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Incidence of Subsequent Pancreatic Adenocarcinoma in Patients with a History of Non-Pancreatic Primary Cancers

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Abstract

Background—Several environmental risk factors are known to predispose to pancreas cancer and up to 15% of pancreatic cancers have an inherited component. Understanding metachronous cancer associations can modify pancreas cancer risk. We sought to investigate the association of non-pancreatic cancers with subsequent pancreatic adenocarcinoma.

Methods—We used data from the U.S. Surveillance, Epidemiology, and End-Results (SEER) registries to identify 1,618,834 individuals with a primary malignancy and subsequent pancreatic adenocarcinoma (n=4,013). We calculated standardized incidence ratios as an approximation of relative risk (RR) for occurrence of pancreatic adenocarcinoma after another primary malignancy.

Results—Among patients diagnosed with a first primary malignancy at ages 20-49, the risk of subsequent pancreatic adenocarcinoma was increased among patients with cancers of the ascending colon (RR 4.62, 95%CI 1.86-9.52), hepatic flexure (5.42, 1.12-15.84), biliary system (13.14, 4.27-30.66), breast (1.32, 1.09-1.59), uterine cervix (1.61, 1.02-2.41), testes (2.78, 1.83-4.05) and hematopoietic system (1.83, 1.28-2.53). Among patients with a first malignancy at ages 50-64, the risk was increased after cancers of the stomach (1.88, 1.13-2.93), hepatic flexure (2.25, 1.08-4.13), lung and bronchus (1.46, 1.16-1.82), pharynx (2.26, 1.13-4.04) and bladder (1.24, 1.03-1.48). Among patients with a primary cancer after age 65, the risk was increased after cancers of the stomach (1.79, 1.23-2.53), hepatic flexure (1.76, 1.06-2.75), biliary system (2.35, 1.17-4.20), and uterus (1.23, 1.03-2.47).

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Conclusions—This population-based dataset suggests that pancreatic adenocarcinoma is associated with certain primary cancers. Genetic predisposition, common environmental and behavioral risk factors may all contribute to this observation. Specific tumor associations will guide future risk-stratification efforts.

Keywords

Pancreas Neoplasms; Surveillance, Epidemiology, and End Results Program; Environmental Risk Factors; Metachronous Neoplasms; Epidemiology

Introduction

Pancreatic cancer is the fourth leading cause of cancer-related mortality in the United States. Cure is only attainable if the cancer is detected at an early, resectable stage. However, only 15-20% of patients are surgical candidates at presentation (1). The current 5 year survival rate is 5%, compared with ~2.5% in 1975-1979 (2). Known risk factors for pancreatic cancer include tobacco use, diabetes mellitus, and chronic pancreatitis. Identifying individuals at risk for pancreatic cancer may result in earlier detection and improved survival.

Up to 15% of pancreatic cancers have a genetic predisposition (3,4). Familial pancreatic cancer is the clustering of pancreatic cancer within a family and may be the result of germline mutations in the palladin or PALB2 genes (5-8). Hereditary chronic pancreatitis involves an autosomal dominant mutation of the cationic trypsinogen gene PRSS1 (9). Other hereditary cancer syndromes that predispose individuals to an increased risk of pancreatic cancer include familial breast and ovarian cancer syndrome (BRCA1/BRCA2) (10-15), Peutz-Jeghers syndrome (PJS) (16-18), familial atypical multiple mole melanoma (FAMMM) syndrome (19-21), and hereditary non-polyposis colorectal cancer syndrome (HNPCC) (22-25). Some have suggested that familial adenomatous polyposis (FAP) is also associated with an increased risk of pancreatic cancer (26).

Recent efforts in pancreatic cancer epidemiology have focused on the role of family history in elucidating possible genetic predispositions. McWilliams and colleagues have shown that first-degree relatives of patients with pancreatic adenocarcinoma have a significantly increased risk of developing the disease themselves and that the median age of onset in probands is younger when a family history of syndromic cancers, such as breast, ovarian, colorectal, or melanoma is present (27,28). A similar study comparing rates of pancreatic cancer in kindreds to those of the general US population found that the presence of a family member with early-onset pancreatic cancer (age <50) conferred an increased risk to familial, but not sporadic cancer kindreds (29). Furthermore, relatives of an individual with pancreatic cancer have an increased risk of dying from breast and ovarian cancers (30). These findings led us to investigate the association of non-pancreatic primary malignancies with the development of a subsequent pancreas cancer in the same individual. We stratified individuals by age, as it is likely that cancers at a younger age have inherited predispositions while cancers at older ages have significant environmental predispositions. We examined whether or not multiple primary cancers associated with environmental or inherited risks occur more frequently than expected within individuals (rather than within families).

The occurrence of multiple primary cancers in an individual may reflect a genetic predisposition, common environmental or behavioral risk factors, iatrogenic effects due to treatment of the first malignancy, or a combination of these factors (31). To date, no population-based study has examined these hypotheses with regards to pancreatic adenocarcinoma. The aim of this study was to use the National Cancer Institute's

Surveillance, Epidemiology, and End-Results (SEER) Program to investigate whether certain primary malignancies are associated with an increased risk of subsequent pancreatic adenocarcinoma, and the extent to which this risk varies with age at onset of the first malignancy. We hypothesized that persons with pancreatic cancer associated syndromic cancers (Table 1) (10-26), common environmental risk factors, and iatrogenic effects of prior treatment would be at an increased risk of subsequent pancreatic adenocarcinoma.

Materials and Methods

The methods used in this paper have been previously described (32). The National Cancer Institute's Surveillance, Epidemiology, and End-Results (SEER) Program collects information on cancer incidence, survival, and patient demographics from cancer registries that previously covered about 14% of the population and was recently expanded to cover approximately 26% of the population of the United States. Approximately 3.7 million *in situ* and invasive cancer cases are included in the SEER 9 database (33).

Using SEER*Stat software (34), Multiple Primary-Standardized Incidence Ratios (MP-SIR) were calculated to investigate the incidence of pancreatic adenocarcinoma with prior metachronous malignancies. Histology codes 8010-8012, 8015, 8020-8022, 8140-8141, 8143, 8147, 8210-8211, 8230-8231, 8260-8263, 8440, 8450, 8452-8453, 8470-8471, 8480-8481, 8490, 8503-8504, 8507-8508, 8510, 8514, 8521, 8560, 8562, 8570-8576 were used to select for adenocarcinoma specifically. The cancer events occurred from January 1, 1973 through Dec 31, 2006. We included all cancers in persons >20 years that were reported as malignant and microscopically confirmed. We excluded diagnoses that were noted solely on the death certificate or at autopsy. For the primary analysis we required a latency period of two years to reduce the possibility of pre-existing or incidental pancreatic adenocarcinoma being discovered during the workup of the initial primary cancer. Results were unchanged when we used a six-month latency period.

Within the limits set above, a cohort with any primary malignancy was followed over time and subsequent pancreatic adenocarcinoma was noted. Follow-up time was calculated in person-years of observation from the date of diagnosis of primary malignancy to the first of either the date of diagnosis of the pancreatic adenocarcinoma or the date of death or censoring by December 31st, 2006. We calculated the cumulative age-, sex- and race-specific person years at risk for each patient and multiplied these by the incidence rate of pancreatic adenocarcinoma in the SEER population to obtain the expected number of subsequent pancreatic adenocarcinomas in the study cohort. We then computed standardized incidence ratios (SIRs), as an approximation of relative risk, by dividing the observed number of subsequent pancreatic adenocarcinomas by the expected number of subsequent pancreatic adenocarcinomas for the various primary malignancies (observed/expected). We calculated 95% confidence intervals using a Byar approximation to the exact Poisson test (35). Data were stratified by age at diagnosis of the first primary malignancy in three groups (20-49, 50-64, 65+).

Results

We identified 1,618,834 individuals diagnosed with a primary malignancy between Jan 1, 1973 to December 31, 2006 who met our eligibility criteria (Table 2). Of these patients, 4,013 were diagnosed with a primary pancreatic adenocarcinoma at least two years after this initial diagnosis.

Association between pancreatic adenocarcinoma and primary malignancies

In patients diagnosed with a primary malignancy, the risk of subsequent pancreatic adenocarcinoma was increased after several malignancies (Table 3). Among patients diagnosed between the ages of 20-49, right-sided colon (ascending colon (RR 4.62, 95%CI 1.86-9.52) and hepatic flexure (5.42, 95%CI 1.12-15.84)), hepatobiliary (13.14, 95%CI 4.27-30.66), breast (1.32, 95%CI 1.09-1.59), testicular (2.78, 95%CI 1.83-4.05), uterine cervix (1.61, 95%CI 1.02-2.41), and hematopoietic malignancies (1.83, 95%CI 1.28-2.53) were associated with a significantly increased risk of pancreatic adenocarcinoma as a second malignancy. Among patients diagnosed between the ages of 50-64, the risk of pancreatic adenocarcinoma was significantly increased after cancers of the hepatic flexure (2.25, 95%CI 1.08-4.13), pharynx (2.26, 95%CI 1.13-4.04), stomach (1.88, 95%CI 1.13-2.93), bladder (1.24, 95%CI 1.03-1.48), and lung/bronchus (1.46, 95%CI 1.16-1.82). Among patients diagnosed with a primary cancer after age 65, we observed a significantly increased risk of subsequent pancreatic adenocarcinoma after cancers of the biliary system (2.35, 95%CI 1.17-4.20), stomach (1.79, 95%CI 1.23-2.53), hepatic flexure (1.76, 95%CI 1.06-2.75) and uterus (1.23, 95%CI 1.03-2.47). Rectal cancer (0.65, 95%CI 0.46-0.87) was associated with a significantly decreased risk of pancreatic adenocarcinoma in this age group. Cancers of the small intestine, ovary, prostate, adrenal, thyroid, and brain as well as melanoma showed no statistically significant association with pancreatic adenocarcinoma at any age group.

Discussion

The occurrence of multiple primary cancers in an individual may reflect a genetic predisposition, although only a small number of cancers are a result of genetic syndromes. Many cancers, particularly in individuals at advanced age, can be a result of common environmental or behavioral risk factors, iatrogenic effects due to treatment of the first malignancy, or a combination of these factors (31). Our analysis is novel because we use a population-based dataset to suggest that the relative risk of subsequent pancreatic adenocarcinoma is increased in persons who have malignancies that are known to be associated with genetic syndromes and environmental risk factors (Tables 1 and 3).

Association between pancreatic adenocarcinoma and known genetic syndromes

Our data suggest an association between early age familial breast cancer (frequently BRCA 1/BRCA2) and pancreatic adenocarcinoma. We observed a significantly increased risk after breast cancer in those diagnosed between the ages of 20-49. The absence of a significant association in the older age groups could be explained by the declining incidence of breast cancer in BRCA1/BRCA2 carriers, as these women increasingly elect for prophylactic mastectomy or oophorectomy (36). In addition, many patients with BRCA mutations undergo screening with MRI and thermal imaging, which may detect pre-malignant breast lesions not otherwise detectable with mammography alone. Sporadic breast cancer also accounts for a higher proportion of cancers in older than younger women (37). We did not see a significantly increased risk of pancreatic adenocarcinoma after ovarian cancer. Approximately 70% of both hereditary and non-hereditary ovarian cancer patients present with stage III or IV disease, limiting survival and hence opportunity to develop a subsequent pancreatic cancer even in individuals with BRCA 1/BRCA2 (38). We did not observe a significantly increased risk after prostate cancer; however, BRCA1/BRCA2 does not predispose to an earlier age of onset of this malignancy (39-42). Patients therefore die with prostate cancer, as opposed to from it, and since we excluded cases reported by autopsy alone, our results are not unexpected.

We did not detect a significantly increased risk of pancreatic adenocarcinoma after melanoma. This result contrasts with two previous studies from 1998 and 2003 that report an association between these malignancies (43, 44). However, our data do not exclude an association between the malignancies of FAMMM syndrome and pancreatic adenocarcinoma. Individuals with FAMMM now undergo intense cancer screening and surveillance, dysplastic lesions are frequently removed at a pre-neoplastic or nevus stage. These data are not reported in SEER. As such, we hypothesize that these patients may develop pancreatic adenocarcinoma in the absence of frank melanoma. We observed a significantly increased risk of pancreatic adenocarcinoma in patients with pharyngeal cancer, an environmentally induced cancer also included in the FAMMM syndrome. (21). As these cancers are also associated with cigarette exposure, the increased risk likely represents the additive effect of a germline mutation and of tobacco exposure.

We detected significant positive associations between HNPCC-associated malignancies, including cancer of the right colon, endometrium, stomach, and hepatobiliary system, and pancreatic adenocarcinoma, specifically in younger age groups. Relative risks ranged from 1.23 to 13.14. These associations have also been noted in prior studies of various metachronous malignancies in large population cohorts (43, 45-46).

Our data cannot be used to support or refute an association between the malignancies seen in PJS and FAP with pancreatic adenocarcinoma. In considering PJS, although we observed a significantly increased risk of pancreatic adenocarcinoma in women after breast cancer, this malignancy is common to BRCA1/BRCA2 as well, and the vast majority of breast cancer cases are not syndromic in nature. Furthermore, cancers of the stomach, lung, and testes are associated to a large degree with environmental risk factors, and thus cannot be attributed to genetic factors alone. With regards to FAP, given its rarity on a population based level, future studies that are more adequately powered than ours must be done to further investigate this hypothesis.

Association between environmental risk factors and pancreatic adenocarcinoma

Pancreatic adenocarcinoma was frequently associated with tobacco-related malignancies. The significantly increased risk among individuals diagnosed with a first primary malignancy between 50-64 years of age after lung, bladder, stomach and pharyngeal cancer support the etiologic role of smoking, as noted by other investigators (43, 45, 47). A significantly increased incidence of pancreatic adenocarcinoma after testicular cancer as well as lymphatic and hematologic malignancies suggests a possible association with therapeutic radiation (45, 48). A review of the SEER therapeutic data suggests that 51% (18/35) of patients with primary testicular and 23% (50/218) of patients with primary hematological malignancies that subsequently developed primary pancreatic adenocarcinoma received therapeutic radiation. The increased risk after stomach cancer among individuals older than 50 years may also suggest the role of *H. pylori* infection as a common cause of non-cardia gastric cancer and pancreatic adenocarcinoma. Although the SEER database cannot be used to investigate the association between pancreatic adenocarcinoma and alcohol intake, BMI, or diet, these are important risk factors that must be examined with future population based studies.

The study has several limitations. First, while a genetic predisposition to cancer is suggested by our data, only a small proportion (fewer than 15%) of pancreatic malignancies are attributable to genetic syndromes (3, 4). Not all susceptibility genes are known and not all syndromes are defined. Although we selected for metachronous cancers, we cannot assume that all of our cases resulted from syndromic processes. Only a minority of patients with second primary pancreatic cancers will have a germline genetic mutation. Second, we were not able to control for important environmental factors such as tobacco, alcohol, *H. pylori*

incidence, BMI, and diet in our analysis. As such, the associations that we observed are likely, in part, attributable to unaccounted for cofactors. Since we could not review data on the actual habits of individuals in our population, we do not know whether or not individuals with malignancies associated with, for example, tobacco use, actually smoked. However, most environmental risk factors predispose to malignancy at advanced ages after cumulative exposure, while many of our observed associations were in the youngest age group when most genetic cancers are manifest. Third, we may have missed true associations due to our small sample size. Although we tried to group anatomic sites together to avoid calculating relative risks based on small expected values, this was not possible for some cancer sites. Finally, we did not have access to the family history of the patients followed. Although we are more concerned with multiple primary cancers in the same individual, information regarding syndromic cancers within families would have been very useful for comparison.

In summary, our data reveal an increased risk of pancreatic adenocarcinoma following some malignancies associated with certain genetic syndromes specifically in the youngest age group. Our results also indicate an increased risk of pancreatic cancer after tobacco-related malignancies, cancers treated with radiation, and possibly other environmental factors, such as *H. pylori* infection. Efforts to decrease the mortality from pancreatic cancer involve both lifestyle modification and screening protocols in appropriate populations, such as those with a positive family history, a genetic syndrome that predisposes to the disease, or environmental risk factors (3, 49-53). An increased awareness of the association between pancreatic cancer and other malignancies may aid future pancreas risk stratification strategies and cancer surveillance efforts.

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Abbreviations

BRCA1/BRCA2	familial breast and ovarian cancer syndrome
FAMMM	familial atypical multiple mole melanoma syndrome

FAP	familial adenomatous polyposis syndrome
HNPCC	hereditary non-polyposis colorectal cancer syndrome
PJS	Peutz-Jeghers syndrome
SEER	Surveillance, Epidemiology, and End-Results
SIR	standardized incidence ratios

Table 1

Hereditary cancer syndromes that predispose to pancreatic cancer as well as cancers commonly associated with environmental risk factors. Associated cancers are listed in order of approximate frequency.

BRCA1/BRCA2	PJS	FAMMM	HNPCC	FAP	Environmental
Breast	Breast	Dysplastic Nevi	Colorectal	Colorectal	Lung
Ovarian	Colon	Melanoma	Endometrial	Duodenal/Periampullary	Bladder
Prostate	Pancreas	Pancreas	Ovarian	Desmoid	Pancreas
Pancreas	Stomach	Head and Neck	Hepatobiliary/Pancreas	Thyroid	Gastric

Table 2

Persons and follow-up years of patients diagnosed with first primary cancer between Jan. 1, 1973 and Dec. 31, 2006 that met eligibility criteria, stratified by age at diagnosis of first primary.

	20-49 years		50-64 years		65+ years		All Age Groups	
Site	**Persons**	**Person Years at Risk**	**Persons**	**Person Years at Risk**	**Persons**	**Person Years at Risk**	**Persons**	**Person Years at Risk**
All Sites	317,515	3,211,151.22	521,358	4,328,123.25	779,961	4,532,142.80	1,618,834	12,071,417.27
Digestive System								
Esophagus	452	2,356.56	2,004	8,102.89	2,377	7,344.65	4,833	17,804.10
Stomach	1,817	13,126.16	4,513	29,111.26	8,468	39,225.28	14,798	81,462.70
Small Intestine	932	7,549.43	1,659	10,787.33	1,956	9,102.02	4,547	27,438.78
Ascending Colon	1,226	11,777.33	4,522	38,885.00	14,443	84,831.02	20,191	135,493.35
Hepatic Flexure	479	4,672.07	1,468	12,577.49	4,438	24,553.17	6,385	41,802.73
Transverse Colon	1,008	10,604.36	3,025	28,618.55	8,317	50,008.49	12,350	89,231.40
Descending Colon	1,008	9,886.80	3,335	32,554.29	6,133	38,255.46	10,476	80,696.55
Rectum	4,909	40,250.84	15,049	120,590.08	22,875	128,950.46	42,833	289,791.38
Liver, Gallbladder, Intrahep Bile Duct and Other Biliary	880	4,583.86	2,093	9,023.02	3,044	10,742.07	6,017	24,348.95
Respiratory System								
Lung and Bronchus	7,226	54,470.52	31,006	169,540.87	38,608	143,441.06	76,840	367,452.45
Skin and Soft Tissue								
Melanoma of the Skin	33,520	365,768.12	21,842	199,931.04	19,687	118,582.82	75,049	684,281.98
Female Breast	88,319	864,204.55	120,194	1,086,733.85	137,253	914,971.04	345,766	2,865,909.44
Female Genital System								
Cervix Uteri	15,749	199,729.26	6,566	67,559.27	4,452	30,104.20	26,767	297,392.73
Corpus Uteri	10,477	130,579.29	33,343	432,522.72	31,158	255,473.71	74,978	818,575.72
Ovary	7,961	84,828.73	9,733	72,011.89	8,140	39,295.57	25,834	196,136.19
Male Genital System								
Prostate	5,345	30,521.89	91,681	619,291.65	221,521	1,268,891.47	318,547	1,918,705.01
Testis	14,808	179,822.90	1,107	11,734.42	238	1,647.80	16,153	193,205.12
Urinary System								

	20-49 years		50-64 years		65+ years		All Age Groups	
Site	**Persons**	**Person Years at Risk**	**Persons**	**Person Years at Risk**	**Persons**	**Person Years at Risk**	**Persons**	**Person Years at Risk**
Kidney and Renal Pelvis	6,686	60,147.83	13,133	102,130.10	14,232	79,912.64	34,051	242,190.57
Urinary Bladder	7,841	100,193.49	26,561	266,651.04	53,251	315,890.71	87,653	682,735.24
Endocrine System								
Thyroid	22,828	267,411.22	8,262	79,644.99	4,528	31,008.61	35,618	378,064.82
Adrenal Gland	203	1,659.19	166	1,150.82	87	446.14	456	3,256.15
Head and Neck								
Pharynx	1,579	12,293.66	2,702	15,548.95	1,882	8,106.13	6,163	35,948.74
All Lymphatic and Hematopoietic Diseases	34,306	313,047.81	36,772	240,511.97	51,207	224,806.38	122,285	778,366.16
Brain and Other Nervous System	7,234	52,492.20	2,119	10,042.91	789	3,093.74	10,142	65,628.85

Table 3

Relative risk of pancreatic adenocarcinoma two or more years after first primary cancer, stratified by age at diagnosis of first primary cancer.

	20-49 years				50-64 years				65+ years			
Site	**Obs**	**Exp**	**RR**	**CI**	**Obs**	**Exp**	**RR**	**CI**	**Obs**	**Exp**	**RR**	**CI**
Digestive System												
Esophagus	1	0.27	3.74	0.09-20.85	5	2.68	1.87	0.61-4.35	2	3.59	0.56	0.07-2.02
Stomach	2	1.52	1.32	0.16-4.75	19	10.13	**1.88**	1.13-2.93	32	17.85	**1.79**	1.23-2.53
Small Intestine	2	0.77	2.59	0.31-9.36	2	3.5	0.57	0.07-2.07	5	4.21	1.19	0.39-2.77
Ascending Colon	7	1.51	**4.62**	1.86-9.52	14	14.04	1	0.55-1.67	48	36.78	1.31	0.96-1.73
Hepatic Flexure	3	0.55	**5.42**	1.12-15.84	10	4.45	**2.25**	1.08-4.13	19	10.78	**1.76**	1.06-2.75
Transverse Colon	2	1.4	1.43	0.17-5.16	17	10.18	1.67	0.97-2.67	27	21.83	1.24	0.82-1.8
Descending Colon	1	1.3	0.77	0.02-4.29	9	11.73	0.77	0.35-1.46	20	17.24	1.16	0.71-1.79
Rectum	7	4.84	1.45	0.58-2.98	37	41.78	0.89	0.62-1.22	38	58.34	**0.65**	0.46-0.89
Liver, Gallbladder, Intrahep Bile Duct and Other Biliary	5	0.38	**13.14**	4.27-30.66	1	2.73	0.37	0.01-2.04	11	4.68	**2.35**	1.17-4.20
Respiratory System												
Lung and Bronchus	9	6.65	1.35	0.62-2.57	81	55.42	**1.46**	1.16-1.82	73	67.77	1.08	0.84-1.35
Skin and Soft Tissue												
Melanoma of the Skin	31	27.92	1.11	0.75-1.58	60	64.41	0.93	0.71-1.20	53	54.68	0.97	0.73-1.27
Female Breast	112	84.76	**1.32**	1.09-1.59	305	305.11	1	0.89-1.12	355	364.04	0.98	0.88-1.08
Female Genital System												
Cervix Uteri	23	14.3	**1.61**	1.02-2.41	23	19.69	1.17	0.74-1.75	14	12.16	1.15	0.60-1.93
Corpus Uteri	18	15.19	1.19	0.70-1.87	120	133.31	0.9	0.75-1.08	124	100.58	**1.23**	1.03-1.47
Ovary	7	6.7	1.04	0.42-2.15	25	19.82	1.26	0.82-1.86	16	15.66	1.02	0.58-1.66
Male Genital System												
Prostate	4	4.42	0.90	0.25-2.31	223	245.72	0.91	0.79-1.03	694	671.78	1.03	0.96-1.11
Testis	27	9.71	**2.78**	1.83-4.05	7	3.96	1.77	0.71-3.64	1	0.83	1.20	0.03-6.68
Urinary System												
Kidney and Renal Pelvis	7	6.85	1.02	0.41-2.11	41	34.59	1.19	0.85-1.61	49	37.67	1.30	0.96-1.72
Urinary Bladder	15	13.59	1.10	0.62-1.82	122	98.57	**1.24**	1.03-1.48	154	151.63	1.02	0.86-1.19
Endocrine System												

	20-49 years				50-64 years				65+ years			
Site	**Obs**	**Exp**	**RR**	**CI**	**Obs**	**Exp**	**RR**	**CI**	**Obs**	**Exp**	**RR**	**CI**
Thyroid	11	17.02	0.65	0.32-1.16	20	23.37	0.86	0.52-1.32	13	13.38	0.97	0.52-1.66
Adrenal Gland	0	0.14	0.00	0.00-25.66	2	0.34	5.94	0.72-21.44	0	0.21	0	0.00-17.34
Head and Neck												
Pharynx	1	1.13	0.89	0.02-4.94	11	4.88	**2.26**	1.13-4.04	5	3.86	1.30	0.42-3.02
All Lymphatic and Hematopoietic Diseases	36	19.72	**1.83**	1.28-2.53	84	75.56	1.11	0.89-1.38	98	102.74	0.95	0.77-1.16
Brain and Other Nervous System	2	2.25	0.89	0.11-3.22	2	2.63	0.76	0.09-2.75	0	1.4	0	0.00-2.63

Table 3 legend: All statistics represent values for combined male and female group. SIR (O/E) in bold are statistically significant at $p < 0.05$. Confidence intervals are 95%.