Associations between first and second primary cancers: a population-based study

Sune F. Nielsen PhD, Børge G. Nordestgaard MD DMSc, Stig E. Bojesen MD PhD

See related commentary by Winget and Yasui at www.cmaj.ca/lookup/doi/10.1503/cmaj.111424

Abstract

Background: Patients surviving certain types of cancer are at increased risk of a second primary cancer. We tested the hypothesis that excess risk of a second primary cancer is due mainly to excess risk of it being the same type of cancer as the first, rather than to excess risk of it being a different type.

Methods: We conducted a nationwide study using data from three dabatases for the entire Danish population (n = 7 493 705) from 1980 through 2007. For each type of cancer, we performed a nested study matching each patient with incident cancer diagnosed in that period with up to five controls who did not have the examined cancer at the time of diagnosis. We used Cox regression models to calculate individual risk estimates and meta-analysis techniques to calculate aggregated risk estimates.

Results: A total of 765 255 people had one or more diagnoses of primary cancer (total 843 118 diagnoses) during the study period. The aggregated hazard ratio (HR) for risk of any second primary cancer after any first cancer was 1.25 (95% confidence interval [CI] 1.24–1.26), with heterogeneity among cancer types. The aggregated HR for risk of a second primary cancer of the same type as the first was 2.16 (95% CI 1.98–2.34). The aggregated HR for risk of a second cancer of a different type from the first was 1.13 (95% CI 1.12–1.15). Results were similar when we excluded second primary cancers occurring within 1, 2, 5 or 10 years after the first cancer. Overall, we observed 74 significant associations among 27 types of first cancer and 27 possible types of second primary cancer.

Interpretation: Excess risk of a second primary cancer was due mainly to a 2.2-fold risk of the second cancer being the same type as the first, whereas the risk of it being a different type was only 1.1-fold. However, heterogeneity among cancer types was substantial.

Competing interests: Stig Bojesen has received research grants from the Danish Cancer Society. No competing interests declared by Sune Nielsen or Børge Nordestgaard.

This article has been peer reviewed.

Correspondence to:
Dr. Stig E. Bojesen,
stebo@heh.regionh.dk

***CMAJ* 2012. DOI:10.1503/cmaj.110167**

Second primary cancers are seen in 15% of cancer survivors, resulting in increased morbidity and mortality.[1] Overall, patients surviving certain types of cancer are at increased risk of a second primary cancer.[2–4] It is unclear, however, whether this excess risk is due mainly to excess risk of the second primary cancer being the same type as the first cancer, or to excess risk of it being a different type from the first. Clinically, this is an important question, because a clear answer may help target continued surveillance of patients with cancer for the development of second primary cancers.

Previously, the risk of second primary cancers was estimated through pair-wise examination of the risk of a specific second primary cancer following a specific first cancer[5–9] and in studies of the risk of a second cancer of the same type as the first.[10–13] We tested the hypothesis that excess risk of a second primary cancer is due mainly to excess risk of it being the same type of cancer as the first, rather than to excess risk of it being a different type. We studied the entire Danish population over a 28-year period using data from three national databases and calculated aggregated risk estimates across all cancer types and individual risk estimates for the different cancer types.

Methods

Study population

We reviewed data from three national databases for all people living in Denmark (about 7.5 million) from 1980 through 2007. We chose this study period because the three databases had complete data for that period. For baseline characteristics of the population, we used data from the national Danish Civil Registration System. This database records all births, immigrations, emigrations and deaths in Denmark through the civil registration number, which uniquely identifies each inhabitant of Denmark and includes information on age and sex. This database is

100% complete, that is, for practical purposes no one is lost to follow-up.

For other characteristics, we collected data from Statistics Denmark on ethnicity, highest obtained level of education and residence (size of city).

Cancer diagnoses

We identified people with incident cancer diagnosed from Jan. 1, 1980, to Dec. 31, 2007, using the national Danish Cancer Registry, which identifies 98% of all incident cancers in Denmark.[14] Since 1987, all doctors in hospitals and private practices are required by law to report all diagnoses of cancer to the registry. The only cancer screening program in Denmark was for cervical cancers, from 1998 to 2007. All diagnoses in the registry are assigned based on results of histologic examination by a fully trained pathologist. The registry uses a conservative strategy to avoid misclassification of relapse of the first cancer and records only true occurrence of a second primary cancer of the same type.[15]

We classified diagnoses according to the International Classification of Diseases (ICD) 7th edition codes 140.0–207.0 for the period 1980–2003, and ICD 10th edition codes C00.0–C96.0 and D00.0–D09.0 for the period 2004–2007 (Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.110167/-/DC1).

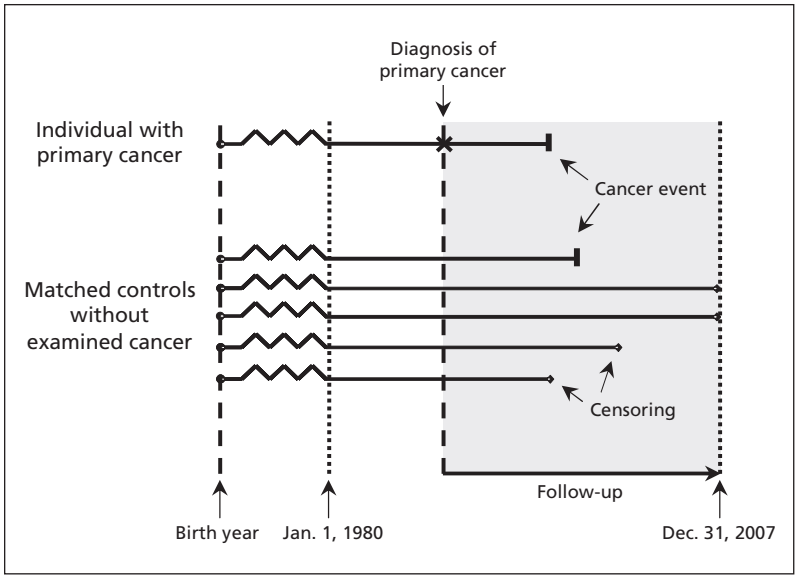

Figure 1: Follow-up of Danish population from 1980 through 2007 for diagnoses of primary cancers. Of 7 493 705 individuals, 765 255 received a diagnosis of one or more primary cancers during the study period, for a total of 843 118 cancer diagnoses. All analyses were based on nested studies, whereby each individual with cancer was matched (by birth year, sex, calendar period at risk and age at diagnosis) with up to five controls who, up until the time of matching, did not have the examined cancer. Four outcomes were possible for both cancer patient and controls: diagnosis of a primary cancer, censoring because of death, censoring because of emigration, and end of follow-up (here illustrated for the controls).

Statistical analysis

All analyses were performed on data for individual participants. All tests were two-sided. We calculated age-standardized incidence rates according to the World Health Organization world standard population.[16] We used Wald tests and Cox regression models with delayed entry at age of diagnosis (left-truncated); Cox regression models were used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs) as a measure of relative risk. We used multivariable models adjusted for age at diagnosis, date of birth, sex, ethnicity, highest obtained level of education and residence. We assessed the assumption of proportional hazards over time graphically and detected no major violations.

All analyses were based on nested studies, whereby each person with cancer was matched (by sex, birth year, calendar period at risk and age at diagnosis of the cancer) with up to five randomly selected controls from the general population who did not have cancer of the same type as the patient's on the date the patient's cancer was diagnosed (but could have had another type of cancer) (Figure 1). The randomly selected control population could therefore differ from analysis to analysis. In all analyses, there was at least one control available for each patient, and no patients were excluded from the analysis. For each matched subset, follow-up of the patient and matched controls began on the date the patient's cancer was diagnosed and ended on the date of emigration, death, Dec. 31, 2007, or diagnosis of a primary cancer, whatever came first. Mortality was accounted for as a competing risk by censoring at date of death for individual participants (information that is 100% complete in Denmark).

We first examined the association between 27 types of cancers and increased risk of any second primary cancer. We used fixed-effect meta-analysis techniques for the individual HR estimates across the 27 cancer types to compute aggregated HR estimates. Because tobacco use is a common risk factor for several cancers, we also calculated aggregated HR estimates according to the relation of the first cancer to tobacco use (related, not related and relation uncertain).[17] Because protocols for treating cancer in children differ from those for treating cancer in adults, we also computed aggregated HR estimates according to whether the first cancer was diagnosed in childhood (< 14 years) or later. We measured heterogeneity among cancer types using the I^2 statistic.

Second, for each of the 27 types of cancer, we examined whether excess risk of a second pri-

mary cancer was due mainly to excess risk of the second cancer being the same type as the first cancer or to excess risk of it being a different type. We used fixed-effect meta-analysis techniques to compute aggregated estimates as described earlier.

Third, we performed sensitivity analyses to examine the potential influence of a relapse of the first cancer being erroneously diagnosed as a second primary cancer of the same type. We advanced the time at entry for patients and controls to 1, 2, 5 and 10 years after the diagnosis of the first cancer of the patient. We computed aggregated estimates as described earlier. In addition, we assessed associations between any of the 27 types of first cancer and any of the 27 types of second primary cancer, for 729 individual associations (minus 12 non-existent sex-specific associations). For these 717 associations, we report HRs with 95% CIs, and we indicate which HRs were significant after Bonferroni correction for multiple comparisons (i.e., $p < 0.05/717 = 0.00007$). Finally, using Poisson regression models, we estimated the absolute risk per 100 of a second primary cancer occurring within five years after diagnosis of the first cancer among both the patients and the controls.

Results

During the 28-year study period, the cohort included 7 493 705 people, with 143 million person-years of follow-up. A total of 765 255 individuals had one or more cancers during the study period, for a total of 843 118 diagnoses of cancer. The number of people with successive cancers and the median time between them are

Type/site of first cancer	No. with primary cancer during follow-up, *n/N*: People with cancer	Controls	HR (95% CI)
Hodgkin disease*	11/545	61/2 725	1.23 (0.64–2.35)
Small intestine*	149/2 103	1 651/10 515	1.52 (1.28–1.80)
Non-Hodgkin lymphoma*	159/4 101	939/20 505	1.47 (1.24–1.74)
Thyroid*	334/4 667	2 607/23 335	1.31 (1.17–1.47)
Sarcoma*	494/7 349	4 106/36 745	1.50 (1.36–1.64)
Testis*	544/7 753	1 928/38 765	1.71 (1.56–1.88)
Multiple myeloma*	473/8 505	6 773/42 525	1.16 (1.06–1.28)
Esophagus†	177/8 537	6 491/42 685	1.23 (1.05–1.43)
Larynx†	1 595/9 333	8 153/46 665	1.87 (1.77–1.97)
Liver†	246/13 254	11 049/66 270	1.52 (1.33–1.73)
Brain*	478/13 747	8 942/68 735	1.38 (1.25–1.51)
Kidney*	930/14 693	11 691/73 465	1.28 (1.19–1.36)
Pharynx†	2 339/17 063	12 664/85 315	1.81 (1.73–1.89)
Uterus	2 419/18 663	14 515/93 315	1.06 (1.01–1.10)
Stomach†	700/19 374	16 587/96 870	1.17 (1.08–1.26)
Leukemia*	1 543/19 991	14 008/99 955	1.66 (1.57–1.75)
Ovary*	1 174/20 085	14 175/100 425	1.16 (1.09–1.23)
Pancreas†	217/20 760	16 588/103 800	1.11 (0.97–1.28)
Melanoma*	3 283/25 222	14 307/126 110	1.42 (1.37–1.48)
Urinary†	2 569/25 310	21 990/126 550	1.39 (1.34–1.45)
Cervix†	3 863/44 495	18 461/222 475	1.34 (1.29–1.39)
Prostate	3 367/51 726	37 876/258 559	0.80 (0.77–0.83)
Breast	9 455/94 616	52 963/473 069	1.25 (1.23–1.28)
Colon*	7 391/96 284	70 332/481 418	1.09 (1.06–1.11)
Lung†	2 014/99 742	80 170/498 686	1.13 (1.08–1.19)
Skin*	22 358/135 858	83 427/679 149	1.31 (1.29–1.33)
Other*	1 059/15 844	12 164/79 220	1.44 (1.35–1.54)
Any first cancer (I^2 = 98.6%)			1.25 (1.24–1.26)
First cancer not related to tobacco use (I^2 = 99.6%)			1.09 (1.07–1.11)
*Relation of first cancer to tobacco use uncertain (I^2 = 96.5%)			1.25 (1.24–1.26)
†First cancer related to tobacco use (I^2 = 97.7%)			1.29 (1.26–1.32)
First cancer as child (< 14 yr) (I^2 = 0.0%)			7.16 (0.62–13.7)
First cancer as adult (≥ 14 yr) (I^2 = 98.3%)			1.27 (1.25–1.28)

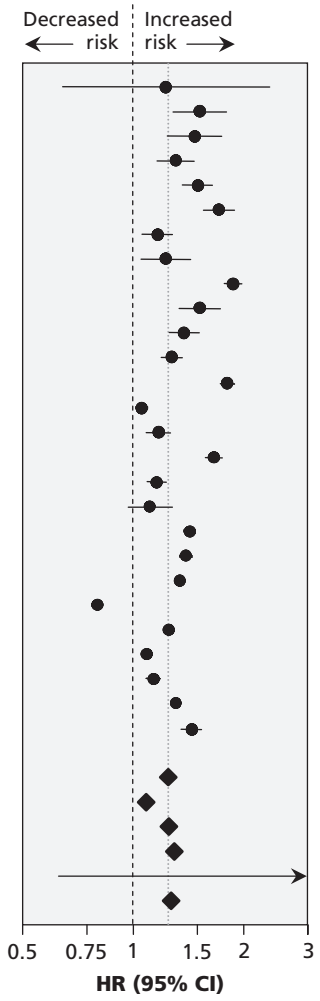

Figure 2: Risk of any second primary cancer after a first primary cancer, by type of first cancer. Hazard ratios (HRs) greater than 1.0 indicate an increased risk of a second primary cancer of any type. CI = confidence interval.

shown in Appendix 2. Age-standardized incidence rates and median age at diagnosis for the 27 cancer types are listed in Appendix 1. Baseline characteristics of the cohort and the 765 255 individuals with cancer are shown in Appendix 3. (The appendices are available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.110167/-/DC1).

Risk of second primary cancer

The risk of any type of second primary cancer after any type of first cancer varied from a reduced risk after prostate cancer (adjusted HR 0.80, 95% CI 0.77–0.83) to an increased risk after cancer of the larynx (adjusted HR 1.87, 95% CI 1.77–1.97) (Figure 2). The aggregated HR for risk of any second primary cancer after any first cancer was 1.25 (95% CI 1.24–1.26), with substantial heterogeneity among cancer types (I^2 = 98.6%). Figure 2 also shows the aggregated HR estimates according to whether the first cancer was related to tobacco use and whether the first cancer was diagnosed in childhood or later.

The risk of a second primary cancer of the same type as the first cancer was reduced after prostate cancer (adjusted HR 0.01, 95% CI 0.00–0.02) and was greatest after sarcoma (adjusted HR 17.8, 95% CI 10.4–30.3) (Figure 3). The aggregated HR for risk of a second cancer of the same type as the first was 2.16 (95% CI 1.98–2.34) for any first cancer, with substantial heterogeneity among cancer types (I^2 = 100%).

The risk of a second primary cancer of a different type from the first cancer was reduced

Type/site of first cancer	No. with primary cancer during follow-up, *n/N*: People with cancer	Controls	HR (95% CI)
Hodgkin disease*	0/545	0/2 725	Not estimable
Small intestine*	1/2 103	3/10 515	5.70 (0.56–57.5)
Non-Hodgkin lymphoma*	2/4 101	10/20 505	1.23 (0.27–5.65)
Thyroid*	8/4 667	9/23 335	5.65 (2.16–14.8)
Sarcoma*	43/7 349	21/36 745	17.8 (10.4–30.3)
Testis*	26/7 753	56/38 765	2.31 (1.45–3.69)
Multiple myeloma*	1/8 505	41/42 525	0.41 (0.06–3.02)
Esophagus†	2/8 537	56/42 685	1.32 (0.31–5.63)
Larynx†	63/9 333	74/46 665	7.33 (5.21–10.3)
Liver†	3/13 254	105/66 270	1.98 (0.60–6.47)
Brain*	18/13 747	80/68 735	4.32 (2.53–7.36)
Kidney*	5/14 693	108/73 465	0.70 (0.28–1.72)
Pharynx†	272/17 063	152/85 315	15.4 (12.6–18.8)
Uterus	8/18 663	353/93 315	0.14 (0.07–0.27)
Stomach†	13/19 374	259/96 870	1.43 (0.81–2.51)
Leukemia*	5/19 991	191/99 955	0.41 (0.17–0.99)
Ovary*	30/20 085	359/100 425	1.08 (0.74–1.57)
Pancreas†	3/20 760	273/103 800	1.18 (0.37–3.77)
Melanoma*	70/25 222	205/126 110	1.93 (1.47–2.54)
Urinary†	317/25 310	583/126 550	5.72 (4.97–6.58)
Cervix†	275/44 495	1 135/222 475	1.20 (1.05–1.37)
Prostate	3/51 726	4 763/258 630	0.01 (0.00–0.02)
Breast	1 625/94 616	7 498/473 080	1.40 (1.32–1.47)
Colon*	1 087/96 284	6 031/481 420	1.83 (1.72–1.95)
Lung†	166/99 742	7 047/498 710	0.96 (0.82–1.12)
Skin*	4 386/135 858	10 279/679 289	1.92 (1.85–1.99)
Other*	49/15 844	133/79 220	6.11 (4.37–8.55)
Any first cancer (I^2 = 100.0%)			2.16 (1.98–2.34)
First cancer not related to tobacco use (I^2 = 100.0%)			0.82 (0.77–0.87)
*Relation of first cancer to tobacco use uncertain (I^2 = 99.2%)			2.33 (2.03–2.63)
†First cancer related to tobacco use (I^2 = 99.3%)			2.77 (2.43–3.11)
First cancer as child (< 14 yr) (I^2 = 89.3%)			184.6 (0.00–389)
First cancer as adult (≥ 14 yr) (I^2 = 100.0%)			1.90 (1.73–2.07)

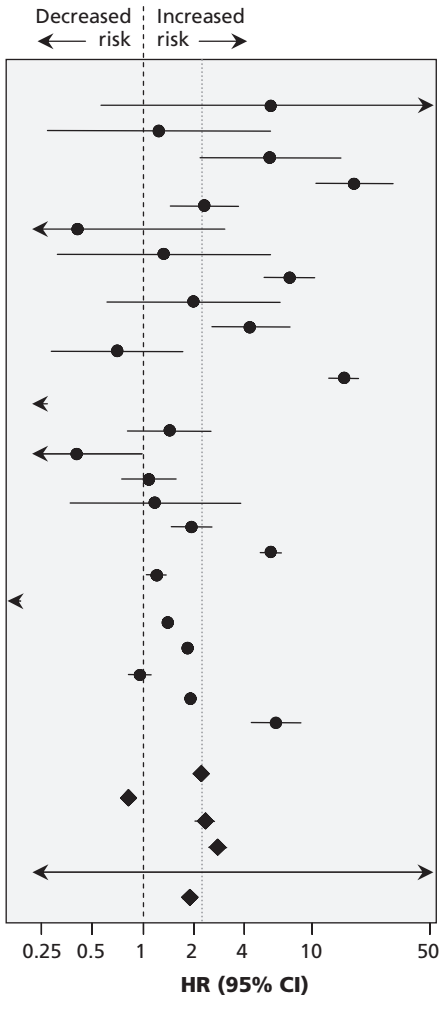

Figure 3: Risk of a second primary cancer of the same type as the first cancer, by type of first cancer. Hazard ratios (HRs) greater than 1.0 indicate an increased risk of a second primary cancer of the same type as the first. The number of controls for each type of cancer in Figures 3 and 4 do not necessarily add up to the number of controls in Figure 2, because the controls were randomly selected for each analysis. CI = confidence interval.

after prostate cancer (adjusted HR 0.79, 95% CI 0.77–0.82) and was greatest after cancer of the larynx (adjusted HR 1.78 (1.68–1.88) (Figure 4). The aggregated HR for risk of a second cancer of a type different from the first was 1.13 (1.12–1.15) for any first cancer, with substantial heterogeneity among cancer types (I^2 = 98.4%).

Sensitivity analyses

In our sensitivity analyses of the potential influence of a relapse being erroneously diagnosed as a second primary cancer of the same type, we found that the results were similar to those of the main analyses when we excluded second primary cancers occurring within 1, 2, 5 and 10 years after the first cancer (Table 1). The aggregated HR estimates for risk of a second primary cancer of the same type as the first cancer increased slightly, from 2.16 (95% CI 1.98–2.34) without exclusion to 2.40 (95% CI 2.00–2.80) after exclusion of second cancers diagnosed within 10 years after the first cancer. The corresponding HRs for risk of a second primary cancer of a different type from the first cancer increased from 1.13 (95% CI 1.12–1.15) for any first cancer to 1.27 (95% CI 1.23–1.31).

When we assessed the association between any of the 27 first types of cancer with any of the 27 possible types of second primary cancer, we observed 74 significant associations ($p < 0.001$) after Bonferroni correction for multiple comparison (Table 2). Corresponding estimates of the five-year absolute risk per 100 among patients and controls are shown in Table 3.

Type/site of first cancer	No. with primary cancer during follow-up, *n/N*: People with cancer	Controls	HR (95% CI)
Hodgkin disease*	11/545	58/2 725	1.32 (0.69–2.54)
Small intestine*	148/2 103	1 605/10 515	1.56 (1.32–1.85)
Non-Hodgkin lymphoma*	157/4 101	1 058/20 505	1.28 (1.08–1.51)
Thyroid*	330/4 667	2 587/23 335	1.28 (1.14–1.44)
Sarcoma*	452/7 349	4 078/36 745	1.39 (1.26–1.53)
Testis*	519/7 753	1 981/38 765	1.59 (1.44–1.76)
Multiple myeloma*	472/8 505	6 731/42 525	1.19 (1.08–1.31)
Esophagus†	175/8 537	6 658/42 685	1.17 (1.00–1.36)
Larynx†	1 546/9 333	8 185/46 665	1.78 (1.68–1.88)
Liver†	243/13 254	10 912/66 270	1.54 (1.35–1.76)
Brain*	461/13 747	8 939/68 735	1.34 (1.22–1.48)
Kidney*	926/14 693	11 756/73 465	1.25 (1.17–1.34)
Pharynx†	2 106/17 063	12 813/85 315	1.59 (1.52–1.67)
Uterus	2 412/18 663	14 628/93 315	1.04 (1.00–1.09)
Stomach†	688/19 374	16 442/96 870	1.15 (1.07–1.25)
Leukemia*	1 539/19 991	14 173/99 955	1.65 (1.57–1.74)
Ovary*	1 148/20 085	14 248/100 425	1.12 (1.06–1.19)
Pancreas†	214/20 760	16 554/103 800	1.11 (0.96–1.27)
Melanoma*	3 230/25 222	14 118/126 110	1.42 (1.37–1.48)
Urinary†	2 287/25 310	21 827/126 550	1.24 (1.19–1.29)
Cervix†	3 621/44 495	18 541/222 475	1.25 (1.20–1.29)
Prostate	3 364/51 726	38 202/258 568	0.79 (0.77–0.82)
Breast	8 020/94 616	52 874/473 071	1.05 (1.02–1.07)
Colon*	6 460/96 284	69 749/481 412	0.95 (0.93–0.98)
Lung†	1 863/99 742	80 242/498 677	1.04 (0.99–1.09)
Skin*	18 896/135 858	83 081/679 159	1.09 (1.07–1.10)
Other*	1 016/15 844	12 120/79 220	1.38 (1.30–1.48)
Any first cancer (I^2 = 98.4%)			1.13 (1.12–1.15)
First cancer not related to tobacco use (I^2 = 99.0%)			0.97 (0.95–0.99)
*Relation of first cancer to tobacco use uncertain (I^2 = 97.9%)			1.16 (1.15–1.18)
†First cancer related to tobacco use (I^2 = 97.4%)			1.20 (1.17–1.23)
First cancer as child (< 14 yr) (I^2 = 0.0%)			5.86 (1.17–10.6)
First cancer as adult (≥ 14 yr) (I^2 = 98.3%)			1.17 (1.16–1.18)

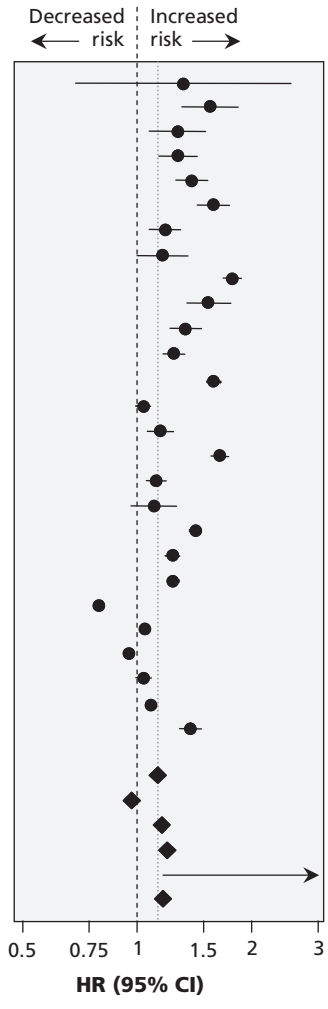

Figure 4: Risk of a second primary cancer of a different type from the first cancer. Hazard ratios (HRs) greater than 1.0 indicate an increased risk of a second primary cancer of a different type from the first. The number of controls for each type of cancer in Figures 3 and 4 do not necessarily add up to the number of controls in Figure 2, because the controls were randomly selected for each analysis. CI = confidence interval.

Interpretation

The principal finding of this nationwide study was that excess risk of a second primary cancer was due mainly to a 2.2-fold risk of the second cancer being the same type as the first, whereas the risk of it being a different type was only 1.1-fold.

For each of the significant associations we observed between the 27 types of first cancer and the 27 possible types of second primary cancer, three possible explanations need to be considered. First, the characteristics of the individual patient in terms of genetic and lifestyle risk factors may predispose the person to both cancer types. For example, the increased risk of a second primary cancer in the thyroid or other endocrine glands after a first thyroid cancer may be due to the known clustering of multiple endocrine neoplasia. Second, the characteristics of ascertainment (i.e., diagnostic procedures) may have been a factor. Some diagnostic or monitoring examinations for one type of cancer may influence the likelihood of detecting another type of cancer. The third possible explanation relates to the characteristics of treatment of the first cancer. Surgical removal of the whole or major parts of the affected organ would tend to reduce the risk of a second primary cancer of the same type as the first, whereas chemotherapy and radiation therapy may increase the risk of a second primary cancer of the same or different type as the first.

The lack of detail in the available registry data prohibited us from determining which mechanisms played a role in the individual associations between first and second primary cancers. Nonetheless, the striking contrast between the 2.2-fold increased risk of a second primary cancer being the same type as the first and the 1.1-fold increased risk of it being different from the first cancer suggests that characteristics of the individual patient were involved. Thus, the risk of a second primary cancer seems to be specific to cancer type and is probably driven by the patient's genetic and lifestyle risk factors.

Table 1: Sensitivity analyses of duration between first and second cancer*

	Characteristic of primary cancer; HR* (95% CI)					
Sensitivity analysis	Any first cancer	Unrelated to tobacco use	Relation to tobacco use uncertain	Related to tobacco use	Diagnosed in childhood (< 14 yr)	Diagnosed in adulthood (≥ 14 yr)
Risk of any second primary cancer						
Period of exclusion, yr						
No exclusion	1.25 (1.24–1.26)	1.09 (1.07–1.11)	1.25 (1.24–1.26)	1.29 (1.26–1.32)	7.16 (0.62–13.7)	1.27 (1.25–1.28)
1	1.28 (1.26–1.30)	1.14 (1.12–1.16)	1.32 (1.31–1.34)	1.32 (1.27–1.36)	5.99 (2.49–9.51)	1.28 (1.27–1.30)
2	1.31 (1.29–1.33)	1.17 (1.15–1.20)	1.34 (1.32–1.36)	1.34 (1.29–1.39)	7.18 (0.86–13.5)	1.31 (1.29–1.33)
5	1.35 (1.33–1.39)	1.26 (1.23–1.29)	1.38 (1.36–1.41)	1.39 (1.32–1.46)	5.71 (1.67–9.74)	1.36 (1.33–1.38)
10	1.38 (1.34–1.43)	1.31 (1.26–1.37)	1.43 (1.39–1.48)	1.36 (1.25–1.46)	4.96 (1.35–8.57)	1.38 (1.34–1.43)
Risk of same second primary cancer						
Period of exclusion, yr						
No exclusion	2.16 (1.98–2.34)	0.82 (0.77–0.87)	2.33 (2.03–2.63)	2.77 (2.03–2.63)	184 (0.00–389)	1.90 (1.73–2.07)
1	2.25 (2.00–2.50)	1.23 (1.16–1.30)	2.28 (1.88–2.68)	2.68 (2.22–3.15)	82.4 (0.00–221)	2.21 (1.90–2.53)
2	2.28 (1.91–2.64)	1.24 (1.17–1.32)	2.22 (1.66–2.80)	2.85 (2.21–3.49)	110 (0.00–322)	2.14 (1.83–2.44)
5	2.58 (2.09–3.05)	1.25 (1.16–1.34)	2.49 (1.72–3.27)	3.35 (2.54–4.16)	528 (0.0–3407)	2.59 (2.11–3.07)
10	2.40 (2.00–2.80)	1.60 (1.44–176)	2.11 (1.58–2.64)	3.22 (2.35–4.09)	–	2.50 (1.94–3.06)
Risk of different second primary cancer						
Period of exclusion, yr						
No exclusion	1.13 (1.12–1.15)	0.97 (0.95–0.99)	1.16 (1.15–1.18)	1.20 (1.17–1.23)	5.86 (1.17–10.6)	1.17 (1.16–1.18)
1	1.19 (1.17–1.20)	1.05 (1.03–1.07)	1.19 (1.18–1.21)	1.26 (1.22–130)	4.25 (1.60–6.89)	1.18 (1.17–1.20)
2	1.21 (1.19–1.23)	1.07 (1.05–1.09)	1.22 (1.19–1.23)	1.28 (1.23–1.33)	4.73 (1.88–7.59)	1.21 (1.19–1.22)
5	1.25 (1.23–1.28)	1.14 (1.11–1.17)	1.25 (1.23–1.28)	1.32 (1.25–1.38)	5.01 (0.0–10.9)	1.25 (1.22–1.27)
10	1.27 (1.23–1.31)	1.17 (1.11–1.22)	1.29 (1.12–1.33)	1.31 (1.20–1.41)	4.49 (0.37–8.62)	1.26 (1.23–1.31)

Note: CI = confidence interval, HR = hazard ratio.
*Values are based on fixed-effects aggregated HRs as in Figures 2, 3 and 4. Estimates were computed by excluding second primary cancers diagnosed 1, 2, 5 or 10 years after the diagnosis of the first primary cancer.

Table 2: Relative risk of second primary cancer after first cancer in Danish population, 1980–2007* (part 1 of 3)

Type/site of first cancer	Hodgkin disease	Small intestine	Non-Hodgkin lymphoma	Thyroid	Sarcoma	Testis	Multiple myeloma	Esophagus	Larynx	Liver	Brain	Kidney	Pharynx	Uterus	Stomach	Leukemia	Ovary	Pancreas	Melanoma	Urinary	Cervix	Prostate	Breast	Colon	Lung	Skin	Other
Hodgkin disease																											
HR	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	2.00	–	1.53	0.75	–
95% CI low	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0.19	–	0.12	0.09	–
95% CI high	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	21.5	–	18.9	6.08	–
Small intestine																											
HR	–	5.70	1.36	2.16	6.41	–	–	1.80	–	2.47	1.62	0.52	–	2.30	1.25	2.13	1.99	**3.88**	–	–	0.54	0.80	1.06	2.24	1.26	0.86	2.66
95% CI low	–	0.56	0.16	0.26	2.33	–	–	0.41	–	0.93	0.37	0.07	–	0.79	0.38	0.83	0.70	2.01	–	–	0.07	0.38	0.52	1.49	0.75	0.52	0.92
95% CI high	–	57.6	11.3	17.7	17.6	–	–	7.94	–	6.53	7.02	3.87	–	6.67	4.06	5.47	5.70	7.46	–	–	4.06	1.72	2.19	3.36	2.10	1.43	7.70
Non-Hodgkin lymphoma																											
HR	–	–	1.23	4.00	2.03	–	1.67	–	0.76	–	–	4.03	1.19	0.85	–	2.10	–	1.41	1.08	0.37	1.52	0.64	1.06	1.55	1.98	1.57	2.54
95% CI low	–	–	0.27	0.97	0.43	–	0.36	–	0.10	–	–	1.50	0.14	0.11	–	0.78	–	0.42	0.24	0.05	0.33	0.29	0.52	0.87	1.18	1.03	0.83
95% CI high	–	–	5.65	16.5	9.55	–	7.76	–	5.94	–	–	10.8	9.83	6.74	–	5.62	–	4.77	4.80	2.72	7.06	1.37	2.15	2.74	3.32	2.40	7.76
Thyroid																											
HR	–	1.39	–	5.65	–	–	2.22	2.49	1.68	0.31	1.44	2.87	2.08	1.35	–	1.94	1.97	–	1.34	0.55	1.63	0.79	1.23	1.17	1.30	1.23	0.73
95% CI low	–	0.17	–	2.16	–	–	0.84	0.93	0.57	0.04	0.60	1.54	1.01	0.71	–	1.04	1.04	–	0.72	0.20	0.98	0.41	0.91	0.81	0.92	0.93	0.26
95% CI high	–	11.5	–	14.8	–	–	5.86	6.61	4.94	2.25	3.44	5.34	4.30	2.57	–	3.63	3.72	–	2.47	1.50	2.71	1.49	1.67	1.71	1.83	1.63	2.01
Sarcoma																											
HR	–	4.72	1.28	1.36	**17.8**	2.60	2.54	1.76	0.27	1.10	2.02	1.64	1.23	0.75	0.64	1.99	1.40	1.27	1.81	0.43	0.24	0.93	1.46	1.38	1.23	**1.72**	–
95% CI low	–	1.22	0.45	0.31	10.5	0.86	1.29	0.69	0.04	0.48	1.05	0.84	0.59	0.27	0.26	1.13	0.70	0.66	1.09	0.19	0.06	0.64	1.06	1.04	0.92	1.39	–
95% CI high	–	18.2	3.66	5.95	30.4	7.84	5.02	4.48	1.98	2.55	3.88	3.20	2.56	2.06	1.58	3.52	2.82	2.44	2.99	0.98	0.99	1.35	2.02	1.84	1.64	2.12	–
Testis																											
HR	8.76	–	1.79	2.52	2.53	2.31	0.54	2.27	0.81	1.99	1.33	2.16	1.04	–†	**3.72**	1.87	–†	1.42	1.39	2.11	–†	1.22	1.78	1.25	1.16	1.55	**3.93**
95% CI low	0.79	–	0.64	0.63	1.27	1.45	0.13	1.20	0.32	0.97	0.74	1.22	0.57	–†	2.27	1.08	–†	0.79	0.88	1.37	–†	0.88	0.18	0.91	0.87	1.24	2.37
95% CI high	96.8	–	5.02	10.1	5.04	3.69	2.29	4.30	2.05	4.08	2.39	3.85	1.87	–†	6.10	3.24	–†	2.56	2.21	3.25	–†	1.70	17.1	1.70	1.56	1.94	6.52
Multiple myeloma																											
HR	–	1.66	–	4.59	2.20	2.69	0.41	1.27	–	1.11	1.40	2.61	1.26	1.63	1.74	1.46	0.92	0.67	2.43	1.20	1.95	0.83	0.73	0.81	1.08	**1.58**	1.09
95% CI low	–	0.37	–	1.42	0.97	0.31	0.06	0.50	–	0.56	0.60	1.51	0.65	0.89	1.00	0.84	0.40	0.33	1.54	0.73	0.74	0.58	0.48	0.60	0.83	1.29	0.57
95% CI high	–	7.37	–	14.8	4.97	23.2	3.02	3.21	–	2.21	3.28	4.50	2.44	3.01	3.00	2.56	2.12	1.36	3.84	1.99	5.14	1.18	1.11	1.09	1.41	1.93	2.08
Esophagus																											
HR	–	5.91	–	5.10	–	–	–	1.32	2.82	1.39	0.47	0.76	**7.11**	1.29	0.54	0.93	1.15	0.71	0.89	0.57	2.10	0.95	–	0.83	1.42	0.76	0.73
95% CI low	–	1.49	–	1.10	–	–	–	0.31	1.16	0.50	0.06	0.18	4.27	0.30	0.13	0.34	0.28	0.22	0.28	0.21	0.48	0.57	–	0.51	0.97	0.48	0.17
95% CI high	–	23.4	–	23.6	–	–	–	5.63	6.86	3.90	3.50	3.16	11.8	5.52	2.21	2.55	4.79	2.28	2.85	1.57	9.23	1.58	–	1.36	2.08	1.20	3.03
Larynx																											
HR	–	1.73	2.38	0.67	1.75	–	–	**4.27**	**7.33**	1.37	–	1.06	**4.75**	0.89	1.04	1.05	1.42	1.62	0.85	**1.72**	2.07	0.77	1.10	1.30	**3.42**	**1.46**	1.20
95% CI low	–	0.66	1.19	0.16	0.96	–	–	3.09	5.21	0.87	–	0.68	3.75	0.38	0.70	0.68	0.77	1.13	0.49	1.34	1.02	0.63	0.79	1.10	3.07	1.27	0.77
95% CI high	–	4.52	4.78	2.82	3.19	–	–	5.91	10.31	2.14	–	1.65	6.03	2.07	1.56	1.60	2.63	2.33	1.48	2.20	4.21	0.95	1.54	1.54	3.80	1.68	1.85
Liver																											
HR	–	**12.5**	2.07	3.46	1.73	5.69	0.62	1.72	1.30	1.98	–	2.34	2.15	0.32	1.35	1.29	3.56	**10.2**	0.31	0.68	–	0.57	0.90	1.13	1.46	0.68	–
95% CI low	–	3.82	0.28	0.77	0.40	0.66	0.08	0.53	0.31	0.60	–	1.12	0.94	0.04	0.59	0.52	1.83	7.48	0.04	0.25	–	0.29	0.52	0.74	1.00	0.43	–
95% CI high	–	40.9	15.3	15.6	7.50	48.7	4.49	5.55	5.44	6.47	–	4.90	4.93	2.31	3.09	3.20	6.93	14.0	2.21	1.86	–	1.11	1.58	1.72	2.13	1.06	–

Table 2: Relative risk of second primary cancer after first cancer in Danish population, 1980–2007* (part 2 of 3)

Type/site of first cancer	Hodgkin disease	Small intestine	Non-Hodgkin lymphoma	Thyroid	Sarcoma	Testis	Multiple myeloma	Esophagus	Larynx	Liver	Brain	Kidney	Pharynx	Uterus	Stomach	Leukemia	Ovary	Pancreas	Melanoma	Urinary	Cervix	Prostate	Breast	Colon	Lung	Skin	Other
Brain																											
HR	20.7	2.81	1.97	2.36	3.21	1.31	0.73	1.30	0.79	1.42	**4.32**	2.06	0.67	1.10	1.19	2.22	0.86	–	**2.80**	0.80	1.04	1.21	0.78	1.19	1.03	1.34	1.67
95% CI low	2.82	0.64	0.84	0.83	1.62	0.39	0.23	0.57	0.25	0.69	2.53	1.20	0.27	0.53	0.61	1.32	0.38	–	1.87	0.42	0.53	0.84	0.53	0.89	0.77	1.07	0.87
95% CI high	152	12.4	4.63	6.74	6.37	4.35	2.34	2.97	2.51	2.95	7.36	3.53	1.63	2.24	2.34	3.75	1.95	–	4.20	1.50	2.07	1.72	1.13	1.59	1.39	1.67	3.20
Kidney																											
HR	–	0.67	2.36	2.28	2.72	–	1.09	1.09	1.35	–	1.89	0.70	1.17	0.68	–	1.02	0.82	1.26	1.17	1.68	0.34	**1.55**	1.18	1.05	**1.46**	1.09	0.97
95% CI low	–	0.09	1.19	1.01	1.46	–	0.55	0.59	0.70	–	1.15	0.28	0.72	0.35	–	0.64	0.44	0.84	0.75	1.25	0.11	1.27	0.92	0.86	1.24	0.92	0.57
95% CI high	–	5.02	4.66	5.16	5.09	–	2.15	2.02	2.59	–	3.10	1.72	1.91	1.34	–	1.63	1.50	1.88	1.83	2.25	1.07	1.89	1.52	1.29	1.73	1.29	1.67
Pharynx																											
HR	6.69	0.79	2.49	1.33	1.11	1.31	0.92	**5.47**	**4.47**	1.46	1.03	0.97	**15.4**	0.58	1.43	1.09	0.96	1.57	1.22	1.19	0.82	0.81	1.27	1.06	**2.52**	**2.02**	0.84
95% CI low	1.09	0.19	1.50	0.60	0.57	0.38	0.54	4.31	3.39	1.05	0.63	0.64	12.6	0.31	1.06	0.78	0.59	1.18	0.86	0.93	0.41	0.68	1.03	0.91	2.28	1.83	0.56
95% CI high	41.0	3.38	4.13	2.94	2.14	4.44	1.56	6.93	5.89	2.05	1.68	1.48	18.9	1.07	1.92	1.53	1.56	2.09	1.73	1.53	1.64	0.97	1.57	1.24	2.78	2.24	1.26
Uterus																											
HR	–	1.15	0.67	1.51	1.92	–†	–	0.67	0.89	1.05	0.95	1.61	0.84	**0.14**	–	0.92	**0.47**	1.12	0.96	1.19	0.48	–†	1.18	1.05	0.85	1.14	0.78
95% CI low	–	0.54	0.35	0.87	1.19	–†	–	0.38	0.46	0.75	0.65	1.21	0.56	0.07	–	0.68	0.35	0.88	0.73	0.90	0.33	–†	1.08	0.94	0.73	1.04	0.56
95% CI high	–	2.43	1.29	2.61	3.10	–†	–	1.18	1.72	1.48	1.40	2.15	1.26	0.27	–	1.25	0.63	1.43	1.27	1.56	0.70	–†	1.30	1.18	0.97	1.26	1.08
Stomach																											
HR	–	2.00	1.73	0.53	1.79	1.30	–	0.72	1.15	1.11	0.93	2.12	0.92	–	1.43	–	1.64	**2.17**	0.88	1.08	1.12	0.85	1.03	1.21	1.08	1.10	0.31
95% CI low	–	0.70	0.70	0.07	0.85	0.17	–	0.32	0.61	0.62	0.43	1.39	0.50	–	0.81	–	0.99	1.55	0.46	0.73	0.52	0.65	0.76	0.99	0.88	0.91	0.11
95% CI high	–	5.69	4.30	3.86	3.74	10.0	–	1.64	2.19	1.99	1.99	3.21	1.68	–	2.51	–	2.74	3.03	1.66	1.61	2.42	1.11	1.39	1.48	1.32	1.32	0.82
Leukemia																											
HR	8.36	1.62	**5.04**	**6.79**	1.83	2.37	0.46	1.27	–	0.95	2.33	**2.16**	2.01	0.88	1.05	0.41	1.11	1.29	**2.05**	1.04	1.41	0.82	0.96	1.16	**1.70**	**2.94**	1.61
95% CI low	1.99	0.57	3.32	3.62	1.03	1.03	0.20	0.75	–	0.59	1.53	1.52	1.39	0.50	0.69	0.17	0.67	0.90	1.49	0.75	0.82	0.66	0.75	0.98	1.47	2.67	1.13
95% CI high	35.1	4.61	7.65	12.7	3.24	5.45	1.04	2.16	–	1.54	3.57	3.07	2.91	1.55	1.59	0.99	1.82	1.83	2.83	1.45	2.42	1.02	1.22	1.36	1.96	3.24	2.30
Ovary																											
HR	–	0.70	1.05	1.17	1.73	–†	0.74	1.92	2.50	1.07	0.73	1.13	1.29	0.81	1.63	1.07	1.08	1.21	0.84	1.34	0.65	–†	1.15	1.23	0.91	0.99	1.04
95% CI low	–	0.17	0.45	0.46	0.98	–†	0.36	1.07	1.31	0.65	0.37	0.68	0.79	0.58	1.10	0.69	0.74	0.85	0.56	0.90	0.43	–†	1.01	1.06	0.75	0.85	0.67
95% CI high	–	2.92	2.42	2.95	3.04	–†	1.51	3.43	4.80	1.75	1.43	1.86	2.10	1.12	2.41	1.65	1.57	1.73	1.26	2.00	0.98	–†	1.30	1.44	1.11	1.15	1.61
Pancreas																											
HR	–	**12.5**	3.48	1.42	–	2.88	1.94	1.35	–	**4.80**	0.30	2.30	–	0.74	1.11	0.82	2.65	1.18	0.80	0.38	–	–	0.64	0.97	0.71	0.83	0.86
95% CI low	–	5.43	0.83	0.19	–	0.34	0.70	0.42	–	2.87	0.04	1.14	–	0.23	0.51	0.33	1.27	0.37	0.25	0.12	–	–	0.34	0.66	0.44	0.56	0.27
95% CI high	–	28.6	14.6	10.9	–	24.5	5.37	4.41	–	8.02	2.17	4.64	–	2.35	2.41	2.01	5.56	3.77	2.57	1.18	–	–	1.20	1.42	1.12	1.22	2.74
Melanoma																											
HR	–	1.40	1.17	1.27	**2.35**	0.58	1.41	0.91	0.83	0.71	1.79	1.19	0.77	1.02	1.41	1.48	0.92	1.12	**1.93**	0.76	0.88	1.22	1.09	1.03	0.93	**2.71**	0.93
95% CI low	–	0.65	0.74	0.68	1.64	0.21	0.97	0.57	0.50	0.47	1.31	0.88	0.54	0.78	1.08	1.15	0.70	0.85	1.47	0.58	0.66	1.05	0.96	0.91	0.82	2.53	0.66
95% CI high	–	3.04	1.86	2.38	3.36	1.64	2.05	1.46	1.38	1.09	2.45	1.62	1.10	1.33	1.84	1.91	1.22	1.48	2.54	1.00	1.17	1.41	1.22	1.16	1.06	2.91	1.30

Table 2: Relative risk of second primary cancer after first cancer in Danish population, 1980–2007* (part 3 of 3)

Type/site of first cancer	Hodgkin disease	Small intestine	Non-Hodgkin lymphoma	Thyroid	Sarcoma	Testis	Multiple myeloma	Esophagus	Larynx	Liver	Brain	Kidney	Pharynx	Uterus	Stomach	Leukemia	Ovary	Pancreas	Melanoma	Urinary	Cervix	Prostate	Breast	Colon	Lung	Skin	Other
Urinary																											
HR	2.19	1.43	0.87	0.31	1.84	0.69	0.50	–	1.37	0.85	1.05	**2.23**	1.26	0.77	1.12	1.06	1.63	0.94	0.77	**5.72**	1.43	**1.30**	1.05	–	**1.82**	0.92	1.57
95% CI low	0.25	0.65	0.44	0.08	1.18	0.16	0.28	–	0.96	0.58	0.67	1.75	0.93	0.45	0.85	0.80	1.05	0.70	0.53	4.97	0.76	1.16	0.83	–	1.66	0.82	1.21
95% CI high	19.4	3.17	1.73	1.28	2.88	2.90	0.89	–	1.94	1.23	1.65	2.84	1.70	1.33	1.48	1.41	2.51	1.25	1.11	6.58	2.69	1.45	1.32	–	2.00	1.03	2.04
Cervix																											
HR	0.61	0.72	1.27	1.38	–	–†	–	1.73	1.52	1.37	1.09	0.94	1.59	0.72	1.20	1.29	**1.51**	1.38	–	**1.95**	1.20	–†	1.07	**1.39**	**2.00**	1.08	**2.78**
95% CI low	0.08	0.29	0.78	0.94	–	–†	–	1.12	0.97	0.96	0.80	0.65	1.21	0.57	0.85	0.97	1.30	1.07	–	1.51	1.05	–†	0.99	1.24	1.81	0.99	2.27
95% CI high	4.91	1.83	2.07	2.01	–	–†	–	2.67	2.37	1.97	1.49	1.36	2.09	0.90	1.68	1.71	1.76	1.79	–	2.52	1.37	–†	1.15	1.57	2.20	1.19	3.40
Prostate																											
HR	0.57	0.79	0.85	0.49	1.10	1.56	0.76	0.78	0.82	**0.49**	0.65	1.08	0.84	–†	0.72	0.87	–†	0.80	0.92	0.85	–†	**0.01**	1.12	**0.83**	**0.60**	0.93	**0.53**
95% CI low	0.07	0.42	0.55	0.20	0.77	0.82	0.57	0.59	0.61	0.36	0.45	0.87	0.66	–†	0.59	0.71	–†	0.66	0.73	0.74	–†	0.00	0.58	0.76	0.54	0.86	0.40
95% CI high	4.39	1.47	1.31	1.21	1.57	2.97	1.03	1.02	1.09	0.66	0.93	1.33	1.06	–†	0.88	1.05	–†	0.98	1.17	0.98	–†	0.02	2.16	0.91	0.65	0.99	0.69
Breast																											
HR	2.26	1.15	1.04	1.06	1.50	–	0.94	1.06	0.77	0.65	0.88	0.89	1.02	**1.22**	1.28	1.06	1.12	0.89	1.09	0.88	**0.72**	1.03	**1.40**	0.97	0.97	**1.14**	**0.57**
95% CI low	0.73	0.76	0.78	0.77	1.17	–	0.75	0.83	0.56	0.52	0.72	0.74	0.85	1.11	1.09	0.91	1.01	0.77	0.96	0.74	0.62	0.60	1.32	0.91	0.91	1.09	0.47
95% CI high	7.07	1.73	1.37	1.45	1.91	–	1.18	1.36	1.06	0.80	1.09	1.07	1.22	1.34	1.49	1.23	1.23	1.02	1.24	1.03	0.83	1.77	1.47	1.03	1.04	1.20	0.69
Colon																											
HR	3.42	**2.76**	0.91	1.62	0.91	0.90	0.83	0.94	0.93	0.80	0.78	**1.42**	0.94	1.04	0.88	0.81	1.03	0.90	0.92	0.91	0.82	0.96	1.03	**1.83**	0.88	1.01	**0.52**
95% CI low	1.24	2.04	0.65	1.15	0.67	0.41	0.66	0.75	0.73	0.67	0.61	1.22	0.79	0.88	0.75	0.68	0.87	0.78	0.78	0.80	0.63	0.89	0.95	1.72	0.82	0.95	0.42
95% CI high	9.46	3.73	1.28	2.27	1.23	1.95	1.05	1.16	1.19	0.97	0.99	1.66	1.13	1.23	1.02	0.95	1.22	1.04	1.09	1.02	1.07	1.04	1.11	1.95	0.94	1.06	0.64
Lung																											
HR	5.65	1.77	1.29	**3.37**	1.48	1.86	0.93	1.58	**2.19**	1.14	0.91	**2.76**	1.53	0.32	0.87	1.24	1.06	1.23	0.88	1.36	1.35	0.95	1.02	0.84	0.96	0.90	0.78
95% CI low	1.25	0.86	0.73	2.12	0.94	0.80	0.61	1.16	1.67	0.84	0.61	2.26	1.17	0.17	0.65	0.95	0.73	0.97	0.63	1.12	0.88	0.82	0.86	0.74	0.82	0.80	0.54
95% CI high	25.5	3.67	2.26	5.35	2.32	4.33	1.43	2.15	2.87	1.54	1.35	3.37	2.00	0.60	1.15	1.61	1.53	1.56	1.23	1.65	2.07	1.09	1.20	0.96	1.12	1.00	1.11
Skin																											
HR	1.67	1.12	**1.50**	1.09	1.30	0.87	0.98	0.92	1.30	0.98	1.07	1.06	**1.57**	0.99	0.95	**1.30**	0.94	0.95	**2.78**	0.86	0.82	0.98	1.10	0.97	**1.11**	**1.92**	1.03
95% CI low	0.78	0.85	1.26	0.84	1.10	0.56	0.85	0.80	1.13	0.87	0.93	0.95	1.43	0.88	0.86	1.19	0.84	0.87	2.58	0.79	0.70	0.93	1.05	0.93	1.06	1.85	0.93
95% CI high	3.57	1.48	1.78	1.43	1.54	1.37	1.13	1.06	1.49	1.09	1.23	1.19	1.73	1.11	1.05	1.42	1.05	1.04	2.99	0.93	0.97	1.03	1.16	1.01	1.15	1.99	1.14
Other																											
HR	6.78	3.53	2.14	1.75	2.93	1.19	1.44	–	2.43	0.87	0.82	1.30	1.41	–	0.67	1.70	**4.82**	1.05	0.80	1.53	**2.22**	1.24	1.21	0.95	**1.62**	1.29	**6.11**
95% CI low	0.60	1.44	1.09	0.61	1.73	0.28	0.79	–	1.44	0.47	0.40	0.80	0.88	–	0.36	1.15	3.74	0.67	0.48	1.12	1.53	0.99	0.97	0.77	1.37	1.11	4.37
95% CI high	76.7	8.63	4.16	5.05	4.97	5.18	2.61	–	4.08	1.60	1.68	2.12	2.27	–	1.22	2.50	6.20	1.66	1.36	2.09	3.22	1.54	1.50	1.17	1.91	1.50	8.55

Note: CI = confidence interval, HR = hazard ratio.
*Hazard ratios were calculated in 1:5 matched nested studies; see Methods for details. Values in bold were significant ($p < 0.05$) after Bonferroni correction for mulitple comparisons.
†These sex-specific estimates do not exist.

Table 3: Five-year absolute risk per 100 of second primary cancer after first cancer in Danish population, 1980–2007* (part 1 of 3)

Type or site of first cancer	Hodgkin disease	Small intestine	Non–Hodgkin lymphoma	Thyroid	Sarcoma	Testis	Multiple myeloma	Esophagus	Larynx	Liver	Brain	Kidney	Pharynx	Uterus	Stomach	Leukemia	Ovary	Pancreas	Melanoma	Urinary	Cervix	Prostate	Breast	Colon	Lung	Skin	Other
Hodgkin disease																											
Patients	–	–	1.15	–	–	–	–	–	–	–	–	–	–	0.00	–	–	–	0.00	0.00	0.00	0.58	0.98	1.40	0.00	0.57	0.58	–
Controls	–	–	0.00	–	–	–	–	–	–	–	–	–	–	0.10	–	–	–	0.10	0.10	0.10	0.10	0.86	0.76	0.72	0.10	0.82	–
Small intestine																											
Patients	–	0.00	0.13	0.13	0.65	0.00	0.00	0.13	0.00	0.65	0.26	0.13	0.00	0.39	0.13	0.13	0.28	1.43	0.00	0.39	0.00	0.99	0.55	2.08	1.43	1.44	0.26
Controls	–	0.02	0.04	0.00	0.11	0.05	0.09	0.05	0.14	0.24	0.07	0.13	0.21	0.15	0.34	0.18	0.60	0.30	0.22	0.27	0.13	1.72	1.76	1.38	1.21	1.49	0.15
Non-Hodgkin lymphoma																											
Patients	–	–	0.15	0.24	0.16	0.00	0.08	0.00	0.08	0.00	0.00	0.48	0.08	0.08	0.00	0.16	0.00	0.24	0.16	0.00	0.08	0.91	1.53	0.88	1.20	1.92	0.32
Controls	–	–	0.04	0.00	0.09	0.04	0.10	0.09	0.05	0.13	0.08	0.09	0.10	0.13	0.17	0.14	0.42	0.22	0.17	0.25	0.03	1.66	1.29	0.89	0.67	1.52	0.06
Thyroid																											
Patients	0.00	0.00	0.00	0.18	0.00	–	0.11	0.04	0.11	0.00	0.04	0.18	0.14	0.25	0.07	0.32	0.31	0.11	0.14	0.07	0.47	0.49	0.87	0.32	0.54	0.61	0.11
Controls	0.01	0.01	0.02	0.01	0.01	–	0.07	0.04	0.04	0.09	0.08	0.07	0.05	0.14	0.11	0.11	0.24	0.14	0.16	0.14	0.20	0.90	1.03	0.58	0.55	0.81	0.10
Sarcoma																											
Patients	–	0.09	0.09	0.03	1.01	0.21	0.09	0.06	0.03	0.06	0.26	0.20	0.00	0.03	0.12	0.23	0.40	0.15	0.32	0.12	0.03	0.92	1.53	0.93	0.87	1.63	0.15
Controls	–	0.02	0.02	0.03	0.03	0.04	0.09	0.08	0.09	0.12	0.06	0.15	0.13	0.06	0.17	0.13	0.26	0.16	0.14	0.19	0.10	1.06	1.07	0.70	0.78	1.09	0.12
Testis																											
Patients	–	0.00	0.02	0.02	0.09	0.19	0.00	0.05	0.00	0.06	0.08	0.06	0.03	–†	0.09	0.14	–†	0.05	0.11	0.03	–†	0.19	–	0.11	0.15	0.39	0.31
Controls	–	0.01	0.01	0.00	0.02	0.05	0.02	0.02	0.03	0.02	0.04	0.04	0.05	–†	0.04	0.02	–†	0.04	0.05	0.07	–†	0.16	–	0.15	0.22	0.29	0.03
Multiple myeloma																											
Patients	–	0.03	0.00	0.09	0.17	0.00	0.03	0.06	0.11	0.17	0.17	0.34	0.23	0.11	0.31	0.23	0.25	0.17	0.43	0.34	0.11	1.43	1.04	1.02	1.45	1.88	0.26
Controls	–	0.02	0.03	0.03	0.05	0.03	0.07	0.15	0.09	0.17	0.12	0.18	0.22	0.15	0.23	0.22	0.43	0.27	0.17	0.35	0.13	1.85	1.58	1.41	1.32	1.67	0.20
Esophagus																											
Patients	0.00	0.21	0.00	0.14	0.00	0.00	0.00	0.07	0.29	0.29	0.07	0.14	1.28	0.14	0.14	0.29	0.45	0.21	0.07	0.21	0.14	1.46	0.89	0.93	1.49	1.00	0.07
Controls	0.00	0.03	0.04	0.04	0.06	0.03	0.13	0.09	0.13	0.14	0.11	0.16	0.21	0.10	0.27	0.28	0.34	0.27	0.22	0.39	0.05	1.65	1.62	1.23	1.31	1.76	0.19
Larynx																											
Patients	0.00	0.05	0.04	0.02	0.20	0.00	0.07	0.52	0.64	0.32	0.11	0.30	1.00	0.04	0.30	0.32	0.72	0.30	0.11	0.66	0.11	1.31	1.12	1.54	4.55	2.15	0.22
Controls	0.01	0.02	0.03	0.04	0.06	0.04	0.11	0.11	0.07	0.17	0.09	0.14	0.19	0.08	0.22	0.23	0.30	0.24	0.15	0.40	0.04	1.43	1.35	1.25	1.30	1.46	0.14
Liver																											
Patients	–	0.27	0.00	0.14	0.14	0.14	0.07	0.20	0.14	0.20	0.00	0.54	0.34	0.07	0.34	0.34	0.93	4.09	0.07	0.34	0.00	1.24	1.06	1.02	1.22	1.02	0.00
Controls	–	0.02	0.03	0.03	0.05	0.03	0.12	0.12	0.11	0.08	0.10	0.17	0.15	0.17	0.27	0.25	0.30	0.25	0.18	0.39	0.10	1.90	1.48	1.39	1.30	1.74	0.21
Brain																											
Patients	–	0.02	0.08	0.04	0.08	0.12	0.00	0.06	0.06	0.11	0.21	0.23	0.08	0.13	0.11	0.17	0.09	0.13	0.42	0.15	0.13	0.59	0.64	0.51	0.61	0.95	0.19
Controls	–	0.02	0.04	0.03	0.05	0.04	0.07	0.07	0.08	0.09	0.04	0.10	0.11	0.13	0.15	0.13	0.19	0.15	0.16	0.19	0.09	0.90	1.12	0.79	0.83	1.04	0.14
Kidney																											
Patients	–	0.02	0.13	0.11	0.11	0.00	0.14	0.13	0.11	0.14	0.18	0.02	0.22	0.13	0.25	0.20	0.31	0.18	0.18	0.67	0.02	1.84	1.36	0.90	1.60	1.30	0.09
Controls	–	0.02	0.04	0.03	0.07	0.03	0.10	0.11	0.09	0.13	0.11	0.09	0.16	0.14	0.22	0.26	0.40	0.27	0.17	0.31	0.07	1.59	1.54	1.13	1.15	1.48	0.21

Table 3: Five-year absolute risk per 100 of second primary cancer after first cancer in Danish population, 1980–2007* (part 2 of 3)

Type or site of first cancer	Hodgkin disease	Small intestine	Non–Hodgkin lymphoma	Thyroid	Sarcoma	Testis	Multiple myeloma	Esophagus	Larynx	Liver	Brain	Kidney	Pharynx	Uterus	Stomach	Leukemia	Ovary	Pancreas	Melanoma	Urinary	Cervix	Prostate	Breast	Colon	Lung	Skin	Other
Pharynx																											
Patients	0.01	0.00	0.12	0.07	0.05	0.02	0.07	0.85	0.34	0.22	0.09	0.16	1.71	0.07	0.35	0.19	0.35	0.34	0.16	0.33	0.07	1.02	1.57	0.86	3.28	2.44	0.15
Controls	0.00	0.02	0.03	0.03	0.06	0.03	0.08	0.11	0.11	0.15	0.10	0.17	0.08	0.13	0.21	0.17	0.37	0.22	0.15	0.32	0.06	1.18	1.37	1.04	1.08	1.42	0.18
Uterus																											
Patients	–	0.03	0.03	0.05	0.08	–†	0.06	0.02	0.03	0.08	0.07	0.22	0.11	0.05	0.11	0.14	0.23	0.19	0.20	0.13	0.20	–†	1.67	0.92	0.61	1.37	0.11
Controls	–	0.03	0.03	0.04	0.05	–†	0.07	0.07	0.05	0.13	0.08	0.11	0.10	0.19	0.15	0.16	0.34	0.21	0.17	0.16	0.18	–†	1.48	0.98	0.72	1.22	0.15
Stomach																											
Patients	–	0.09	0.02	0.02	0.16	0.04	0.07	0.09	0.11	0.25	0.09	0.48	0.18	0.07	0.09	0.18	0.46	0.41	0.09	0.34	0.09	1.38	1.68	1.36	1.13	1.29	0.07
Controls	–	0.03	0.03	0.03	0.07	0.03	0.13	0.13	0.13	0.19	0.10	0.19	0.22	0.11	0.14	0.24	0.40	0.33	0.17	0.44	0.07	1.86	1.46	1.35	1.33	1.80	0.23
Leukemia																											
Patients	0.00	0.02	0.22	0.10	0.10	0.08	0.05	0.15	0.09	0.16	0.16	0.30	0.15	0.09	0.18	0.03	0.31	0.22	0.26	0.25	0.09	1.07	1.26	1.11	1.59	3.31	0.26
Controls	0.00	0.02	0.03	0.02	0.05	0.02	0.10	0.09	0.10	0.17	0.10	0.15	0.16	0.13	0.22	0.11	0.35	0.24	0.19	0.34	0.08	1.52	1.21	1.07	1.14	1.51	0.20
Ovary																											
Patients	0.00	0.01	0.01	0.04	0.10	–†	0.03	0.07	0.01	0.13	0.04	0.09	0.09	0.34	0.17	0.12	0.15	0.14	0.11	0.13	0.23	–†	1.27	1.03	0.52	0.91	0.08
Controls	0.00	0.02	0.02	0.03	0.04	–†	0.07	0.04	0.02	0.14	0.08	0.11	0.09	0.33	0.13	0.16	0.15	0.18	0.17	0.16	0.22	–†	1.38	0.98	0.70	1.21	0.16
Pancreas																											
Patients	–	0.58	0.05	0.05	0.00	0.11	0.16	0.16	0.00	1.05	0.00	0.47	0.10	0.16	0.21	0.16	0.62	0.15	0.10	0.10	0.00	1.80	0.62	1.25	0.89	1.10	0.00
Controls	–	0.04	0.05	0.03	0.05	0.02	0.12	0.11	0.10	0.17	0.10	0.18	0.21	0.18	0.27	0.24	0.37	0.14	0.19	0.39	0.09	1.92	1.54	1.37	1.27	1.71	0.21
Melanoma																											
Patients	0.00	0.04	0.05	0.03	0.12	0.04	0.07	0.04	0.03	0.07	0.11	0.13	0.10	0.14	0.19	0.21	0.19	0.13	0.19	0.15	0.15	1.34	1.34	0.73	0.62	3.20	0.08
Controls	0.00	0.02	0.02	0.02	0.04	0.05	0.05	0.06	0.06	0.09	0.07	0.09	0.10	0.12	0.12	0.13	0.24	0.14	0.07	0.19	0.18	1.02	1.06	0.70	0.69	0.97	0.14
Urinary																											
Patients	0.01	0.05	0.06	0.02	0.12	0.01	0.05	0.16	0.22	0.23	0.14	0.56	0.33	0.07	0.34	0.28	0.54	0.32	0.15	2.30	0.08	3.21	1.61	1.39	2.65	1.63	0.37
Controls	0.00	0.04	0.06	0.04	0.08	0.02	0.14	0.16	0.17	0.19	0.11	0.18	0.19	0.11	0.31	0.29	0.40	0.30	0.19	0.27	0.05	2.12	1.50	1.51	1.56	2.00	0.25
Cervix																											
Patients	0.00	0.00	0.01	0.03	0.01	–†	0.02	0.02	0.01	0.02	0.03	0.04	0.04	0.06	0.02	0.05	0.21	0.07	0.11	0.06	0.34	–†	0.61	0.28	0.34	0.31	0.17
Controls	0.00	0.01	0.00	0.02	0.02	–†	0.02	0.01	0.02	0.03	0.04	0.03	0.03	0.09	0.04	0.04	0.11	0.05	0.11	0.03	0.26	–†	0.59	0.22	0.20	0.38	0.05
Prostate																											
Patients	0.00	0.03	0.05	0.02	0.12	0.03	0.13	0.15	0.15	0.12	0.09	0.30	0.22	–†	0.31	0.32	–†	0.35	0.21	0.67	–†	0.01	–	1.60	1.32	2.41	0.16
Controls	0.01	0.04	0.07	0.03	0.10	0.02	0.21	0.22	0.22	0.29	0.16	0.29	0.29	–†	0.48	0.44	–†	0.40	0.24	0.83	–†	1.40	–	2.03	2.30	2.70	0.32
Breast																											
Patients	0.00	0.02	0.03	0.04	0.04	–	0.05	0.05	0.04	0.06	0.08	0.10	0.08	0.36	0.16	0.13	0.36	0.16	0.20	0.10	0.19	–	1.05	0.71	0.51	1.28	0.06
Controls	0.00	0.02	0.03	0.03	0.04	–	0.07	0.04	0.03	0.11	0.08	0.10	0.09	0.31	0.13	0.13	0.31	0.20	0.17	0.14	0.25	–	0.76	0.87	0.68	1.19	0.13
Colon																											
Patients	0.00	0.08	0.05	0.05	0.06	0.01	0.09	0.12	0.10	0.16	0.11	0.27	0.19	0.19	0.24	0.17	0.48	0.23	0.18	0.36	0.10	1.92	1.53	1.25	1.03	1.72	0.07
Controls	0.00	0.03	0.04	0.03	0.06	0.02	0.12	0.12	0.11	0.20	0.12	0.19	0.20	0.20	0.29	0.26	0.38	0.31	0.20	0.42	0.11	2.12	1.63	0.75	1.40	1.89	0.24

Table 3: Five-year absolute risk of second primary cancer after first cancer in Danish population, 1980–2007* (part 3 of 3)

Type or site of first cancer	Hodgkin disease	Small intestine	Non–Hodgkin lymphoma	Thyroid	Sarcoma	Testis	Multiple myeloma	Esophagus	Larynx	Liver	Brain	Kidney	Pharynx	Uterus	Stomach	Leukemia	Ovary	Pancreas	Melanoma	Urinary	Cervix	Prostate	Breast	Colon	Lung	Skin	Other
Lung																											
Patients	0.00	0.04	0.06	0.11	0.07	0.03	0.08	0.21	0.27	0.22	0.14	0.62	0.25	0.05	0.22	0.27	0.32	0.33	0.15	0.47	0.11	1.55	1.42	0.87	0.65	1.26	0.15
Controls	0.00	0.03	0.04	0.03	0.07	0.03	0.12	0.14	0.13	0.19	0.12	0.19	0.20	0.15	0.28	0.26	0.38	0.29	0.21	0.45	0.08	1.96	1.57	1.41	0.80	1.77	0.22
Skin																											
Patients	0.00	0.02	0.07	0.03	0.09	0.03	0.11	0.11	0.14	0.18	0.12	0.18	0.28	0.17	0.25	0.33	0.34	0.24	0.61	0.32	0.10	1.75	1.68	1.25	1.38	2.25	0.22
Controls	0.00	0.02	0.04	0.03	0.06	0.03	0.10	0.11	0.11	0.18	0.11	0.16	0.17	0.17	0.25	0.23	0.33	0.26	0.18	0.39	0.11	1.95	1.52	1.31	1.26	0.93	0.22
Other																											
Patients	0.02	0.06	0.04	0.06	0.24	0.04	0.08	0.08	0.14	0.12	0.04	0.22	0.20	0.20	0.04	0.34	1.85	0.24	0.16	0.56	0.44	2.12	1.44	0.83	1.42	1.79	0.63
Controls	0.00	0.02	0.04	0.02	0.05	0.04	0.08	0.11	0.07	0.16	0.09	0.15	0.16	0.16	0.26	0.22	0.31	0.26	0.19	0.39	0.13	1.86	1.43	1.25	1.13	1.60	0.11

*Values were calculated in 1:5 matched nested studies; see Methods and Figure 1 for details.
†These sex-specific estimates do not exist.

The contrast between the risk of a second primary cancer being the same as the first and the risk of it being different from the first was higher in the group of tobacco-related cancers than in the group of cancers not related to tobacco use or whose relation to tobacco use was uncertain. This observation suggests that, even though risk factors display a pleiotropic association at the population level with increased risk of multiple cancer types, the increased risk at the individual level may still be specific to cancer type.

Our findings from the sensitivity analyses underline that codiagnosis of a second primary cancer probably does not influence our main findings. Second, because the risk of a second primary cancer of the same type as the first changed only slightly after we excluded all primary cancers diagnosed up to 10 years after the first cancer, short-term malignant progression of dysplastic cells in anatomic proximity of the first cancer seems less likely as the only explanation for the observed 2.2-fold risk of a second cancer of the same type as the first. Rather, we speculate that in general, risk factors acting over the long term seem to be type specific in the individual patient. However, other explanations are also plausible: effects of treatment and an increase (or decrease) in diagnostic surveillance could change observed risk of cancer in the same organ as opposed to other organs.

Limitations

One limitation of our study is the possible misclassification of cancer diagnoses. However, classification errors likely did not have a major effect on our findings because all diagnoses of cancer from the national Danish Cancer Registry are assigned based on histologic examination by a fully trained pathologist. Misclassification of relapse of the first cancer as a second primary cancer was also a possible source of bias; however, observed associations did not change significantly even after we excluded second cancers diagnosed up to 10 years after the first cancer. If anything, the national Danish Cancer Registry underreports second primary cancers of the same type as the first cancer.[15] Another limitation concerns the availability and completeness of the diagnostic information; however, the Danish Cancer Registry captures 98% of all cancer diagnoses in Denmark.[14,18]

The broad-stroke nature of the aggregated HR estimates of all cancer types combined disregards the substantial heterogeneity in risk across individual types of cancer, as illustrated by the high I^2 values. The interplay of risk factors differs for individual types of cancer; therefore, the aggregated risk estimates may have limited clini-

cal relevance. However, in Table 2 we provide all of the associations between the 27 individual first cancers and the 27 individual second primary cancers without Bonferroni correction for multiple comparison.

Conclusion

In this nationwide study, the excess risk of a second primary cancer was due mainly to a 2.2-fold risk of the second primary cancer being the same type as the first, whereas the risk of it being a different type was only 1.1-fold. Future studies of individual pairs of first and second primary cancers should clarify whether the association is due to shared genetic or lifestyle risk factors, codiagnosis of a primary cancer in close anatomic proximity to the first cancer, treatment of the first cancer, or the timing of diagnosis of the first cancer (in childhood v. adulthood). Our present findings may assist clinicians in designing surveillance programs for their patients who have cancer, for example by focusing on second primary cancers with the highest five-year absolute risks.

References

1. Curtis RE, Freedman DM, Ron E, et al. *New malignancies among cancer survivors: SEER cancer registries, 1973–2000*. Bethesda (MD): National Cancer Institute; 2006.
2. Amundadottir LT, Thorvaldsson S, Gudbjartsson DF, et al. Cancer as a complex phenotype: pattern of cancer distribution within and beyond the nuclear family. *PLoS Med* 2004;1:e65.
3. Dong C, Hemminki K. Second primary neoplasms in 633,964 cancer patients in Sweden, 1958–1996. *Int J Cancer* 2001;93:155-61.
4. Olsen JH, Möller T, Anderson H, et al. Lifelong cancer incidence in 47 697 patients treated for childhood cancer in the Nordic countries. *J Natl Cancer Inst* 2009;101:806-13.
5. Ahsan H, Neugut AI, Bruce JN. Association of malignant brain-tumors and cancers of other sites. *J Clin Oncol* 1995;13:2931-5.
6. Berrington de Gonzalez A, Curtis RE, Gilbert E, et al. Second solid cancers after radiotherapy for breast cancer in SEER cancer registries. *Br J Cancer* 2010;102:220-6.
7. Levi F, Randimbison L, Te VC, et al. Risk of prostate, breast and colorectal cancer after skin cancer diagnosis. *Int J Cancer* 2008; 123:2899-901.
8. Maule M, Scélo G, Pastore G, et al. Risk of second malignant neoplasms after childhood leukemia and lymphoma: an international study. *J Natl Cancer Inst* 2007;99:790-800.
9. Travis LB, Curtis RE, Boice JD Jr, et al. Second malignant neoplasms among long-term survivors of ovarian cancer. *Cancer Res* 1996;56:1564-70.
10. Brada M, Ford D, Ashley S, et al. Risk of second brain tumour after conservative surgery and radiotherapy for pituitary adenoma. *BMJ* 1992;304:1343-6.
11. Buist DS, Abraham LA, Barlow WE, et al. Diagnosis of second breast cancer events after initial diagnosis of early stage breast cancer. *Breast Cancer Res Treat* 2010;124:863-73.
12. Hemminki K, Li X, Dong C. Second primary cancers after sporadic and familial colorectal cancer. *Cancer Epidemiol Biomarkers Prev* 2001;10:793-8.
13. Teppo L, Salminen E, Pukkala E. Risk of a new primary cancer among patients with lung cancer of different histological types. *Eur J Cancer* 2001;37:613-9.
14. Storm HH, Michelsen EV, Clemmensen IH, et al. The Danish Cancer Registry — history, content, quality and use. *Dan Med Bull* 1997;44:535-9.
15. Storm HH, Lynge E, Osterlind A, et al. Multiple primary cancers in Denmark 1943–80 — influence of possible underreporting and suggested risk factors. *Yale J Biol Med* 1986;59:547-59.
16. Ahmad O, Boschi-Pinto C, Lopez A, et al. *Age standardization of rates: a new WHO standard*. Geneva (Switzerland): World Health Organization; 2001.
17. International Agency for Research on Cancer. *Tobacco smoke and involuntary smoking*. Geneva (Switzerland): World Health Organization; 2002.
18. Storm HH. The Danish Cancer Registry, a self-reporting national cancer registration system with elements of active data collection. *IARC Sci Publ* 1991;95:220-36.

Affiliation: From the Department of Clinical Biochemistry, Herlev Hospital, Copenhagen University Hospital, and the Faculty of Health Sciences, University of Copenhagen, Herlev, Denmark

Contributors: All of the authors designed the study. Sune Nielsen obtained the necessary permissions to use the data from the individual registries, processed and organized the data for analysis, and performed the statistical analyses. All of the authors analyzed and interpreted the data. Sune Nielsen drafted the manuscript, and Børge Nordesgaard and Stig Bojesen critically revised it for important intellectual content. All of the authors approved the final version submitted for publication.

Funding: The study was funded by the Herlev Hospital, Copenhagen University Hospital.