought to test this hypothesis by investigating if personal and family history of skin cancer were similarly associated with risk for developing an internal malignancy. While the association between a personal history of skin cancer and increased risk for internal cancer was well supported in our research, the results for a family history of skin cancer were less consistent. In **Aim 1** a family history of skin cancer was not significantly associated with increased risk for developing an internal malignancy (HR: 0.80, 95% CI: 0.58-1.11). However, in **Aim 3** a family history of skin cancer was associated with increased risk for developing breast cancer (OR: 1.44, 95% CI: 1.03-2.02). These results appear contradictory as **Aim 1** implies no association or a weak protective effect for developing internal cancer while **Aim 3** shows increased risk for developing the most common internal cancer in the United States [3]. However, there is a difference between the data sources for the two papers. The NHIS data used for **Aim 3** included age at cancer diagnosis for relatives while **Aim 1** did not. This additional

information may have allowed our **Aim 3** to differentiate between familial and non-familial skin cancers.

One of the challenges of studying a family history of cancer is separating heritable cancers from malignancies that developed due to non-heritable risk factors. One instance would be if a patient's mother developed lung cancer. The mother's disease could be due to a genetic risk factor or it could be due to the mother's history of smoking, the challenge then becomes determining if the lung cancer is heritable. A relative's age at cancer diagnosis can be used to detect familial cancers as prior research has observed that people with a relative diagnosed with cancer at an earlier age are often at greater risk for developing their relative's cancer compared to people with a relative diagnosed later in life [87,88,99,100]. For example, among patients with a *BRCA2* mutation and a 1st degree relative with breast cancer, those with a relative diagnosed before the age of 30 were at 4.47% annual risk for developing breast cancer, but those with a relative diagnosed above the age of 60 were at 0.73% annual risk [87]. This association has been observed at several other cancer sites including the lung, pancreas, and skin [87,88,99,100]. This trend of a relative diagnosed early in life conferring greater risk to the patient has to do with cancer development. Cancer is the result of multiple cellular abnormalities working in conjunction to dysregulate the cell cycle and cause unchecked growth [26,27]. One reason age is a powerful predictor of cancer risk is that these mutations take years to accrue [26,27]. Thus when a patient develops cancer at an early age, their early diagnosis is often the sign of a genetic risk factor as that patient had fewer mutations to accrue or an inherited mutation makes it easier to develop further mutations and thus developed the cancer earlier [26,27].

Using the theory that a relative diagnosed earlier in life is an indicator of a heritable cancer, perhaps **Aim 1** did not observe an association between a family history of skin cancer

and risk for developing an internal cancer because the NHEFS data set lacked the information necessary to differentiate between hereditary and non-hereditary cancers. Given skin cancer's high incidence and the role of ultraviolet radiation (UVR) in skin cancer development, many of the relatives with a history of skin cancer reported in the NHEFS cohort likely developed their skin cancer later in life. This situation was observed in the NHIS data set. Of the 3,523 participants that reported having a family history of skin cancer, only 1,291 or ~37% reported that their relative developed skin cancer before the age of 50.

Therefore this dissertation found evidence that a family history of skin cancer is indicative of increased risk for developing breast cancer. Further research is needed to determine if a personal history of skin cancer and a family history of skin cancer are similarly associated with increased risk for cancer at other sites. This future research may require the development of validated questionnaires to capture sufficient information for a family history of skin cancer. Our results signal the necessity of including a relative's age at diagnosis when studying the impact of a family history of skin cancer in future research and validated tools for measuring a family history of skin cancer.

VI.B.2.c. Skin cancer and risk for mortality

Aim 2 showed overall decreased risk for all-cause mortality in the presence of a personal history of skin cancer and no association with cancer-specific mortality. This result came as a surprise as **Aim 1** also drew data from the NHEFS cohort but we observed an association between a personal history of skin cancer and increased risk for developing an internal cancer.

There are two plausible explanations for this outcome. First, **Aim 2** was affected by the lack of differentiation between KC's subtypes in the NHEFS cohort. A personal history of squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) have been associated with

increased risk for developing an internal cancer (SCC standardized relative risk (SRR): 1.17, 95% CI 1.12-1.23; BCC SRR: 1.09, 95% CI 1.01-1.17) [6]. However, SCC and BCC have been observed to carry different associations with cancer mortality. In previous research, SCC has been associated with increased risk for cancer-specific mortality (RRs of 1.63 to 2.17) while BCC has been associated with null or slightly increased risk (RRs of 1.01 to 1.15) [3, 5]. In the NHEFS cohort the majority of skin cancers recorded at the 1987 and 1992 interviews were identified as KC. However, we could not differentiate between SCC and BCC diagnoses in the NHEFS cohort. Thus, it is possible that the NHEFS cohort had a higher than expected number of BCC patients. These BCC patients could contribute to the observation of increased risk for developing an internal cancer but not to the observation of increased risk for mortality and could have overpowered the associations between other types of skin cancer and risk for mortality.

Alternatively, it is possible that a personal history of skin cancer is indicative of decreased risk for mortality, in particular for other common causes of death such as heart disease. If that situation were the case, this protective effect could have been derived from physical activity or other factors associated with UVR exposure. Even a protective effect for heart disease from UVR derived vitamin D would be plausible, as patients who have received oral vitamin D supplementation in clinical trials have shown decreased risk for heart disease [66,83]. However, vitamin D supplementation has also been shown to decrease risk for developing cancer of the breast, colon, and prostate as well as at other sites[66,83]. Observing a protective effect from UVR derived vitamin D for heart disease but not from cancer would not match with prior evidence. Further research with greater specificity regarding KC subtypes is necessary to better understand the relationship between a personal history of skin cancer, internal cancer incidence, and mortality.

VI.D. Future research

VI.D.1. Testing family history of skin cancer in the NHIS Data Set

Aim 3's observation that a family history of skin cancer was associated with increased risk for developing breast cancer was a surprise given the null results of **Aim 1** and **Aim 2**. A plausible answer as to why **Aim 3** found significant results while the other two aims did not is the presence of data for age at cancer diagnosis for 1st degree relatives. While our work with the NHIS data set focused upon specifically breast cancer risk, it would be of interest to assess risk for developing internal cancer at other sites. Previous research has observed that a personal history of KC is associated with increased cancer risk for at least 26 internal sites and melanoma with increased risk for at least 12 [4,5,8]. Additionally the association between skin cancer and internal cancer risk is theorized to be genetic, partly due to the wide breadth of internal cancers associated with a personal history of skin cancer [4,5]. If having a relative diagnosed with skin cancer before the age of 50 were similarly associated with increased risk at multiple sites, then that association would lend more credence to the theory that the underlying susceptibility is heritable. The NHIS data set is well suited to answer these questions as it tracks a personal and family history of 25 internal cancers and has a good number of internal cancer cases. For comparison, our first aim observed 748 internal cancer cases using the NHEFS data set but our third aim observed 1,419 breast cancer cases alone. The additional cancer cases in the NHIS data set may enable our future research to asses risk for joint effects that our first two aims were not powered to detect. Thus one of the next steps for our research is to test the association between a having a 1st degree relative diagnosed with skin cancer before the age of 50 and risk for developing any internal cancer and for specific cancer sites.

VI.D.2. Improving the Gail+SCM model

Calibrating the Gail model for a personal and family history of skin cancer improved sensitivity for a specific subsection of women, but the calibration methodology is limited in its application. Most notably, the calibration method we used did not allow for investigating interaction effects between new risk factors and the Gail model risk factors. The Gail model, without modification, predicted greater risk for breast cancer among participants with a personal history of skin cancer compared to without a personal history of skin cancer, implying that at least one of the Gail model risk factors is associated a personal history of skin cancer. An association between a personal and family history of skin cancer and Gail model risk factors could possibly be used to improve risk estimates for Gail model risk factors. A more thorough method to explore this association is to use the methodology set by Dr. Gail to rebuild the Gail model with a new logistic regression analysis with the Gail model risk factors, variables for a patient's personal and family history of skin cancer, and any pertinent interaction effects [30]. However, this method is data intensive and requires a study to produce risk estimates equal in quality to that of the original Gail model. Our work here was not capable of doing so as the NHIS dataset contained only a third as many breast cancer cases as the data set Dr. Gail used to build his model [30]. Those additional cases are necessary to produce accurate risk estimates, particularly when evaluating possible interaction effects. Thus, the next step for this research is to find a prospective cohort with the necessary information for the Gail model risk factors, information for a personal and family history of skin cancer, and more breast cancer cases. Once we have acquired the requisite data, we will use the methodology published by Dr. Gail to create a new Gail model that accounts for the association between skin cancer and Gail model risk factors [30].

VI.E. Closing remarks

This Dissertation investigated the role of a personal and family history of skin cancer in determining a patient's risk for adverse health outcomes. In doing so, our study largely agreed with the theory that there is an underlying susceptibility factor responsible for the association between skin cancer and risk for developing other forms of cancer, found evidence suggestive that the susceptibility factor may be genetic, and uncovered a potential way to improve a common breast cancer risk model. Ultimately, a personal and family history of skin cancer and its role as a marker for increased risk for developing an internal malignancy makes skin cancer a rich opportunity to investigate the processes common to cancer development at several cancer sites. Our study added to the literature regarding the association between skin cancer and risk for internal cancer and mortality, but there is still a great number of unanswered questions and avenues of research regarding skin cancer left to pursue.

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Appendix

Supplemental Tables Aim 1:

Supplemental Table 3.1: Age and gender adjusted risk for developing an internal cancer according to which relative had cancer				
Relative	**N**	**Did not develop an internal cancer**	**Developed an internal cancer**	**HR (95% CI)**
Parent	386 (4.59%)	365 (94.56%)	21 (5.44%)	0.83 (0.50-1.37)
Sibling	234 (2.78%)	208 (88.89%)	26 (3.48%)	0.97 (0.63-1.50)
Child	56 (0.67%)	50 (89.29%)	6 (10.71%)	0.74 (0.33-1.69)

Supplemental Table 3.2: Number of relatives with skin cancer in the NHEFS cohort.				
Number of relatives with skin cancer	**Frequency**	**Percent**	**Cumulative Frequency**	**Cumulative Percent**
0	7811	92.90	7811	92.90
1	534	6.35	8345	99.25
2	50	0.59	8395	99.85
3	8	0.10	8403	99.94
4	3	0.04	8406	99.98
5	2	0.02	8408	100.00

Supplemental Table 3.3: Age and gender adjusted risk for internal cancer regressed on number of relatives with cancer.		
Number of relatives with skin cancer, categorized	**N**	**HR (95% CI)**
0	7811	1.00 (ref)
1	534	0.84 (0.60-1.19)
≥2	63	0.75 (0.23-2.39)

Supplemental Table 3.4: Description of time of follow-up, age at start of cohort, and age at cancer diagnosis for the full NHEFS cohort						
Variable	**Mean**	**Std Dev**	**95% CL for Mean**	**Lower Quartile**	**Median**	**Upper Quartile**
Years of follow-up	8.23	2.37	8.18-8.28	9	9	10
Age at the 1982 interview	56.48	14.76	56.16-56.79	44	54	69
Age at internal cancer diagnosis	69.22	13.14	68.28-70.17	60	71	80

Supplemental Table 3.5: Description of time of follow-up, age at start of cohort, and age at cancer diagnosis for participants without a family history of skin cancer in the NHEFS cohort						
Variable	**Mean**	**Std Dev**	**95% CL for Mean**	**Lower Quartile**	**Median**	**Upper Quartile**
Years of follow-up	8.20	2.41	8.15-8.25	9	9	10
Age at the 1982 interview	56.80	14.76	56.47-57.13	44	55	69
Age at internal cancer diagnosis	69.42	13.13	68.45-70.40	60	71	80

Supplemental Table 3.6: Description of time of follow-up, age at start of cohort, and age at cancer diagnosis for the participants with a family history of skin cancer in the NHEFS cohort						
Variable	**Mean**	**Std Dev**	**95% CL for Mean**	**Lower Quartile**	**Median**	**Upper Quartile**
Years of follow-up	8.67	1.78	8.53-8.82	9	9	10
Age at the 1982 interview	52.27	14.23	51.13-53.41	40	49	62
Age at internal cancer diagnosis	66.15	13.03	62.28-70.02	56	66.5	76

Supplemental Table 3.7: Age and gender adjusted risk for developing an internal cancer regressed on family history of skin cancer among the lowest and highest age quartiles.				
	Age Restrictions	**N**	**HR (95% CI)**	**P-value**
Full cohort	NA	8408	0.83 (0.61-1.14)	0.25
Lowest Quartile	≤44	2287	0.73 (0.27-1.96)	0.54
Second Quartile	45-54	1937	1.06 (0.58-1.91)	0.58
Third Quartile	55-68	2026	1.02 (0.54-1.94)	0.54
Highest Quartile	≥69	2158	0.59 (0.32-1.08)	0.09

Supplemental Table 3.8: Hazards ratios (HRs) and 95% confidence intervals (CIs) for developing an internal cancer with varying levels of adjustment during 10-year follow-up of the NHEFS cohort, N=8408						
Variable	**Unadjusted[1] Results HR (95% CI)**	**Age Adjusted Results HR (95% CI)**	**Gender Adjusted Results HR (95% CI)**	**Minimally Adjusted[3] Results HR (95% CI)**	**Fully Adjusted[4] Results HR (95% CI)**	**Fully Adjusted[4] P-value**
Age at 1982 interview	1.05 (1.05-1.06)	1.05 (1.05-1.06)	1.05 (1.05-1.06)	1.05 (1.05-1.06)	1.05 (1.04-1.06)	<0.01
Gender						
Men (N=3223)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	
Women (N=5185)	1.05 (0.88-1.26)	0.93 (0.78-1.11)	1.05 (0.88-1.26)	0.93 (0.78-1.11)	1.02 (0.83-1.26)	0.86
Smoking habit in 82						
Never Smoked (N=3825)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	
Previous Smoker (N=2347)	1.25 (0.99-1.56)	1.35 (1.08-1.69)	1.29 (1.02-1.64)	1.37 (1.07-1.75)	1.34 (1.04-1.72)	0.02
Current Smoker (N=2236)	1.14 (0.90-1.45)	1.65 (1.29-2.11)	1.17 (0.92-1.49)	1.66 (1.29-2.13)	1.63 (1.27-2.09)	0.01
Regular aspirin use						
No (N=6282)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	
Yes (N=2126)	1.50 (1.24-1.82)	1.36 (1.12-1.64)	1.50 (1.24-1.82)	1.37 (1.13-1.66)	1.36 (1.12-1.66)	<0.01
Highest completed level of education						
Less than high school (N=2981)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	
High school graduate (N=3198)	0.60 (0.49-0.73)	0.86 (0.70-1.06)	0.60 (0.49-0.73)	0.87 (0.70-1.07)	0.86 (0.70-1.06)	0.16
More than high school (N=2229)	0.51 (0.41-0.64)	0.77 (0.62-0.97)	0.51 (0.41-0.64)	0.77 (0.61-0.96)	0.77 (0.62-0.96)	0.02

Supplemental Table 3.8: Hazards ratios (HRs) and 95% confidence intervals (CIs) for developing an internal cancer with varying levels of adjustment during 10-year follow-up of the NHEFS cohort, N=8408 (continued)						
Variable	**Unadjusted[1] Results HR (95% CI)**	**Age Adjusted Results HR (95% CI)**	**Gender Adjusted Results HR (95% CI)**	**Minimally Adjusted[2] Results HR (95% CI)**	**Fully Adjusted[4] Results HR (95% CI)**	**Fully Adjusted[4] P-value**
Personal History of Skin Cancer						
No (N=7110)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	
Yes (N=1298)	1.72 (1.43-2.07)	1.31 (1.07-1.60)	1.73 (1.44-2.09)	1.30 (1.07-1.59)	1.33 (1.09-1.61)	<0.01
Family history of skin cancer						
No (N=7811)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	
Yes (N=597)	0.69 (0.51-0.95)	0.83 (0.60-1.13)	0.69 (0.51-0.94)	0.83 (0.61-1.14)	0.80 (0.58-1.11)	0.18
Family history of internal cancer						
No (N=4408)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	
Yes (N=4000)	1.29 (1.10-1.52)	1.19 (1.00-1.40)	1.29 (1.09-1.53)	1.20 (1.01-1.41)	1.18 (0.99-1.40)	0.06

1- Results are not adjusted for any other covariate
2- Results are adjusted for Age and Gender
3- Results are adjusted for Age, Gender, Smoking Habit, Regular Aspirin Use, and Highest Completed Level of Education
4- Results are adjusted for all other variables in the model.

Supplemental Table 3.9: Comparison of methods for measuring a family history of cancer. Two dichotomous variables versus one combined variable	
Family history treated as two dichotomous variables	
Family history of skin cancer	**HR (95% CI)**
No (N=7811)	1.00 (ref)
Yes (N=597)	0.80 (0.58-1.11)
Family history of internal cancer	
No (N=4408)	1.00 (ref)
Yes (N=4000)	1.18 (0.99-1.40)
Family history treated as a single variable	
Family history of cancer	**HR (95% CI)**
No history of cancer (N=4132)	1.00 (ref)
Skin only (N=276)	0.50 (0.21-1.17)
Internal Only (N=3679)	1.14 (0.96-1.36)
Both skin and internal (N=321)	1.12 (0.76-1.64)

Supplemental table 3.10: Counts of the ten most common internal cancer tumors reported among family members in the NHEFS cohort at the 1982 interview.	
Cancer site	**Number of cancer cases**
Breast	554
Lung	515
Stomach	412
Colon	363
Uterus	267
Prostate	215
Liver	196
Leukemia	173
Female Genital	130
Lip, oral, and pharynx NEC	120

Supplemental table 3.11: Counts of the ten most common internal cancer tumors reported among family members in the NHEFS cohort at the 1992 interview.	
Cancer site	**Number of cancer cases**
Breast	413
Lung	353
Colon	243
Prostate	193
stomach	97
cervix	90
Leukemia	73
Liver	68
Oral	60
Brain	59

Supplemental Table 3.12: Types of internal cancer considered for family history of internal cancer, personal history of internal cancer, and the end point of incident internal cancer		
Categories used in 1982	**Categories used in 1987**	**Categories used in 1992**
Bladder	Bladder	Bladder
Bone or articular cartilage	Blood (lymphomas, multiple myeloma)	Bone
Brain	Bone	Bone marrow
Breast (female)	Brain	Brain
Breast (male)	Breast	Breast
Cervix	Cervix	Cancer spread throughout body
Colon, Large, Intestine	Colon (rectum, anus, intestines)	Cervix
Connective or other soft tissue including diaphragm	Female genital	Colon
Digestive organs NEC	Kidney	Endometrium or corpus
Esophagus	Larynx	Esophagus
Eye	Leukemia	Female cancer, non-specified
Female genital organ or tract, female genitourinary tract NEC	Liver	Gastrointestinal
Gallbladder	Lung	Hodgkin’s disease
Gum	Neck and head	Kidney
Heart, thymus gland	Other GI	Larynx
Hodgkin's Disease, Hodgkin's lymphoma	Pancreas	Leukemia
Kidney, renal, urinary organ or system NEC	Possible metastatic	Liver
Larynx, laryngeal	Prostate	Lung
Leukemia	Spine	Lymph glands
Lip	Stomach	Non-hodgkin's lymphoma
Lip, oral cavity, and pharynx NEC	Throat	Oral
Liver	Uterus	Ovary
Lung, bronchus, trachea		Pancreas
Lymph Gland, lymphoma, lymph node NEC, marrow (bone) NEC		Prostate
Lymphosarcoma and reticulosarcoma		Rectum
Male genital organ or tract, male genitourinary tract NEC		Stomach
Mouth NEC		Testicular
Nasopharynx, nasopharyngeal		Throat
Nervous system - (central) NEC		Thyroid
Oropharynx, tonsil		
Other and ill-defined sites		
Ovary		
Pancreas		

Supplemental Table 3.12: Types of internal cancer considered for family history of internal cancer, personal history of internal cancer, and the end point of incident internal cancer (continued)		
Categories used in 1982	**Categories used in 1982**	**Categories used in 1982**
Prostate gland		
Rectum, anus		
Respiratory organs or systems, respiratory tract NEC		
Small Intestine		
Stomach		
Thyroid Gland		
Tongue		
Unspecified		
Uterus, uterine		

Supplemental Table 3.13: distribution of age and gender in the full NHEFS cohort and subdivided by personal history of skin cancer				
	Entire cohort	**Personal history of skin cancer**		**P-value**
		No, N (%)	**Yes, N (%)**	
Number of participants	8408	7110	1298	
Mean age (standard deviation)	56.5 (14.8)	55.4 (14.7)	62.6 (13.7)	<0.01
Mean time of follow-up (standard deviation)	8.2 (2.4)	8.3 (2.4)	8.1 (2.4)	<0.01
Gender				<0.01
Men	3223	2627 (37.0)	596 (45.9)	
Women	5185	4483 (63.0)	702 (54.1)	

Supplemental Table 3.14: Hazards ratios (HRs) and 95% confidence intervals (CIs) for developing an internal cancer during 10-year follow-up of the NHEFS cohort, N=8408					
Variable	**Unadjusted Results HR (95% CI)**	**Gender Adjusted Results HR (95% CI)**	**Age Adjusted Results HR (95% CI)**	**Age and Gender Adjusted Results HR (95% CI)**	**Fully Adjusted Results HR (95% CI)**
Age	1.05 (1.05-1.06)	NA	1.05 (1.05-1.06)	1.05 (1.05-1.06)	1.05 (1.04-1.06)
Gender					
Male	1.00 (ref)	1.00 (ref)	NA	1.00 (ref)	1.00 (ref)
Female	1.05 (0.88-1.26)	1.08 (0.90-1.29)	NA	0.93 (0.78-1.11)	1.02 (0.83-1.26)
Personal History of Skin Cancer					
No	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes	1.72 (1.43-2.07)	1.73 (1.44-2.09)	1.31 (1.07-1.60)	1.31 (1.07-1.60)	1.33 (1.09-1.61)

Supplemental Tables Aim 2:

Supplemental Table 4.1: All-cause mortality hazard ratios (HR) and 95% confidence intervals (CI) during 10-year follow-up of the NHEFS cohort with various levels of adjustment, From years 1982 to 1992 N=8622					
Variable	**Unadjusted[1] Results HR (95% CI)**	**Age Adjusted Results HR (95% CI)**	**Gender Adjusted Results HR (95% CI)**	**Minimally Adjusted[2] Results HR (95% CI)**	**Fully Adjusted[3] Results HR (95% CI)**
Age at 1982 interview	1.10 (1.09-1.11)	1.10 (1.09-1.11)	1.10 (1.10-1.11)	1.10 (1.10-1.11)	1.10 (1.10-1.11)
Gender:					
Male (3282)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Female (5340)	0.72 (0.64-0.81)	0.58 (0.51-0.65)	0.72 (0.64-0.81)	0.58 (0.51-0.65)	0.57 (0.50-0.65)
BMI:					
Underweight (222)	3.00 (2.26-3.98)	2.10 (1.55-2.85)	3.15 (2.38-4.18)	2.34 (1.73-3.17)	2.05 (1.50-2.79)
Normal weight (3827)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Over weight (3076)	0.90 (0.79-1.02)	0.88 (0.78-1.00)	0.83 (0.73-0.94)	0.81 (0.71-0.91)	0.79 (0.70-0.88)
Obese (1497)	0.86 (0.71-1.04)	0.99 (0.82-1.19)	0.84 (0.69-1.01)	1.03 (0.85-1.25)	0.96 (0.80-1.14)
Smoking habit in 82					
Never smoked (3935)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Previous smoker (2435)	1.47 (1.22-1.77)	2.09 (1.73-2.52)	1.34 (1.10-1.62)	1.81 (1.49-2.21)	1.8 (1.50-2.17)
Current smoker (2252)	1.15 (0.98-1.36)	2.44 (2.12-2.79)	1.08 (0.92-1.28)	2.17 (1.89-2.49)	2.08 (1.83-2.38)
How many years since patient quit smoking					
Less than 5 (865)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
More than 5 (1570)	0.82 (0.66-1.01)	0.66 (0.54-0.83)	0.81 (0.65-1.00)	0.63 (0.50-0.78)	0.64 (0.52-0.79)
Highest completed level of education					
Less than high school (3055)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
High school graduate (3278)	0.42 (0.37-0.47)	0.79 (0.69-0.90)	0.42 (0.37-0.48)	0.82 (0.72-0.93)	0.83 (0.73-0.94)
More than high school (2289)	0.35 (0.29-0.42)	0.70 (0.58-0.84)	0.34 (0.28-0.41)	0.68 (0.57-0.82)	0.74 (0.62-0.89)
Hypertension					
No (5656)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes (2966)	1.99 (1.76-2.24)	1.26 (1.11-1.43)	2.02 (1.79-2.28)	1.33 (1.17-1.51)	1.40 (1.24-1.59)
Diabetes					
No (8086)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes (1403)	2.97 (2.51-3.51)	2.04 (1.75-2.39)	2.95 (2.49-3.51)	2.03 (1.73-2.38)	2.04 (1.72-2.42)

Supplemental Table 4.1: All-cause mortality hazard ratios (HR) and 95% confidence intervals (CI) during 10-year follow-up of the NHEFS cohort with various levels of adjustment, From years 1982 to 1992 N=8622 (continued)					
Variable	**Unadjusted[1] Results HR (95% CI)**	**Age Adjusted Results HR (95% CI)**	**Gender Adjusted Results HR (95% CI)**	**Minimally Adjusted[2] Results HR (95% CI)**	**Fully Adjusted[3] Results HR (95% CI)**
Personal history of skin cancer					
No (7219)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes (1403)	1.16 (0.98-1.39)	0.75 (0.63-0.88)	1.14 (0.95-1.36)	0.69 (0.58-0.83)	0.71 (0.60-0.84)
Personal history of internal cancer up to 1982					
No (8264)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes (376)	3.18 (2.59-3.91)	1.94 (1.59-2.37)	3.40 (2.78-4.15)	2.04 (1.68-2.48)	2.25 (1.84-2.75)
Family history of skin cancer					
No (8002)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes (620)	0.65 (0.50-0.85)	0.86 (0.68-1.08)	0.67 (0.51-0.87)	0.92 (0.74-1.15)	0.99 (0.78-1.25)
Family history of internal cancer					
No (4451)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes (4171)	0.83 (0.73-0.96)	0.74 (0.66-0.84)	0.85 (0.74-0.98)	0.78 (0.69-0.89)	0.82 (0.72-0.93)

1- Results are not adjusted for any other covariate
2- Results are adjusted for Age and Gender
3- Results are adjusted for Age, Gender, BMI, Smoking Habit, Time Since Former Smoker Quit, Highest Completed Level of Education, Hypertension, Diabetes, Personal History of Skin Cancer, Personal History of Internal Cancer, Family History of Skin Cancer, and Family History of internal Cancer

Supplemental Table 4.2: Cancer-specific mortality hazard ratios (HR) and 95% confidence intervals (CI) during 10-year follow-up of the NHEFS cohort with various levels of adjustment, From years 1982 to 1987 N=8622					
Variable	**Unadjusted[1] Results HR (95% CI)**	**Age Adjusted Results HR (95% CI)**	**Gender Adjusted Results HR (95% CI)**	**Minimally Adjusted[2] Results HR (95% CI)**	**Fully Adjusted[3] Results HR (95% CI)**
Age at 1982 interview	1.08 (1.07-1.09)	1.08 (1.07-1.09)	1.08 (1.07-1.09)	1.08 (1.07-1.09)	1.08 (1.07-1.10)
Gender:					
Male (3282)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Female (5340)	0.55 (0.45-0.66)	0.60 (0.48-0.76)	0.55 (0.45-0.66)	0.60 (0.48-0.76)	0.63 (0.48-0.82)
Smoking habit in 82					
Never smoked (3935)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Previous smoker (2435)	1.92 (1.36-2.70)	2.55 (1.82-3.59)	1.78 (1.23-2.57)	2.28 (1.58-3.28)	2.15 (1.49-3.09)
Current smoker (2252)	1.76 (1.29-2.41)	3.29 (2.38-4.57)	1.68 (1.23-2.30)	3.02 (2.17-4.19)	2.88 (2.07-3.99)
How many years since patient quit smoking					
Less than 5 (865)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
More than 5 (1570)	0.75 (0.52-1.07)	0.62 (0.43-0.91)	0.74 (0.52-1.06)	0.60 (0.41-0.87)	0.59 (0.40-0.88)
Highest completed level of education					
Less than high school (3055)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
High school graduate (3278)	0.44 (0.33-0.57)	0.73 (0.55-0.97)	0.45 (0.34-0.58)	0.76 (0.57-1.01)	0.74 (0.56-0.96)
More than high school (2289)	0.29 (0.20-0.41)	0.51 (0.36-0.74)	0.28 (0.20-0.39)	0.50 (0.34-0.72)	0.54 (0.38-0.76)

Supplemental Table 4.2: Cancer-specific mortality hazard ratios (HR) and 95% confidence intervals (CI) during 10-year follow-up of the NHEFS cohort with various levels of adjustment, From years 1982 to 1987 N=8622 (continued)					
Variable	**Unadjusted[1] Results HR (95% CI)**	**Age Adjusted Results HR (95% CI)**	**Gender Adjusted Results HR (95% CI)**	**Minimally Adjusted[2] Results HR (95% CI)**	**Fully Adjusted[3] Results HR (95% CI)**
Personal history of skin cancer					
No (7219)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes (1403)	1.54 (1.19-1.98)	1.05 (0.81-1.36)	1.50 (1.16-1.95)	0.99 (0.75-1.29)	0.95 (0.72-1.25)
Personal history of internal cancer up to 1982					
No (8264)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes (376)	7.02 (5.13-9.60)	4.62 (3.32-6.44)	7.57 (5.52-10.39)	4.89 (3.50-6.83)	4.82 (3.41-6.81)
Family history of skin cancer					
No (8002)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes (620)	0.50 (0.27-0.93)	0.64 (0.34-1.19)	0.51 (0.27-0.95)	0.68 (0.36-1.26)	0.68 (0.38-1.23)
Family history of internal cancer					
No (4451)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes (4171)	1.27 (0.99-1.63)	1.15 (0.89-1.48)	1.30 (1.01-1.67)	1.21 (0.93-1.56)	1.21 (0.92-1.58)

1 Results are not adjusted for any other covariate
2 Results are adjusted for Age and Gender
3 Results are adjusted for Age, Gender, Smoking Habit, Time Since Smoker Quit Smoking, Highest Completed Level of Education, Personal History of Skin Cancer, Personal History of Internal Cancer, Family History of Skin Cancer, and Family History of internal Cancer

Supplemental Table 4.3: Sources of Missing Information in the NHEFS cohort	
Variable	**Number of Missing Observations**
Total Missing	390
Lost to Follow Up	233
Time to Censoring	0
Gender	0
BMI	37
Smoking	17
Diabetes	15
Hypertension	19
Education	39
Personal History of Cancer	3
Family History of Cancer	33

Supplemental Table 4.4: Sources of Missing Information for the Survival Analysis Among Patients Lost to Follow Up	
Variable	**Number of Missing Observations**
Lost to Follow Up	233
Time to Censoring	0
Gender	0
BMI	0
Smoking	0
Diabetes	0
Hypertension	1
Education	4
Personal History of Cancer	0
Family History of Cancer	5

Supplemental Table 4.5: Frequency of the four most common cancer related deaths and skin cancer death in the NHEFS cohort			
Cause of Death	**Number of Deaths**	**% of cancer deaths (N=434)**	**% of all deaths (N=1775)**
trachea, bronchus, and lung	113	26%	6%
Colon	47	11%	3%
Female Breast	39	9%	2%
Prostate	35	8%	2%
Skin	9	2%	1%
Total from these 5 cancers	243	56%	14%

Supplemental Table 4.6: distribution of age and gender in the full NHEFS cohort and subdivided by personal history of skin cancer				
	Entire cohort	**Personal history of skin cancer**		**P-value**
		No, N (%)	**Yes, N (%)**	
Number of participants	8622	7219	1403	
Mean time of follow-up	8.4 (2.2)	8.3 (2.4)	8.0 (2.4)	<0.01
Mean age	57.1 (14.8)	55.9 (17.8)	63.1 (13.6)	<0.01
Gender				<0.01
Men	3282	2641 (36.6)	641 (45.7)	
Women	5340	4578 (63.4)	762 (54.1)	

Supplemental Table 4.7: All-cause mortality hazard ratios for patients in the NHEFS with various levels of adjustment, From years 1982 to 1992 N=8,622					
Variable	Unadjusted Results HR (95% CI)	Gender Adjusted Results HR (95% CI)	Age Adjusted Results HR (95% CI)	Age and Gender Adjusted Results HR (95% CI)	Fully Adjusted Results HR (95% CI)
Age	1.10 (1.09-1.10)	NA	1.10 (1.09-1.11)	1.10 (1.10-1.11)	1.10 (1.10-1.11)
Gender					
Male	1.00 (ref)	1.00 (ref)	NA	1.00 (ref)	1.00 (ref)
Female	0.72 (0.64-0.81)	0.72 (0.64-0.81)	NA	0.58 (0.51-0.65)	0.57 (0.50-0.65)
Personal History of Skin Cancer					
No	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes	1.16 (0.98-1.39)	1.14 (0.95-1.36)	0.75 (0.63-0.88)	0.69 (0.58-0.83)	0.71 (0.60-0.84)

Supplemental Table 4.8: Cancer-specific mortality hazard ratios for patients in the NHEFS with various levels of adjustment, From years 1982 to 1992 N=8,622					
Variable	Unadjusted Results HR (95% CI)	Gender Adjusted Results HR (95% CI)	Age Adjusted Results HR (95% CI)	Age and Gender Adjusted Results HR (95% CI)	Fully Adjusted Results HR (95% CI)
Age	1.08 (1.07-1.09)	NA	1.08 (1.07-1.09)	1.08 (1.07-1.09)	1.08 (1.07-1.10)
Gender					
Male	1.00 (ref)	1.00 (ref)	NA	1.00 (ref)	1.00 (ref)
Female	0.72 (0.64-0.81)	0.73 (0.58-0.91)	NA	0.60 (0.48-0.76)	0.63 (0.48-0.82)
Personal History of Skin Cancer					
No	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes	1.54 (1.19-1.98)	1.50 (1.16-1.95)	1.05 (0.81-1.36)	0.99 (0.75-1.29)	0.95 (0.72-1.25)

Supplemental Tables Aim 3:

Supplemental Table 5.1: Mean and median predicted risk according to the Gail and Gail+SCM models by patient personal history of cancer			
	Model	**Mean predicted risk (95% CI)**	**Median predicted risk (interquartile range)**
Controls without skin cancer (N=7953)	Gail	1.31 (1.29-1.33)	1.16 (0.74-1.62)
	Gail+SCM	1.27 (1.25-1.29)	1.12 (0.71-1.56)
Controls with skin cancer (N=385)	Gail	1.66 (1.56-1.75)	1.47 (1.06-1.96)
	Gail+SCM	2.73 (2.57-2.90)	2.39 (1.68-3.24)
Cases without skin cancer (N=321)	Gail	2.27 (2.04-2.49)	1.55 (1.02-2.85)
	Gail+SCM	2.23 (2.01-2.45)	1.50 (0.99-2.78)
Cases with Skin Cancer (N=27)	Gail	2.85 (1.97-3.71)	2.15 (1.37-3.84)
	Gail+SCM	4.46 (3.14-5.78)	3.67 (2.31-5.49)

Supplemental Table 5.2: Age-adjusted results for regressing 5-year risk of developing breast cancer on different forms of family history of skin cancer based on the training data (N=26058).		
	OR (95% CI)	**P-Value**
Relative with melanoma before age 50 (N=346)	1.46 (0.88-2.40)	0.14
Relative with KC before age 50 (N=308)	1.34 (0.70-2.58)	0.38
Relative with unknown skin cancer before age 50 (N=339)	1.30 (0.73-2.32)	0.37
Relative with any skin cancer before age 50 (N=961)	1.44 (1.03-2.02)	0.03