

## Cancer Incidence and Mortality in the Oldest Old: a Nationwide Study in Finland

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Conflict of interest: none declared.

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This work was supported by a grant from Cancer Foundation Finland and Academy of Finland grant 312044 to the Center of Excellence in Tumor Genetics Research.

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## ABSTRACT

The world's population is aging rapidly. This study reports the burden of cancer in the oldest old ( $\geq 85$  years) in Finland in 1953-2017 and estimates age-specific cancer rates in the old population (65-99 years) in 1988-2017. The Finnish Cancer Registry provided data on all cancer diagnoses, cancer deaths and other deaths in cancer patients in Finland in 1953-2017. Between 1953-1957 and 2013-2017, the proportion of incident cancers in those aged  $\geq 85$  years increased from 1.5% to 9.6% (597 to 15,360 new cases), and in 2013-2017, more new cancers were diagnosed at age  $\geq 85$  years than age  $< 50$  years. Cancer incidence and excess mortality attributable to cancer peaked at age 85-94 years and declined subsequently, whereas cancer-specific mortality continued to increase or plateaued. Due to demographic changes, the number of new cancers in the oldest old has increased substantially in Finland, and currently, nearly one in 10 cancers are diagnosed in this age group. The increasing cancer burden in the oldest old poses a major challenge for healthcare and needs to be addressed in designing clinical research and reporting of cancer registries. In old populations with competing risks of death, we propose excess cancer mortality as a measure of cancer-related mortality.

Keywords: Aging, Neoplasms, Incidence, Mortality

Abbreviations: CI, confidence interval; FCR, Finnish Cancer Registry; RR, rate ratio.

Cancer is more common at old age than earlier in life. Populations are aging rapidly around the world, which has increased the number of older adults with cancer. People aged 85 years and older (85+) are known as the oldest old. In the World Population Prospects study, the number of people aged 85+ in the European region was projected to rise from 19 million in 2020 to 40 million by 2050, while the total population was expected to change only slightly (1).

Because of challenges in cancer surveillance and registration in very old people, few population-based studies have provided reliable estimates of cancer rates in the oldest old, and by convention, many studies have reported cancer statistics for age 85+ as a single age group. In the Nordic countries, approximately 8% of all new cancers, excluding non-melanoma skin cancers, occur in the oldest old (2) (<https://www.ancr.nu/>). Cancer incidence appears to increase until a peak age of 75-90 years and decline thereafter (3–5). Whether cancer mortality declines at very old age remains uncertain. In an international study of 16 countries, cancer mortality peaked and declined with age in 11 countries, while in some countries, cancer mortality increased through the oldest age groups (6).

This study reports the burden of cancer in the oldest old (85+) in Finland in 1953-2017 and provides estimates of age-specific cancer rates in the old population (age 65-99 years) in three recent decades (1988-1997, 1998-2007 and 2008-2017).

## METHODS

### Data sources

The Finnish Cancer Registry (FCR) registers data on Finnish residents with cancer or selected precancerous lesions. All Finnish residents have a unique personal identity code, which allows for linkage between various data sources and reliable follow-up of cancer patients. The FCR receives notifications from physicians, hospitals and pathology and hematology laboratories. Based on special legislation, institutions and personnel are obliged to report cancer cases without patient consent. The FCR has high coverage overall and covers at least 96% of solid and 86% of non-solid tumors diagnosed in Finland in 2009-2013 (7). In 1985-1988, more than 99% of solid tumors were recorded (8). Multiple primary tumors are registered according to coding guidelines presented in the International Classification of Diseases for Oncology, 3rd Edition (9). Extensions, recurrences or metastases of previously recorded primary cancers are not included as separate cases. The Population Register Centre continuously provides information on the vital status and place of residence of cancer patients. Causes of deaths for cancer patients are received electronically from Statistics Finland once per year.

The FCR provided nationwide data on all cancer diagnoses, cancer deaths and other deaths in cancer patients in Finland in 1953-2017. Non-melanoma skin cancers were excluded from all

analyses. The proportion of registered cancers based on death certificate only was higher at age 85+ (6.8% in 1998-2007 and 6.9% in 2008-2017) than at age <85 years (1.0% and 0.9%, respectively). Similarly, the proportion of cancers of unknown primary site was higher at age 85+ (6.6% in 1998-2007 and 5.0% in 2008-2017) than at age <85 years (2.2% and 1.6%, respectively). Cancer patients were followed from the date of cancer diagnosis until the date of death, date of emigration or December 31, 2017, whichever came first. Population counts and all-cause mortality rates were obtained from Statistics Finland.

### Statistical analysis

Crude numbers and proportions of incident cancers were calculated by age group (0-39, 40-84, 85+), 5-year calendar period and sex. Age-standardization of cancer incidence is described in Web Appendix 1. The median and 95<sup>th</sup> percentile of age at cancer diagnosis, together with 95% confidence intervals (CIs), were estimated using quantile regression.

To estimate age-specific cancer incidence and cancer-specific mortality in the old population, incident cancers, cancer deaths and follow-up time were stratified by age group (65-69, 70-74, ..., 95-99), 10-year calendar period and sex. Data for the three oldest age groups (85-89, 90-94 and 95-99) were scarce before the 1980s, and therefore, period-specific cancer rates were analyzed in the three most recent decades. Because cancer-specific mortality is sensitive to misclassification of cause of death, we also studied excess mortality attributable to cancer (referred to as excess cancer mortality). Excess cancer mortality is defined as the excess number of deaths in cancer patients  $n(u - u^*)$  divided by the follow-up time in the total population  $N$ ,

where  $n$  is the follow-up time in the cancer population,  $u$  is the all-cause mortality rate in the cancer population and  $u^*$  is the all-cause mortality rate in the non-cancer population (10). To estimate excess cancer mortality, the number of deaths and follow-up time were stratified by one-year age group, calendar year and sex. Patients who died on the day of cancer diagnosis were included in the cancer population.

Age-period-cohort models, which allow age, calendar period and birth cohort to be analyzed as continuous variables, were used to describe the effect of age on cancer incidence (11). Details of the age-period-cohort models are given in Web Appendix 2.

Trends in cancer incidence and cancer-specific mortality in the oldest old were estimated in the three most recent study decades (1988-1997, 1998-2007 and 2008-2017). Age-standardization was based on the total follow-up time in each age group (85, 86, ..., 100+) over the entire 30-year-period (1988-2017). CIs of the age-standardized rate ratios (RRs) were based on an approximation described in reference 12. Poisson regression models adjusted for age group (85-89, 90-94, 95-99, 100+) were used to estimate log-linear period trends (RRs per 10-year increase) in 1988-2017.

Statistical analyses were performed using R 3.6.1 software (R Foundation for Statistical Computing, Vienna, Austria; <https://www.r-project.org>) with packages Epi 2.38, popEpi 0.4.7 and quantreg 5.51.

## RESULTS

### Age distribution of new cancer cases

1,144,704 new primary cancers, excluding non-melanoma skin cancers, had been registered in the FCR in 1953-2017. Of these, 73,619 (6.4%) had been diagnosed at age 85+. Between 1953-1957 and 2013-2017, the proportion of incident cancers diagnosed at age 85+ increased from 2.0% to 11% in females (398 to 8,886 in terms of new cases) and from 1.0% to 7.9% in males (199 to 6,474 in terms of new cases) (Table 1). For comparison, the number of cancers diagnosed before age 50 years in 2013-2017 was 9,187 (12%) in females and 5,496 (6.7%) in males. Between the same periods, age-standardized cancer incidence in the oldest old increased 1.5-fold in females (95% CI: 1.4, 1.7) and 2.4-fold in males (95% CI: 2.2, 2.6) (Web Table 1). The median age at cancer diagnosis increased from 62.3 to 68.4 years in females (difference, 6.1 years; 95% CI: 5.8, 6.4) and from 62.4 to 70.1 years in males (difference, 7.7 years; 95% CI: 7.4, 7.9), whereas the 95<sup>th</sup> percentile increased from 81.7 to 89.1 years in females (difference, 7.4 years; 95% CI: 7.1, 7.7) and from 79.8 to 86.9 years in males (difference, 7.1 years; 95% CI: 6.9-7.4).

### Age-specific cancer rates in the old population

Age-specific cancer rates in females and males aged 65-99 years in 1988-2017 are shown in Figure 1. Cancer incidence peaked at age 85-94 years in females and age 85-89 years in males and declined thereafter in both sexes. Estimates from age-period-cohort models were consistent with a peak and decline in age-specific cancer incidence regardless of whether the net drift

(+1.20% per year in females and +0.79% per year in males) was included in the period or cohort effect (Web Figure 1). Cancer-specific mortality continued to increase through the oldest age groups or possibly plateaued between age 90-94 and 95-99 years. Excess cancer mortality increased in parallel with cancer-specific mortality until age 85-89 years but declined after age 90-94 years in both sexes. With regard to calendar period, cancer-specific mortality and excess cancer mortality declined over time in most of the age groups.

#### Cancer incidence and cancer-specific mortality in the oldest old

To examine recent trends in cancer incidence and cancer-specific mortality in the oldest old (85+), we compared the two latest study decades (1998-2007 and 2008-2017; Figure 2). Detailed results for 1988-1997, 1998-2007 and 2008-2017 are shown in Web Tables 2-5. In 1998-2017, the oldest old population in Finland was followed for 2.06 million (M) person-years (females, 1.52 M; males, 0.54 M), during which 46,583 incident cancers and 35,985 cancer deaths were registered. The crude incidence of any cancer at age 85+ was 3,390 per 100,000 person-years in males and 1,854 per 100,000 person-years in females (age-standardized RR, 1.82; 95% CI: 1.78, 1.86), whereas the crude mortality from any cancer was 2,683 per 100,000 person-years in males and 1,409 per 100,000 person-years in females (age-standardized RR, 1.95; 95% CI: 1.90, 1.99). In females, the age-standardized incidence of any cancer remained constant between 1998-2007 and 2008-2017 (RR, 1.00; 95% CI: 0.98, 1.02), but the absolute number of incident cancers increased from 11,594 to 16,536. In males, the age-standardized incidence of any cancer decreased (RR, 0.91; 95% CI: 0.89, 0.94), but the absolute number of incident cancers increased from 7,170 to 11,283. Cancer-specific mortality decreased in both females (RR, 0.95; 95% CI:



0.92, 0.97) and males (RR, 0.91; 95% CI: 0.88, 0.94), but the absolute number of cancer deaths increased from 9,061 to 12,319 in females and from 5,700 to 8,905 in males.

Age-standardized cancer incidence increased significantly in both sexes for melanoma (RR, 1.45 in females and 1.86 in males); in females for breast (RR, 1.10), lung and trachea (RR, 1.28) and corpus uteri (RR, 1.24); and in males for brain (RR, 1.53). A significant decrease in the age-standardized cancer incidence was observed in both sexes for stomach (RR, 0.75 in females and 0.62 in males); in females for bladder and urinary tract (RR, 0.88), gallbladder and bile ducts (RR, 0.78), esophagus (RR, 0.73) and cervix uteri (RR, 0.72); and in males for prostate (RR, 0.71) and lip (RR, 0.65). The cancer-specific mortality rates for these sites changed in the same direction as the incidence rates or showed no significant change. Of the other cancer sites, age-standardized cancer mortality increased significantly for vulva (RR, 1.60) and decreased significantly for colon and rectum in females (RR, 0.92), thyroid gland in females (RR, 0.71) and gallbladder and bile ducts in males (RR, 0.74). Poisson model-based estimates (age-adjusted RRs per 10-year period increase) for 1988-2017 were largely consistent with the aforementioned trends (Web Tables 2-5).

## DISCUSSION

This register-based study of the entire population of Finland in 1953-2017 describes a substantial and increasing burden of new cancers in the oldest old (85 years and older), which is predominantly explained by the demographic changes of population aging and total population growth, but also by an increase in age-standardized cancer incidence especially in the earlier

decades. In 2013-2017, nearly one in 10 cancers in Finland were diagnosed at age 85+, which exceeded the number of cancers diagnosed before age 50 years. In 1953-1957, however, the oldest old accounted for only 1.5% of all new cancers. Among the oldest old, the majority of new cancers occurred in females who, in terms of person-time, outnumbered males by 2.8 to 1 in the two most recent decades.

Cancer incidence and excess mortality attributable to cancer increased through most of adulthood but declined after a peak age of 85-94 years. Because of limited life expectancy or poor general health, older patients and their physicians may choose to avoid burdensome diagnostic investigations, which may lead to detection bias and underestimation of cancer incidence. On the other hand, advanced age and comorbidities are associated with nonspecific presentations of cancers, which complicates diagnostic evaluation. Indications of diagnostic uncertainty in the oldest old were the relatively high proportions of cancers of unknown primary site and cancers registered by death certificate only (5.6% and 6.8% in the FCR in 1998-2017, respectively). If fatal cancers are less likely to remain undiagnosed than non-fatal cancers, it would be expected that measures of cancer-related mortality are less influenced by detection bias than cancer incidence. In old patients with comorbidities, however, it may be challenging to determine an unambiguous cause of death. In this setting, excess cancer mortality, which is not influenced by misclassification of cause of death, may be a better measure of cancer-related mortality than cancer-specific mortality (10). Excess cancer mortality may be underestimated if i) non-cancer mortality in persons with diagnosed cancer is lower than in those without diagnosed cancer, ii) cancer patients with increased mortality risk are incompletely registered or iii) missing dates of

death or emigration in cancer patients lead to overestimation of follow-up time in the cancer population.

In addition to the methodological limitations, biological factors may contribute to the decline in cancer incidence and excess cancer mortality in those aged 95 years and older - a strongly selected population due to the healthy survivor effect, which may be explained by healthy lifestyle habits and environments, as well as low susceptibility to major diseases such as cancer. It has been suggested that age-related biological processes such as cellular senescence may reduce cancer risk in the very old, but there is only limited evidence of such mechanisms (13).

Global life expectancy has increased from under 30 years in 1800 to 71 years in 2010-2015 (1,14). Early increases in life expectancy were mainly due to reductions in infant and child mortality, but since the mid-20th century, large gains in life expectancy have also come from reductions in death rates at older ages (15). In Finland between 1951-1955 and 2015-2017, life expectancy increased from 70 to 84 years in females and from 63 to 79 years in males (16). Correspondingly, the proportion of people who reach age 85+ has increased over successive birth cohorts, and therefore, the population characteristics of the oldest old may have changed. Cancer incidence in men and women aged 85+ increased steadily in Finland in 1953-1987. The increase was larger for men than for women. This trend may reflect increased prevalence of risk factors (such as smoking, unhealthy diets, physical inactivity or obesity) in the oldest old, as well as improved diagnostics.

Cancer rates in the oldest old showed several trends that may have implications for cancer prevention and treatment. Cancers with increasing incidence in the oldest old included lung cancer in women and melanoma in both sexes. Smoking and ultraviolet radiation, the major risk factors for lung cancer and melanoma, respectively, should be considered as preventable causes of cancer in the oldest old. Breast cancer and cancer of the corpus uteri showed increasing incidence in the oldest old women. In postmenopausal women, obesity has been implicated as a risk factor for both breast and endometrial cancer, whereas hormone therapy with progestins is likely to increase the risk of breast cancer and decrease the risk of endometrial cancer (17–19). Vulvar cancer mortality and incidence increased, although only the increase in mortality was statistically significant. Chronic dermatoses such as lichen sclerosus are an important risk factor for vulvar cancer in older women. Also, reactivation of human papillomavirus has been described in older women, but the associated cancer risk is unknown (20). Primary brain tumors, excluding meningeal tumors, showed a recent increase in incidence and mortality in the oldest old men but not in women, a disparity that requires further investigation.

In the next few decades, population aging has been projected to continue at a rapid rate in both developed and developing countries (1). The oldest old are heterogeneous in health status, but many have comorbidities, functional disabilities, cognitive impairment and poor nutritional status that put them at high risk of complications from cancer and its treatment. For these vulnerable patients, it may be particularly difficult to establish a treatment plan that avoids both undertreatment and overtreatment. To respond to these challenges, we need a sufficient number of trained professionals in geriatric oncology and related specialties (21). Moreover, older patients have been underrepresented in clinical trials, which has led to a relative lack of

evidence-based treatment recommendations and uncertainty in extrapolating treatment effects from younger patients (22). Therefore, there is an increasingly urgent need for clinical research that takes into account the current and anticipated age distribution of cancer patients.

The burden of cancer in the oldest old has increased substantially, which is expected to reflect a global trend in the coming decades. This needs to be addressed in the planning of healthcare resources and services, education of specialists, designing clinical research and standard reporting of cancer registries. In old populations with comorbidities and competing risks of death, excess cancer mortality may be a better measure of cancer-related mortality than cancer-specific mortality, which has been more commonly reported in the literature. The decline in cancer incidence and excess cancer mortality after a peak age of 85-94 years may be relevant for research on aging biology, but additional studies are required to determine how much of the decline is due to changes in diagnostics (detection bias) and in the prevalence of risk factors (healthy survivors).

## **ACKNOWLEDGMENTS**

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This work was supported by a grant from Cancer Foundation Finland and Academy of Finland grant 312044 to the Center of Excellence in Tumor Genetics Research.

Conflict of interest: none declared.

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**Table 1.** Number of Incident Cancers by Age (Years), Period and Sex in Finland in 1953-2017 (Total, 1,144,704 New Primary

Period	Females								Males							
	0-39		40-64		65-84		85+		0-39		40-64		65-84		85+	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1953-1957	1,804	9.1	9,466	47.9	8,109	41.0	398	2.0	1,428	7.2	10,176	51.3	8,034	40.5	199	1.0
1958-1962	1,892	8.6	10,339	46.9	9,285	42.1	530	2.4	1,479	6.5	11,520	50.3	9,562	41.7	345	1.5
1963-1967	1,936	7.9	11,299	46.0	10,599	43.2	726	3.0	1,549	6.0	12,409	48.0	11,431	44.3	440	1.7
1968-1972	1,997	7.3	12,069	43.9	12,496	45.4	953	3.5	1,686	5.7	13,206	44.3	14,346	48.1	597	2.0
1973-1977	2,195	7.0	12,524	40.2	15,155	48.6	1,283	4.1	1,790	5.5	12,736	39.2	17,123	52.8	801	2.5
1978-1982	2,607	7.2	13,385	36.7	18,558	50.9	1,883	5.2	1,974	5.4	12,670	34.9	20,550	56.6	1,108	3.1
1983-1987	2,948	7.1	14,622	35.0	21,275	51.0	2,876	6.9	2,161	5.5	13,471	34.2	22,134	56.2	1,590	4.0
1988-1992	2,992	6.4	17,085	36.5	23,177	49.5	3,536	7.6	2,118	5.1	13,604	32.8	23,704	57.1	2,062	5.0
1993-1997	3,153	6.0	19,709	37.6	24,960	47.6	4,626	8.8	2,143	4.4	14,847	30.2	29,132	59.2	3,083	6.3
1998-2002	3,142	5.5	22,548	39.4	26,221	45.8	5,384	9.4	2,208	3.9	17,526	31.3	32,857	58.6	3,455	6.2
2003-2007	2,998	4.8	25,304	40.5	28,034	44.8	6,210	9.9	2,348	3.5	22,450	33.6	38,289	57.3	3,715	5.6
2008-2012	3,106	4.4	27,575	39.4	31,705	45.3	7,650	10.9	2,523	3.5	23,792	32.9	41,144	56.9	4,809	6.7
2013-2017	3,736	4.8	27,235	34.8	38,473	49.1	8,886	11.3	2,820	3.5	22,328	27.3	50,104	61.3	6,474	7.9

<sup>a</sup> Proportions are shown for each period and sex.

Cancers)<sup>a</sup>

ORIGINAL UNEDITED MANUSCRIPT

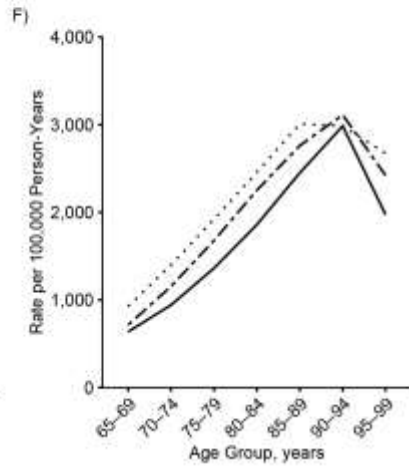
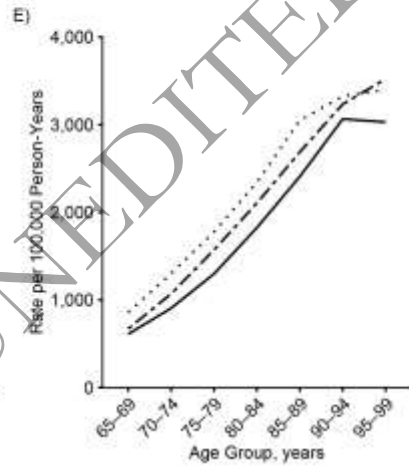
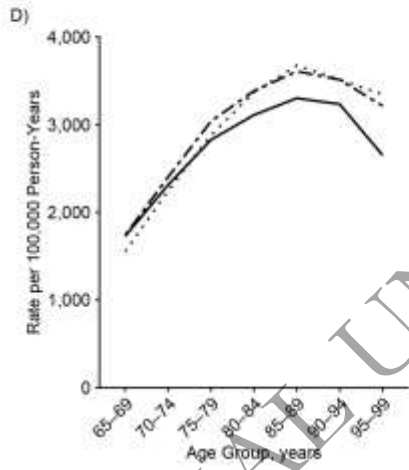
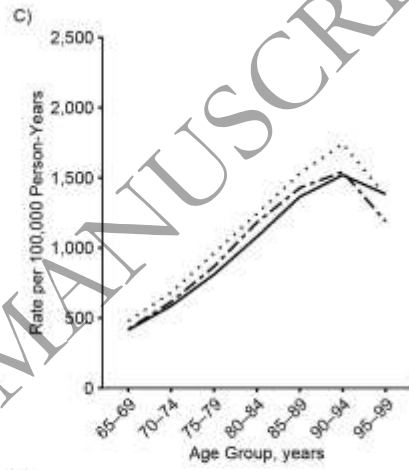
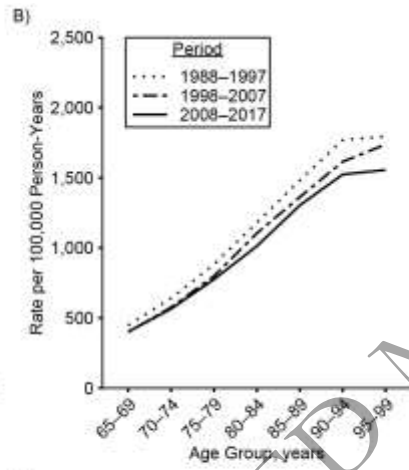
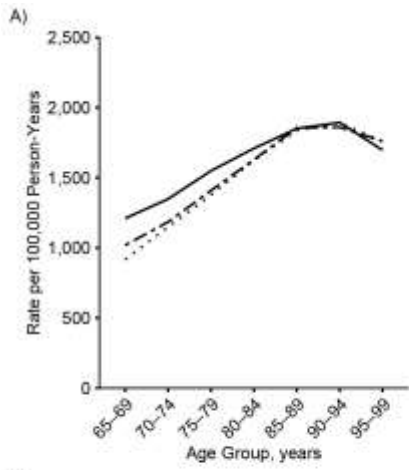
## FIGURE LEGENDS

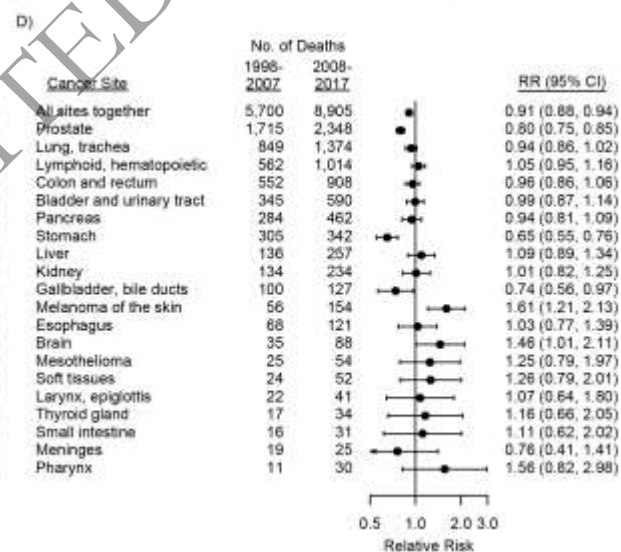
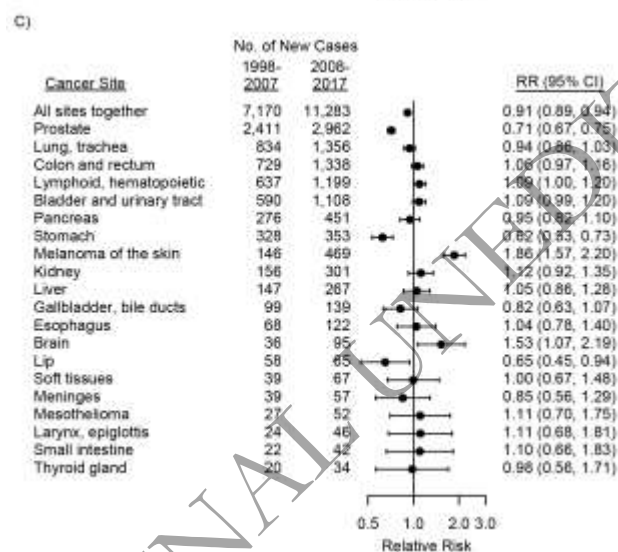
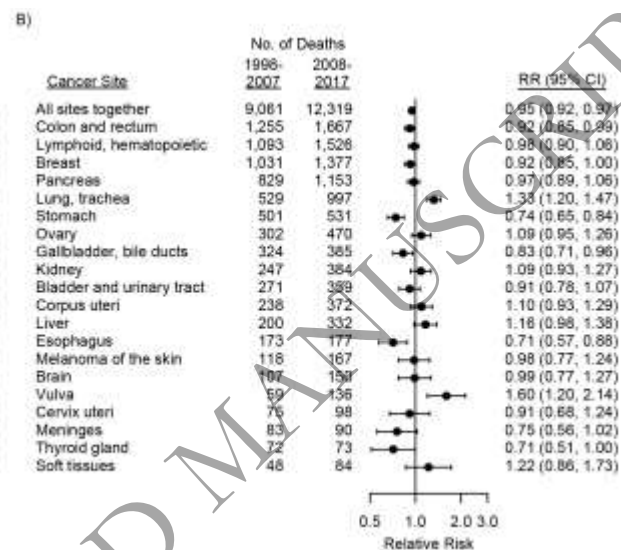
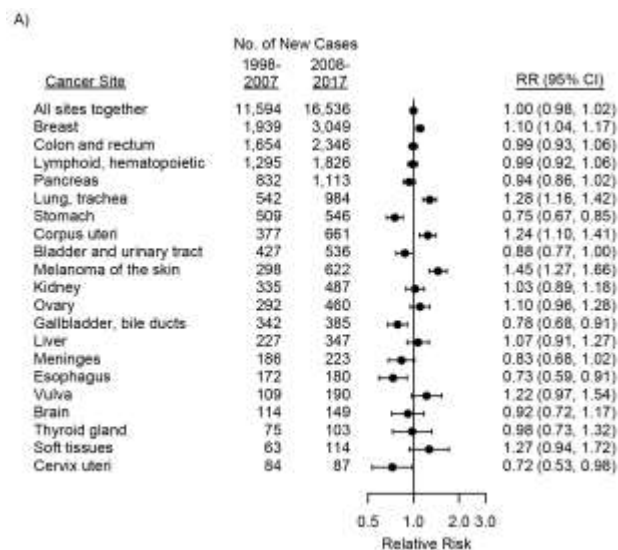
**Figure 1.** Age-specific cancer rates in females and males aged 65-99 years in Finland in 1988-2017. Non-melanoma skin cancers were excluded. A, cancer incidence in females; B, cancer-specific mortality in females; C, excess cancer mortality in females; D, cancer incidence in males; E, cancer-specific mortality in males; and F, excess cancer mortality in males.

**Figure 2.** Trends in cancer incidence and cancer-specific mortality in females and males aged  $\geq 85$  years in Finland between 1998-2007 and 2008-2017. The reference period for age-standardized rate ratios (RRs) was 1998-2007. A, cancer incidence in females; B, cancer-specific mortality in females; C, cancer incidence in males; and D, cancer-specific mortality in males. 20 cancer sites with highest incidence (panels A and C) and highest cancer-specific mortality (panels B and D) are shown. Horizontal bars indicate 95% confidence intervals (CIs).

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