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Research Article

Cancer Epidemiology, Biomarkers & Prevention

Cancer Incidence and Survival Trends by Subtype Using Data from the Surveillance Epidemiology and End Results Program, 1992–2013

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Abstract

Background: Cancers are heterogeneous, comprising distinct tumor subtypes. Therefore, presenting the burden of cancer in the population and trends over time by these tumor subtypes is important to identify patterns and differences in the occurrence of these subtypes, especially to generalize findings to the U.S. general population.

Methods: Using SEER Cancer Registry Data, we present incidence rates according to subtypes for diagnosis years (1992–2013) among men and women for five major cancer sites: breast (female only), esophagus, kidney and renal pelvis, lung and bronchus, and thyroid. We also describe estimates of 5-year relative survival according to subtypes and diagnosis year (1992–2008). We used Joinpoint models to identify years when incidence rate trends changed slope. Finally, recent 5-year age-adjusted incidence rates (2009–2013) are presented for each subtype by race and age.

Results: Hormone receptor–positive and HER2-negative was the most common subtype (about 74%) of breast cancers. Adenocarcinoma made up about 69% of esophagus cases among men. Adenocarcinoma also is the most common lung subtype (43% in men and 52% in women). Ninety percent of thyroid subtypes were papillary. Distinct incidence and survival patterns emerged by these subtypes over time among men and women.

Conclusions: Histologic or molecular subtype revealed different incidence and/or survival trends that are masked when cancer is considered as a single disease on the basis of anatomic site.

Impact: Presenting incidence and survival trends by subtype, whenever possible, is critical to provide more detailed and meaningful data to patients, providers, and the public. *Cancer Epidemiol Biomarkers Prev; 26(4); 632–41. ©2016 AACR.*

Introduction

The conventional method of reporting population-based cancer statistics, solely by anatomic site, does not leverage advances in characterization of neoplasms based on their detailed biological characteristics (1). Cancer subtypes are increasingly defined by detailed anatomic site (2, 3), histology (4, 5), or molecular characteristics (6). Important patterns of cancer occurrence emerge when cancers are examined on the basis of these biologic characteristics. Thus, reporting cancer statistics by these clinically important subtypes from population-based registries may identify important trends within the U.S. population or among population subgroups that would otherwise not be evident.

Patterns of disparity can emerge when characterizing cancers based on underlying biology, such as the elevated rate of triple-negative breast cancer among African American women, which is a more aggressive subtype than the predominant HR^+/HER^- breast cancer subtype (6, 7). Cancer subtypes may also often have distinct risk factors associated with particular histologies. Understanding trends over time and risk may be useful in targeting interventions or prevention strategies to specific subgroups (8–10). Furthermore, providing data by subtypes such as biomarker presence or genetic test result is essential for determining the impact of major improvements in cancer therapy such as targeted therapies at the population level outside of clinical trials (11).

The Surveillance Epidemiology and End Results (SEER) Program has traditionally presented cancer statistics by organ site (12); however, presenting cancer statistics by tumor subtypes is an important contribution that reflects advances in knowledge about the heterogeneity of cancer and to understand the differential burden of cancer in populations. In this report, SEER cancer incidence and survival data are presented for selected cancer subsites. The objective of this population-based report is to illustrate unique patterns of incidence, time trends, and survival for breast, esophageal, thyroid, lung, kidney and renal pelvis cancer subtypes that represent one change in how SEER data will be presented in the future.

Materials and Methods

Population-based cancer incidence data have been collected by the National Cancer Institute's SEER Program since 1973.

Division of Cancer Control and Population Sciences, Surveillance Research Program, National Cancer Institute, Bethesda, Maryland.

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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Incidence and survival data included in this report are from the SEER 13 registries which cover about 13% of the U.S. population. Cancers from 5 organ sites diagnosed from 1992 to 2013 were selected to illustrate the potential value in examining tumor subtypes and include female breast, esophagus, kidney and renal pelvis, lung and bronchus, and thyroid. Because joint expression of hormone receptor and HER2 status to classify breast cancer subtypes was not collected until 2010, only female breast cancer cases diagnosed from 2010 to 2013 were included.

The SEER site recode variable based on the World Health Organization International Classification of Disease for Oncology, 3rd edition (ICD-O-3), was used to define the primary site. All cases were included in reporting by the primary site as is done in standard reports (1, 13). Subtypes for each cancer site were defined by histologic type and restricted to cases with microscopic confirmation of histology (Supplementary Table S1). Two exceptions were that clinically relevant subtypes for breast cancer were defined by hormone receptor and HER2 status and kidney and renal pelvis were defined by anatomy; so these were not restricted to cases with histologic confirmation. Although kidney and renal pelvis tumors were defined by anatomy, each subsite had a predominant histologic type. The vast majority of renal pelvis tumors were transitional cell carcinomas, whereas kidney nitric oxide synthetase (NOS) tumors were almost all adenocarcinomas and renal cell carcinomas.

Five-year cancer incidence rates (2009–2013) and 4-year rates (2010–2013) for breast cancer are presented for each subtype by race and age. Race groups include white, black, Asian and Pacific Islander (API), and American Indian/Alaska Native (AI/AN). Differences between race and age groups were compared using the relative rate ratio and its 95% confidence interval (14). All incidence rates were age-adjusted to the 2000 U.S. standard population. The population estimates used as the denominators to calculate incidence rates were a modification of the intercensal and Vintage 2014 (15).

Incidence rates were estimated from 1992 to 2013. In addition, trends and changes over time were estimated using a Joinpoint model (16). This is a technique that fits a series of joined straight lines on a logarithm scale to the age-adjusted rates over time, a maximum of 4 joinpoints were considered for fitting trends. Breast cancer trends were not estimated, as data were only available from 2010. Incidence rates used to calculate trends were also adjusted for reporting delay which may occur because of a lag in reporting to the cancer registry or data corrections (17). Delay adjustment factors were not available by subtype; therefore, these rates are adjusted by the overall reporting delay for that primary site. In this report, trends that are reported as increasing or decreasing refer to statistically significant increasing or decreasing trends estimated from the Joinpoint model. Nonstatistically significant trends are referred to as stable.

Finally, we present estimates of 5-year relative survival according to cancer subtypes and diagnosis year among men and women. Relative survival was calculated as the ratio of observed all-cause survival to expected survival using the actuarial method in SEER*Stat (18, 19). It represents survival associated with a cancer diagnosis and it is the standard method for reporting cancer-specific survival from registry data as it does not rely on causes of death which may be missing or misclassified (20). Expected survival rates were calculated using life tables on the basis of individual year 1970 to 2011, individual age 0 to 99 years, sex, and race [white, black, other (AI/AN, API)] and were matched on age, sex, year of diagnosis, and race (white, black, and other) to the cancer cohort (21). Survival analyses included cases diagnosed in 1992 to 2008 and follow-up until December 31, 2012. Cases diagnosed in 2009 and after are not included because we do not have complete 5 years of follow-up for them. For the same reasons, we were unable to examine 5-year survival data for breast cancer cases diagnosed after 2010.

Results

Female breast cancer

Hormone receptor–positive and HER2-negative ($HR^+/HER2^-$) breast cancer was the most common subtype comprising 74% of all cases (Supplementary Fig. S1). Incidence rates for breast cancer subtype varied by race. For example, white women had the highest incidence rate for this subtype followed by black, API, and AI/AN women (Table 1). In contrast, triple-negative breast cancer which made up the second largest component at 11% of cases had the highest rates among black women. The $HR^+/HER2^+$ and $HR^-/HER2^+$ subtypes had relatively small difference in incidence in white compared with black women.

In addition, incidence peaked among women aged 65 to 74 years among all subtypes. The HER2-overexpressing tumors (i.e., $HR^-/HER2^+$) were the least common subtypes with fewer observed variations by race or age groups compared with both the $HR^+/HER2^-$ and triple-negative subtypes.

Esophageal cancer

The overall trend for esophageal cancer shows a decline in incidence for both men and women (Fig. 1). The 5-year survival is relatively stable over time; however, there are differences between the subtypes for both incidence and survival. Specifically, the incidence trends by subtype, in particular for men, revealed an increasing incidence for adenocarcinoma contrasted with a decline for squamous cell and other histologic subtypes (Supplementary Table S2). Incidence for squamous cell carcinoma is declining for women, but incidence among the other subtypes remains stable. Among men who have much higher rates of esophageal cancer than women, adenocarcinoma makes up approximately 69% of all esophageal cancers, whereas squamous cell carcinoma makes up the second largest component at 27% (Supplementary Fig. S1).

The incidence rates by race show that while white men have the highest rates of adenocarcinoma (5.7 per 100,000), black men have the highest rate of squamous cell carcinoma (4.5 per 100,000; Table 1). Incidence rates for squamous cell carcinoma are also higher among AI/AN and API than white men (2.0 and 2.3 vs. 0.3, respectively). Incidence for adenocarcinoma is similar for white and black women, but black women had higher rates of squamous cell carcinoma than white and API women (Table 1).

There are also differences in incidence by age for both men and women. Incidence increased dramatically for men by age for both adeno- and squamous cell carcinoma (Table 2). However, men had the highest incidence of adenocarcinoma for all age groups compared with women. There is an increased risk with advancing age in men for both adeno- and squamous cell carcinoma compared with the youngest age group. For women, the highest incidence was squamous cell carcinoma and similar to men, the incidence increased after the age of 55 years (Table 2).

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Table 1. Five-year incidence rates (2009–2013) for men and women by race

		Race										
		White[a]		Black			AI/AN			API		
	Total N	*n*	Rate	*n*	Rate	RR (95% CI)	*n*	Rate	RR (95% CI)	*n*	Rate	RR (95% CI)
Men												
Esophagus												
Adenocarcinoma	4,639	4,372	5.7	121	1.4	0.2 (0.2–0.3)	28	3.4	0.6 (0.4–0.9)	118	1.0	0.2 (0.1–0.2)
Squamous cell	1,796	1,108	1.5	388	4.5	3.1 (2.7–3.5)	15	2.0	1.4 (0.7–2.3)	285	2.3	1.6 (1.4–1.8)
Other	304	257	0.3	24	0.3	0.9 (0.6–1.4)	∼			21	0.2	0.5 (0.3–0.8)
Kidney and Renal Pelvis												
Kidney, NOS	19,406	4,816	6.6	901	10.5	1.6 (1.5–1.7)	56	8.6	1.3 (1.0–1.7)	708	6.1	0.9 (0.9–1.0)
Renal pelvis	1,082	937	1.3	44	0.6	0.5 (0.3–0.6)	∼			96	0.8	0.6 (0.5–0.8)
Lung and bronchus												
Squamous	13,022	10,277	14.1	1,547	20.6	1.5 (1.4–1.5)	90	15.3	1.1 (0.9–1.4)	1,108	9.7	0.7 (0.6–0.7)
Small cell	6,173	5,095	6.7	549	6.8	1.0 (0.9–1.1)	47	7.1	1.1 (0.8–1.4)	482	4.1	0.6 (0.6–0.7)
Adenocarcinoma	22,187	16,660	22.5	2,644	31.4	1.4 (1.3–1.5)	99	14.9	0.7 (0.5–0.8)	2,784	23.2	1.0 (1.0–1.1)
Large cell	926	704	0.9	143	1.7	1.8 (1.5–2.2)	∼			78	0.6	0.7 (0.5–0.9)
Malignant neoplasm and carcinoma unspecified	6,481	4,816	6.6	901	10.5	1.6 (1.5–1.7)	56	8.6	1.3 (1.0–1.7)	708	6.1	0.9 (0.9–1.0)
Thyroid												
Papillary	6,137	5,100	6.5	262	2.7	0.4 (0.4–0.5)	38	4.1	0.6 (0.4–0.9)	737	5.4	0.8 (0.8–0.9)
Follicular	558	433	0.6	52	0.6	1.0 (0.7–1.4)	∼			69	0.5	1.0 (0.7–1.3)
Medullary	176	148	0.2	13	0.1	0.7 (0.4–1.3)	∼			14	0.1	0.6 (0.3–1.0)
Anaplastic	98	74	0.1	8	0.1	0.9 (0.4–2.0)	∼			16	0.1	1.5 (0.8–2.6)
Women												
Breast												
$HR^+/HER2^+$	10,968	8,159	9.6	1,257	10.1	1.1 (1.0–1.1)	101	9.7	1.0 (0.8–1.2)	1,451	9.0	0.9 (0.9–1.0)
$HR^-/HER2^+$	4,832	3,386	3.9	602	4.9	1.2 (1.1–1.4)	37	3.7	0.9 (0.7–1.3)	807	4.9	1.2 (1.1–1.3)
$HR^+/HER2^-$	80,317	63,608	72.4	7,075	59.4	0.8 (0.8–0.8)	491	51.8	0.7 (0.7–0.8)	9,143	56.8	0.8 (0.8–0.8)
Triple-negative	12,143	8,555	10.0	2,330	18.9	1.9 (1.8–2.0)	67	7.1	0.7 (0.5–0.9)	1,191	7.4	0.7 (0.7–0.8)
Esophagus												
Adenocarcinoma	784	717	0.8	37	0.3	0.4 (0.3–0.6)	∼			22	0.1	0.2 (0.1–0.3)
Squamous cell	1,057	726	0.8	212	1.8	2.2 (1.9–2.6)	∼			114	0.7	0.9 (0.7–1.1)
Other	110	89	0.1	15	0.1	1.5 (0.8–2.6)	∼			∼		
Kidney and renal pelvis												
Kidney, NOS	10,807	8,450	9.6	1,376	11.6	1.2 (1.1–1.3)	155	16.0	1.7 (1.4–2.0)	826	5.2	0.5 (0.5–0.6)
Renal pelvis	815	663	0.7	58	0.6	0.8 (0.6–1.0)	∼			91	0.6	0.8 (0.6–1.0)
Lung												
Squamous	7,905	6,495	7.4	924	8.5	1.2 (1.1–1.2)	65	8.0	1.1 (0.8–1.4)	421	2.7	0.4 (0.3–0.4)
Small cell	6,068	5,185	5.8	566	5.0	0.9 (0.8–0.9)	47	5.1	0.9 (0.6–1.2)	270	1.7	0.3 (0.3–0.3)
Adenocarcinoma	24,720	18,911	21.1	2,758	23.7	1.1 (1.1–1.2)	86	9.9	0.5 (0.4–0.6)	2,965	18.9	0.9 (0.9–0.9)
Large cell	747	585	0.7	106	0.9	1.4 (1.1–1.7)	∼			51	0.3	0.5 (0.4–0.7)
Malignant neoplasm and carcinoma unspecified	5,110	3,971	4.4	697	6.0	1.4 (1.3–1.5)	31	4.0	0.9 (0.6–1.3)	411	2.7	0.6 (0.5–0.7)
Thyroid												
Papillary	20,401	15,973	20.2	1,378	11.0	0.5 (0.5–0.6)	152	15.2	0.8 (0.6–0.9)	2,898	18.2	0.9 (0.9–0.9)
Follicular	1,381	1,025	1.3	179	1.5	1.2 (1.0–1.4)	14	1.5	1.2 (0.6–2.1)	163	1.0	0.8 (0.7–1.0)
Medullary	290	237	0.3	33	0.3	0.9 (0.6–1.3)	∼			19	0.1	0.4 (0.3–0.7)
Anaplastic	167	133	0.1	11	0.1	0.7 (0.3–1.3)	∼			23	0.2	1.1 (0.6–1.7)

[a]Reference group.
∼Counts of 10 or less were suppressed.

Five-year relative survival for esophageal cancer overall is modestly increasing over time for both men and women (Fig. 1). Survival is higher among those with adenocarcinoma than those with squamous cell among men (20.5% vs. 16.6% in 2008). However, there is not any difference in survival among the subtypes for women.

Kidney and renal pelvis cancer

The overall incidence trend for kidney and renal pelvis cancer was increasing from 1992 to 2008 but it is now stable among both men and women. The overall trend is driven by the incidence in kidney cancer, as these comprise more than 90% of cases. Indeed, the incidence trend for kidney cancer followed the same pattern. Cancer of the renal pelvis has a much smaller incidence rate and has been stable since 1992. Although the pattern is similar among men and women, the incidence is lower among women.

The incidence rates of kidney cancer are highest among Black and AI/AN men (10.5 and 8.6 per 100,000, respectively; Table 1). Black and AI/AN women also have higher rates than white women. In contrast, incidence rates for cancer of the renal pelvis are highest among whites for both men and women. The incidence rates for cancer of both kidney and renal pelvis increase by age among men and women (Table 2). However, the increase by age is far greater for cancer of the renal pelvis than for kidney.

Five-year relative survival for kidney cancer is increasing over time among both men and women (Fig. 2). Specifically, 5-year survival rate was 58.6% in 1992 and increased to 74.2% in men and increased from 61.2% to 78.3% in women. Survival

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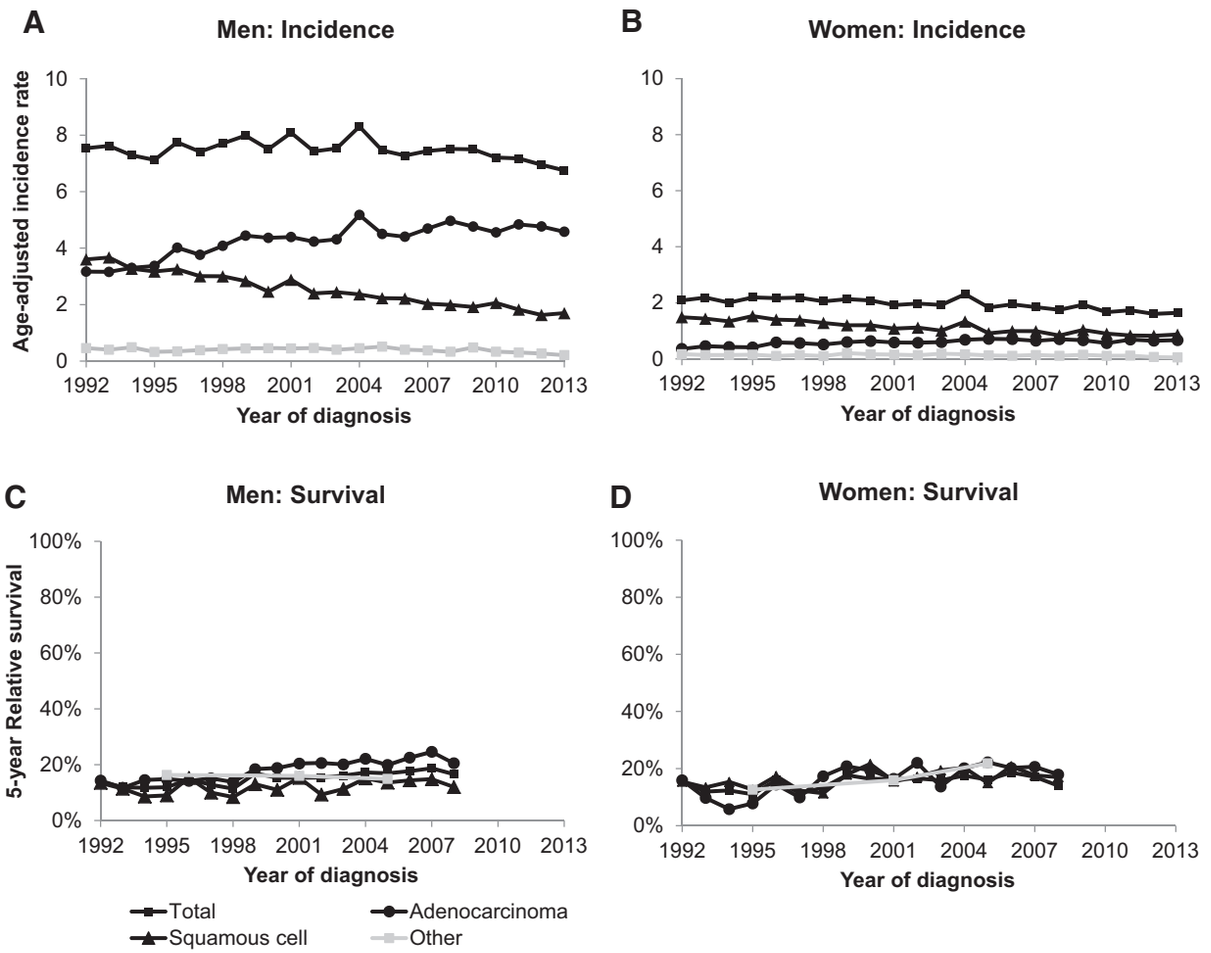

Figure 1.

Esophageal cancer age-adjusted incidence rates and 5-year relative survival over time by subtype for men and women. Survival estimates for other are based on 5-year groups (1992–1998, 1999–2003, 2004–2008).

is lower for cancer of the renal pelvis but variable due to small case counts.

Lung and bronchus cancer

The overall trend for lung cancer is declining among both men and women (Fig. 3). This decline is also seen among men and women with small cell, large cell, and malignant neoplasm and carcinoma unspecified subtypes (Supplementary Table S2). However, adenocarcinoma, which is the most common subtype making up 45% of the cases among men and 55% of the cases among women, is increasing among both sexes (Supplementary Fig. S1). Squamous cell carcinoma, the second most common histologic subtype comprising 17% of cases among men and 12% among women, is decreasing among men but stable among women.

The incidence rates by race show that black men have a higher incidence for all subtypes except small cell than white men (Table 1). This difference in particularly pronounced for squamous cell, malignant neoplasm and unspecified carcinomas, and large cell carcinoma subtypes. AI/AN men had a higher rate of malignant neoplasms and unspecified carcinoma and a lower rate of adenocarcinoma than white men. API men had overall lower rates for all lung subtypes than white men with the exception of adenocarcinoma. Compared with white women, black women have higher rates for large cell carcinoma, malignant neoplasms and unspecified carcinoma, and squamous cell carcinoma (Table 1). Incidence rates for adenocarcinoma are nearly equivalent for black and white women. Small cell carcinoma was higher among white women than black women. AI/AN and API women had lower rates for all subtypes compared to white women with the only exception of a higher rate of squamous cell carcinoma among AI/AN than white women. Among both men and women, incidence rates of lung subtypes by age show each of the subtype incidence rates increases with age (Table 2). Lung cancer incidence for all subtypes is highest among men and women aged 75 years and older.

Five-year relative survival by lung cancer histologic subtype indicates an increase in survival for each subtype among both men and women (Fig. 3), although survival among women is generally higher than among men. Among men, those with the adeno- and squamous cell carcinoma had the highest 5-year

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Table 2. Five-year incidence rates (2009–2013) for men and women by age

	<55 y[a]		55–64 y			65–74 y			75+ y		
	n	Rate	*n*	Rate	RR (95% CI)	*n*	Rate	RR (95% CI)	*n*	Rate	RR (95% CI)
Men											
Esophagus											
Adenocarcinoma	644	0.8	1,348	11.4	14.9 (13.5–16.4)	1,381	21.6	28.2 (25.7–31.0)	1,288	27.8	36.3 (33.0–40.0)
Squamous cell	218	0.3	525	4.4	17.7 (15.1–20.9)	545	8.5	34.1 (29.0–40.1)	515	11.1	44.5 (37.9–52.4)
Other	32	0.0	85	0.7	19.0 (12.5–29.6)	95	1.5	39.2 (25.9–60.7)	96	2.1	54.3 (35.9–83.9)
Kidney and renal pelvis											
Kidney, NOS	5,144	6.3	5,503	46.6	7.4 (7.1–7.7)	5,148	80.0	12.8 (12.3–13.3)	3,838	83.2	13.3 (12.7–13.8)
Renal pelvis	80	0.1	214	1.8	19.3 (14.8–25.2)	325	5.1	54.3 (42.3–70.4)	472	10.1	107.6 (84.6–138.3)
Lung											
Squamous	819	0.9	2,722	23.0	24.4 (22.5–26.4)	4,532	72.1	76.5 (70.9–82.5)	5,006	108.4	114.9 (106.6–123.9)
Small cell	579	0.7	1,577	13.3	19.9 (18.1–22.0)	2,236	35.0	52.4 (47.7–57.5)	1,801	39.1	58.5 (53.2–64.3)
Adenocarcinoma	2,205	2.6	5,267	44.5	17.3 (16.4–18.1)	7,247	114.3	44.3 (42.2–46.5)	7,571	163.9	63.5 (60.5–66.6)
Large cell	104	0.1	238	2.0	16.6 (13.1–21.1)	310	4.8	39.9 (31.8–50.4)	277	6.0	49.7 (39.5–62.9)
Malignant neoplasm and carcinoma unspecified	608	0.7	1,518	12.8	18.1 (16.4–19.9)	2,009	31.6	44.5 (40.6–48.8)	2,381	51.2	72.0 (65.8–78.9)
Thyroid											
Papillary	3,352	4.2	1,415	12.0	2.9 (2.7–3.1)	986	15.3	3.7 (3.4–3.9)	479	10.4	2.5 (2.3–2.8)
Follicular	246	0.3	126	1.1	3.5 (2.8–4.4)	112	1.8	5.8 (4.6–7.3)	81	1.8	5.9 (4.5–7.6)
Medullary	97	0.1	34	0.3	2.4 (1.6–3.6)	28	0.4	3.6 (2.3–5.6)	21	0.5	3.8 (2.3–6.2)
Anaplastic	15	0.0	20	0.2	10.0 (4.8–21.1)	33	0.5	29.8 (15.6–59.2)	31	0.7	39.5 (20.5–78.7)
Women											
Breast											
$HR^+/HER2^+$	4,790	5.9	2,902	22.9	3.9 (3.7–4.1)	1,911	25.4	4.3 (4.1–4.6)	1,459	21.0	3.6 (3.4–3.8)
$HR^-/HER2^+$	1,985	2.4	1,399	11.1	4.6 (4.3–4.9)	828	11.0	4.6 (4.2–5.0)	653	9.5	3.9 (3.6–4.3)
$HR^+/HER2^-$	24,066	29.1	20,796	163.5	5.6 (5.5–5.7)	19,592	262.6	9.0 (8.9–9.2)	16,501	240.3	8.3 (8.1–8.4)
Triple-negative	4,840	5.9	3,201	25.2	4.3 (4.1–4.4)	2,274	30.4	5.1 (4.9–5.4)	1,923	27.6	4.7 (4.4–4.9)
Esophagus											
Adenocarcinoma	102	0.1	181	1.4	12.0 (9.3–15.5)	187	2.6	21.6 (16.8–27.8)	318	4.3	36.3 (28.8–45.9)
Squamous cell	116	0.1	239	1.9	14.4 (11.5–18.2)	321	4.4	33.7 (27.1–42.1)	390	5.5	42.2 (34.1–52.5)
Other	10	0.0	15	0.1	10.3 (4.3–25.7)	24	0.3	30.1 (13.7–70.6)	62	0.9	76.5 (38.4–168.0)
Kidney and renal pelvis											
Kidney, NOS	2,853	3.5	2,682	21.1	6.1 (5.8–6.4)	2,681	36.2	10.5 (9.9–11.1)	2,697	38.9	11.3 (10.7–11.9)
Renal pelvis	48	0.1	97	0.8	13.6 (9.5–19.7)	218	3.0	53.3 (38.7–74.6)	459	6.4	113.9 (84.1–157.2)
Lung											
Squamous	428	0.5	1,283	10.0	20.8 (18.6–23.2)	2,781	38.0	78.7 (71.0–87.3)	3,435	51.3	106.1 (95.8–117.7)
Small cell	626	0.7	1,472	11.5	16.3 (14.9–18.0)	2,107	28.5	40.4 (36.9–44.3)	1,884	28.6	40.4 (36.9–44.4)
Adenocarcinoma	2,851	3.3	5,440	42.7	13.0 (12.4–13.6)	7,787	106.0	32.3 (30.9–33.7)	8,759	128.9	39.3 (37.6–41.0)
Large cell	88	0.1	190	1.5	14.8 (11.4–19.3)	227	3.1	30.2 (23.4–39.1)	244	3.7	36.4 (28.3–47.1)
Malignant neoplasm and carcinoma unspecified	568	0.6	1,030	8.1	12.4 (11.2–13.8)	1,499	20.5	31.6 (28.7–34.9)	2,039	29.5	45.4 (41.3–50.0)
Thyroid											
Papillary	13,586	16.9	3,910	30.9	1.8 (1.8–1.9)	2,244	29.6	1.8 (1.7–1.8)	1,007	15.5	0.9 (0.9–1.0)
Follicular	778	1.0	260	2.1	2.1 (1.9–2.5)	226	3.1	3.2 (2.7–3.7)	147	2.3	2.4 (2.0–2.8)
Medullary	132	0.2	72	0.6	3.5 (2.6–4.7)	57	0.8	4.8 (3.4–6.6)	31	0.5	2.9 (1.8–4.3)
Anaplastic	9	0.0	28	0.2	21.3 (9.7–51.6)	45	0.6	61.7 (29.4–144.3)	85	1.1	110.7 (54.8–252.0)

[a]Reference group.

relative survival (22.4% and 20.5% in 2008, respectively). A similar pattern was seen for among women with a 5-year relative survival 28.6% in 2008 for adenocarcinoma and 22.6% for squamous cell carcinoma.

Thyroid cancer

The overall incidence trend for thyroid cancer is increasing among men and women (Fig. 4). However, the overall trend is driven by the papillary subtype, as it accounts for about 90% of the cases among both men and women (Table 1). Indeed, incidence trends for the papillary subtype are increasing among men and women (Supplementary Table S2). The less common subtypes, in descending order of incidence, are follicular, medullary, and anaplastic. The incidence rates for these subtypes are low; however, medullary thyroid cancer has been increasing among men and women. The trend for anaplastic thyroid cancer is stable among men and women.

Among men the highest incidence rates for the papillary subtype occurred among whites and APIs with lower rates among blacks and AI/ANs (Table 1). Incidence rates of papillary subtype increased with age, peaked among men aged 65 to 74 years and then decreased among men older than 75 years (Table 2). Incidence rates for other thyroid cancer subtypes were lower and typically increased with age.

Among women incidence rates for papillary subtype were higher than those of men, with higher rates among whites and APIs than among blacks and AI/ANs (Table 1). Rates across racial and ethnic groups were similar for nonpapillary subtypes. Incidence rates of papillary subtype peaked among women at 55 to 64 years (Table 2). Incidence rates for follicular and medullary subtypes peaked at 65 to 74 years and those for anaplastic peaked at 75+ years.

Among both men and women, overall 5-year relative survival is driven by the papillary subtype for which the survival

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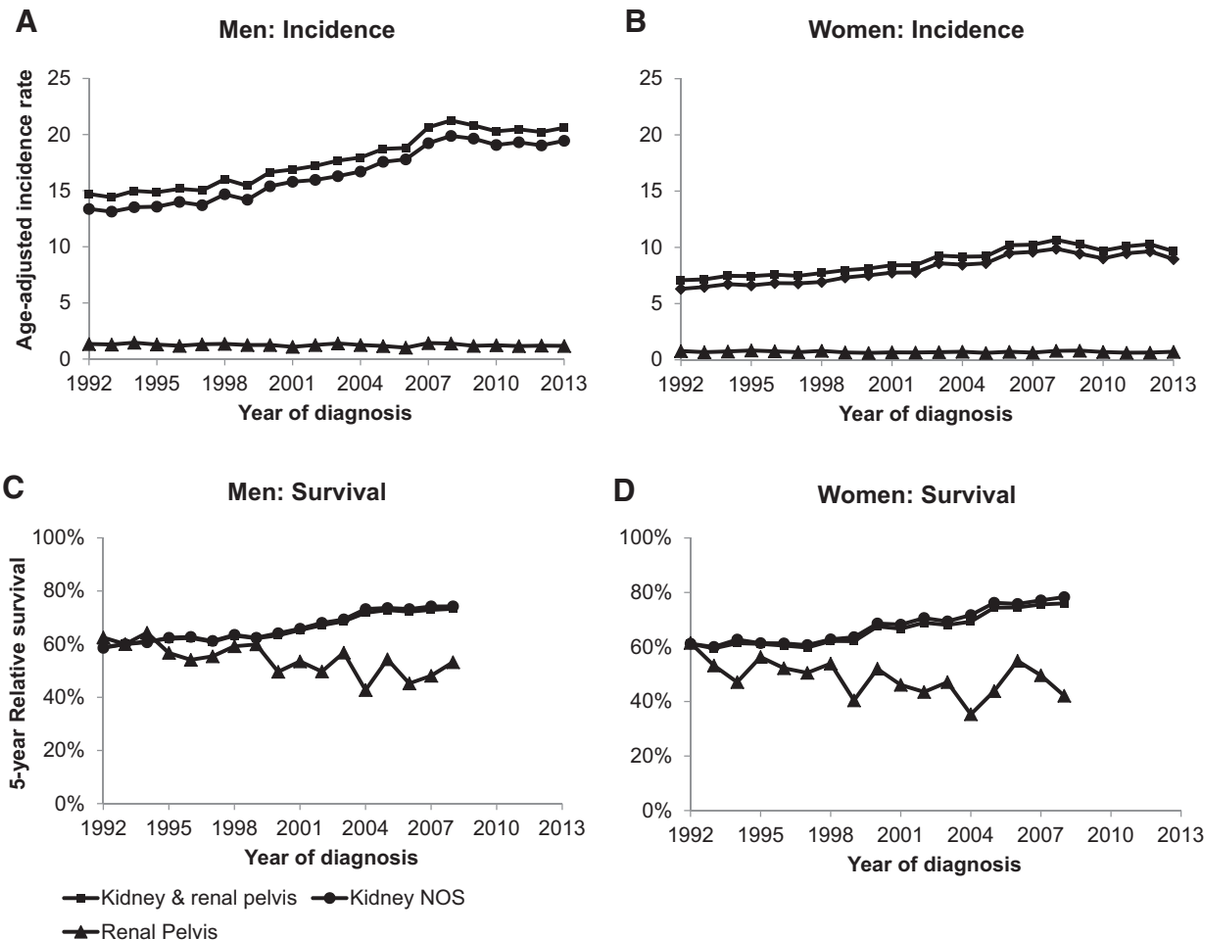

Figure 2.
Kidney and renal pelvis cancer age-adjusted incidence rates and 5-year relative survival for men and women.

is very high (Fig. 4); specifically, 99% in 2008 for men and 99.8% for women. However, survival from the other subtypes is poorer including a very poor survival from the anaplastic subtype (<10% five-year survival).

Discussion

For the 5 cancer sites presented in this report, the analysis by histologic or molecular subtype reveals important differences in incidence trends that are not apparent when only the anatomic site is considered. For example, triple-negative breast cancer occurs at a higher rate among black women than white women. Esophageal squamous cell carcinoma incidence rates decreased in men over time, as adenocarcinomas emerged to become the predominant esophageal cancer subtype among men in the mid-1990s. Similarly, the increasing incidence of papillary thyroid cancer explains almost the entire increase in thyroid cancer incidence.

Differences in survival also emerge when the subtypes are examined. Specifically, papillary thyroid cancer subtypes have favorable survival compared with less common subtypes of these anatomic sites. Patients with small cell carcinoma of the lung had worse survival than those diagnosed with squamous, adeno-, and other specified carcinomas of the lung. These results clearly illustrate the importance of providing data according to more clinically relevant categories for assessing risk and outcomes, as well as for investigating health disparities. These results can also inform areas of need for targeted drug development and highlight areas where orphan drugs may be required to improve survival for specific cancer subtypes.

Changes in risk factors over time may affect the incidence trends differentially by subtype. For example, tobacco smoking is most strongly related to squamous cell subtype of esophageal and lung cancer (22–24). The declining prevalence of smoking over time in the U.S. general population (25) may have contributed to the decreasing incidence in the squamous cell subtype of esophageal and lung cancer over time. However, changes in tobacco blends and inhalation depth may be resulting in increasing peripheral adenocarcinomas of the lung (26–28). Thus, the reporting by subtype is necessary to connect risk factor behavior in the population with clinical awareness and surveillance.

Cancers associated with excess weight such as adenocarcinoma of the esophagus, kidney cancer, and postmenopausal

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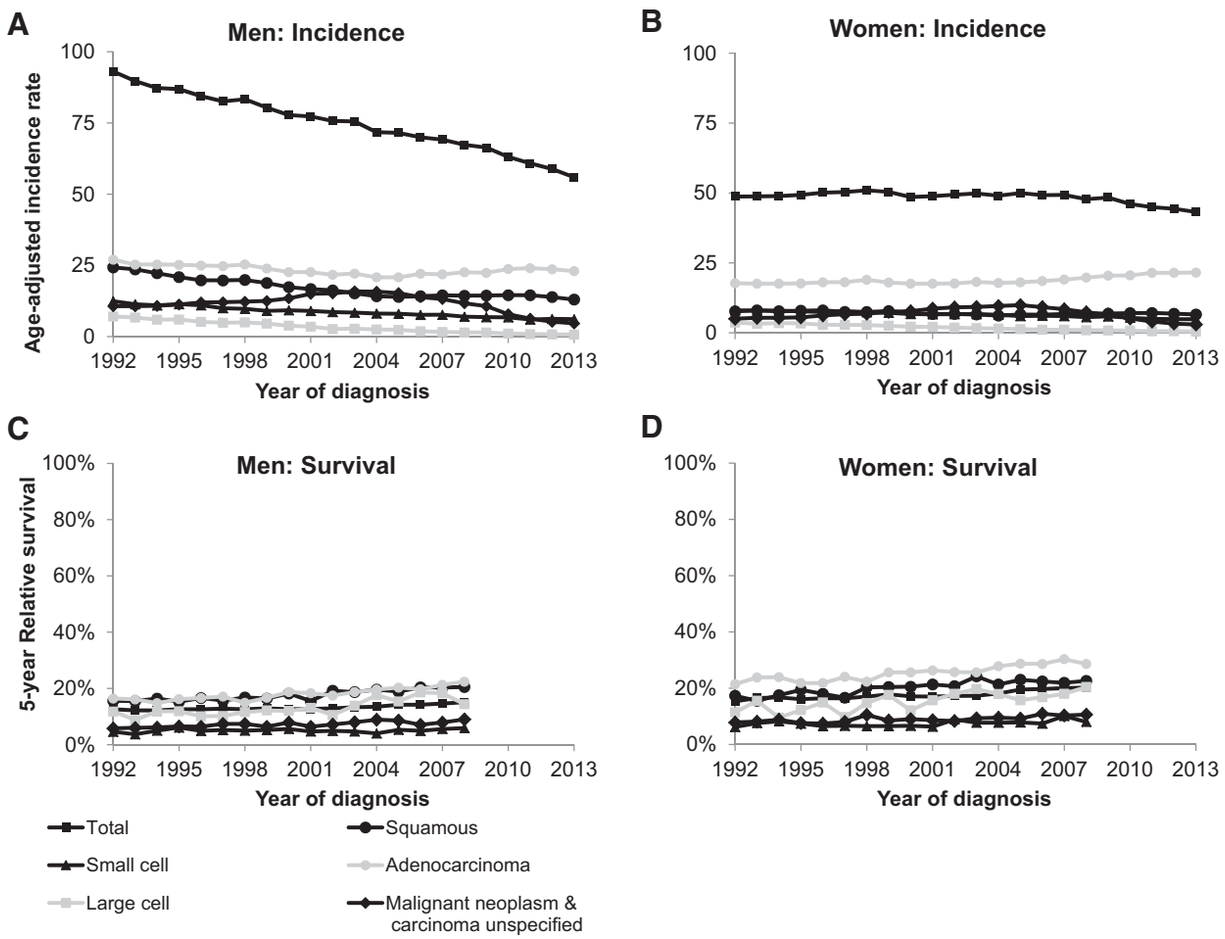

Figure 3.
Lung and bronchus cancer age-adjusted incidence rates and 5-year relative survival for men and women.

breast cancer (29, 30) showed increasing trends among both men and women. Some of the observed patterns may reflect an increase in the rates of overweight and obesity starting from the 1970s (31). The prevalence of overweight and obesity has slowed since 2000 (32) and may be leveling off in more recent years (33). While the trends for these cancers are influenced by other risk factors, the high prevalence of excess weight likely contributed to these increases (34).

Finally, cancer screening may differentially affect subtype detection. For example, HR^- breast cancers are twice as likely to be missed by mammographic screening compared with HR^+ breast cancers (6, 35). There are other risk factors such as reproductive history, lactation, weight, physical activity, and postmenopausal hormone use that could explain the apparent differences in breast cancer incidence rates (36). Papillary thyroid cancers are also differentially detected by screening compared with the other more fatal subtypes (37, 38). Also, some of the increasing rates in kidney cancer may be due to an increase in incidental diagnoses resulting from diagnostic imaging for other health conditions unrelated to symptoms of kidney cancer (39, 40). Risk factors are only one component contributing to changes in incidence rates over time. Improvements in screening methods and changes in screening behaviors as well as changes in disease classification or data collection procedures and delays in cancer reporting can also affect observed trends over time.

Our results illustrate the direction that population-based cancer surveillance must take to support contemporary cancer research and to provide the most informative information to both clinicians and patients. According to the classical paradigm of cancer surveillance, there are approximately 60 different organs where cancer could develop. More recently, it has been estimated that there are several hundred cancer subtypes. Our understanding of cancer diversity is almost certain to expand with discoveries based on proteomic, genomic, and methylomic characterization. The SEER cancer registry program recognizes the need to integrate these advances to support cancer research initiatives. This will enable estimation of the burden of specific cancer subtypes, disparities in the population, and the potential benefits of targeted therapies.

Strengths of the present study include the ability to examine long-term incidence and survival trends for cancer subtypes, including by age, race, and sex. However, there are also challenges, as we move to presenting data in more meaningful categories.

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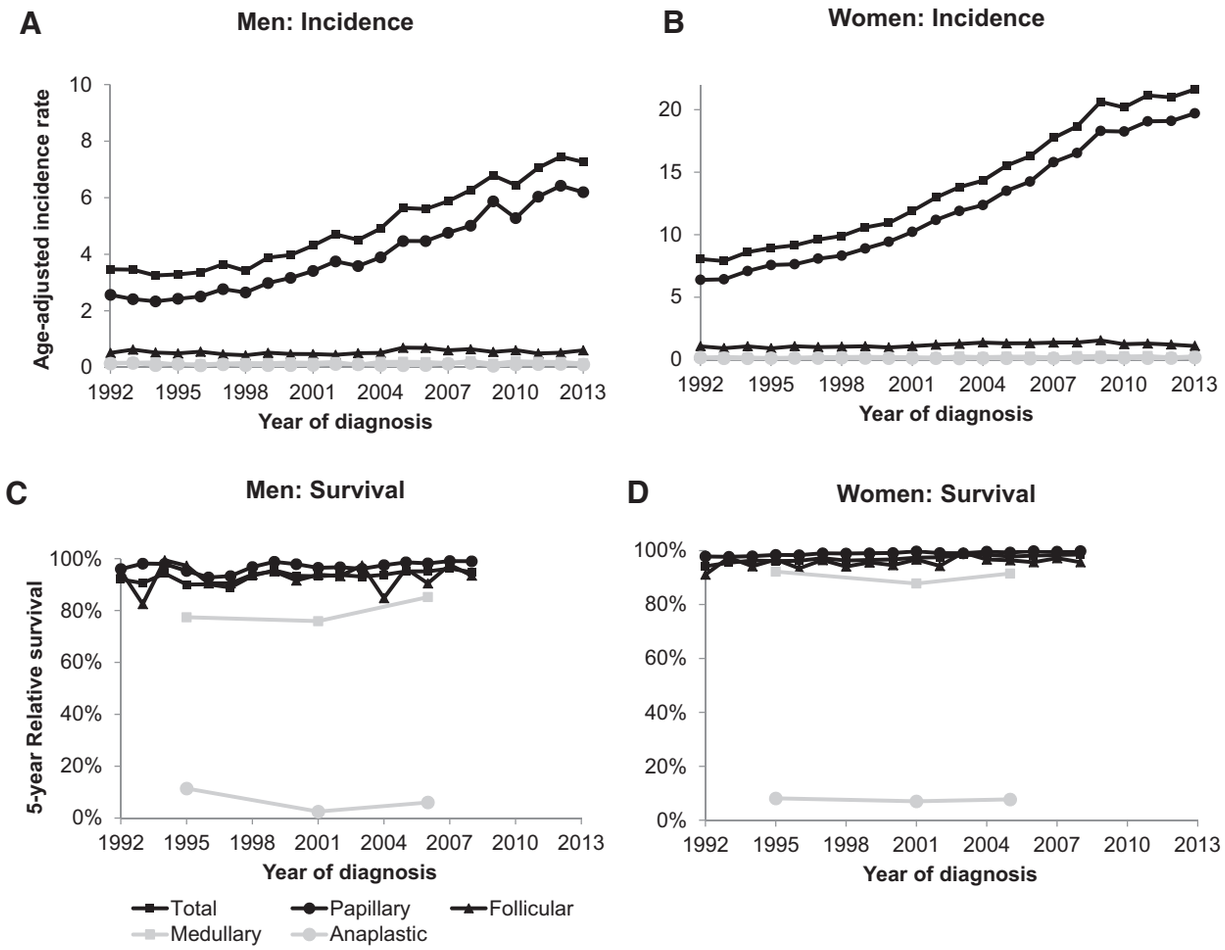

Figure 4.

Thyroid cancer age-adjusted incidence rates and 5-year relative survival over time by subtype for men and women. Survival estimates for medullary and anaplastic are based on 5-year groups (1992–1998, 1999–2003, 2004–2008).

These challenges will require both a clear understanding of the data collected including how it changes over time and how the use and development of new methods for surveillance affect the data. For example, cases can be assigned to different histology codes over time on the basis of new biologic knowledge and these changes can complicate the interpretation of trends. There have been changes in histology coding for lung cancer that affect trends by moving cases from one histologic subtype to another (24). Previous work has presented approaches to obtain consistent trends over time through grouping of codes (24) or through imputation (41, 42). These methods aim to prevent artificial changes in the trends over time created by coding changes. Researchers analyzing subtypes need to be familiar with the changes in histology classification over the time to ensure the proper interpretation of trends. As the classification of histologic codes in an analysis is at the discretion of the authors, it is of upmost importance that when publishing results by histologic subtype that the definitions are clearly reported so that the results can be compared across studies.

Other potential challenges are that certain cases that have not been microscopically confirmed and cannot be classified into a histologic subtype and cases that are microscopically confirmed but are a nonspecific histology and therefore excluded from this analysis. The proportion of cases not microscopically confirmed is small for esophageal and thyroid cancer (<4%) and moderate for kidney and lung cancer (10% each); however, these proportions are stable over time and so should not impact the trends. Similarly, the proportion of cases excluded from the analysis is small (<5%) and also stable over time.

In addition, even when microscopically confirmed, the information to define the subtype may be missing or unknown for some organ sites resulting in cases being excluded from the subtype analysis, particularly in the early years of reporting. In this analysis, the proportion of cases microscopically confirmed and excluded from the analysis is small (<5%) and also stable over time. One approach that has been used to address this issue is imputation of missing values (6, 7). When interpreting trends by subtype, the impact of cases unable to be categorized should be considered by either including the trend for unknown subtype or applying statistical methods such as imputation to assign cases to specific subtypes.

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Despite the challenges described above, presenting trends by more clinically relevant subcategories is useful to provide more detailed and meaningful information to patients, providers, and the public. This report highlights that for 5 cancer sites analysis by histologic or molecular subtype reveals different incidence and/or survival trends that are masked when only the generic organ site trends are considered. As precision medicine and targeted therapies are developed, it will be increasingly necessary to report population-based cancer rates and trends by clinically meaningful subgroups so that cancer incidence and outcomes remain relevant to patients and researchers.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: A.-M. Noone, K.A. Cronin, N. Howlader, D.R. Lewis, V.I. Petkov, L. Penberthy
Development of methodology: A.-M. Noone, S.F. Altekruse, V.I. Petkov
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S.F. Altekruse
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A.-M. Noone, K.A. Cronin, S.F. Altekruse, D.R. Lewis, L. Penberthy
Writing, review, and/or revision of the manuscript: A.-M. Noone, K.A. Cronin, S.F. Altekruse, N. Howlader, D.R. Lewis, V.I. Petkov, L. Penberthy
Study supervision: A.-M. Noone

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