Multiple Primary Cancers in Denmark 1943–80; Influence of Possible Underreporting and Suggested Risk Factors

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The risk of developing a second primary cancer was studied among 171,749 men and 208,192 women who were reported to the Danish Cancer Registry between 1943 and 1980. Only those who survived at least two months were included in the analysis, and more than 1.7 million person-years of observation were accrued. Altogether, 15,084 second primary cancers developed, of which 13,231 were in organs other than the initial or adjacent site [relative risk (RR) = 1.01]. Adjustment for possible underreporting of multiple primary cancers increased the RR to 1.24, which stresses the need for detailed knowledge of registration procedures interpreting results from cancer registries. The unadjusted RR for all sites increased with time, from 0.94 during the first decade of follow-up (excluding the first year) to 1.13 among 30-year survivors, whereas the adjusted RR increased from 1.08 to 1.41. Elevated risks were observed for sites thought to have a common etiology. For example, cancers of smoking-related sites were increased in both directions following cancers of the oral cavity, respiratory tract, and urinary organs. For cancers suspected to have a hormone- or dietary fat-related association, significant reciprocal relationships were seen among cancers of the endometrium, ovary, and colon. Cancer treatment probably is an important factor in second cancer development, even when judged indirectly in the present study. For example, radiotherapy may have been responsible for an elevated risk of subsequent cancers of the thyroid, breast, colon, rectum, bladder, and connective tissue in long-term survivors. Chemotherapy may have increased the risk of subsequent leukemias. Our data further indicate that cancer patients have no general susceptibility to develop new malignant tumors, although high rates may be found for particular sites sharing common risk factors. Conversely, the occurrence of one cancer does not appear to protect against developing a new cancer.

Development of multiple primary cancers in the same individual constitutes a constant challenge to the medical profession and scientists working in cancer research. Should such events be attributed to host susceptibility, could two or more cancers be due to the same exogenous risk factor, or were the subsequent cancers induced by previous anticancer therapy?

Previous studies have shown that cancer patients are not a random sample of the general population, and Schoenberg [1] found that the site and the risk of second primary cancer development varied considerably by index site. This observation was recently confirmed in a collaborative study between the National Cancer Institute, U.S.A., the Connecticut Tumor Registry, and the Danish Cancer Registry [2,3,4]. The population-based cancer registry may provide new information for the evaluation and quantification of the risk of second primary cancer development, especially among long-term survivors. Among the latter group, risks associated with medical procedures,

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e.g., radiotherapy, are most likely to be seen. In contrast, etiologic similarities between cancers of different sites, including host susceptibility, are likely to result in increased risks that are not dependent on the duration of survival after the first tumor. Reciprocal associations, i.e., in both directions between sites, would strengthen hypotheses of possible common etiology [5].

The relative risks of developing second primary cancers of specific sites have been presented in detail elsewhere, according to organ system of the first primary cancer [4,6–14]. The present paper evaluates the possible influence of underreporting and draws attention to associations indicating common etiology and to the role that treatment for the first cancer has for subsequent cancer risk.

MATERIAL AND METHODS

Cancer Registration in Denmark

Since 1943, incident cases of cancer in Denmark have been reported to the Danish Cancer Registry by hospital departments, pathology institutes, and practicing physicians. Follow-up for vital status is undertaken annually by record linkage with the National Death Registry. All tumors in the Cancer Registry are coded and classified in accordance with a modified version of the Seventh Revision of the International Classification of Diseases [15]. A conservative attitude has been taken toward accepting multiple primary cancers with similar morphologies in adjacent organs, and new tumors arising within the same organ or organ pair are generally not recorded. Examination of the development of a new independent cancer in paired organs was thus not possible. Details on the procedures of the Registry have been described elsewhere [16]. Registration is voluntary but, for practical purposes, reporting of initial cancers may be regarded as complete and valid [17,18].

The records of the Cancer Registry were by means of record linkage compared with a national patient registry (LPR) holding diagnosis for all patients discharged from hospitals in Denmark in 1977 [17]. The results of that study, as well as from a detailed study of cervix cancer patients 1943–1980 [19], were used in order to evaluate possible underreporting of multiple primary cancers.

Study of Multiple Primary Cancers 1943–80

Persons with multiple primary cancers were identified by automated record linkage performed within the Registry and the risk of multiple primary cancer development determined [4]. All non-melanoma skin cancers, precancerous lesions, and duplicate notifications of the same tumor were excluded. Patients who survived less than two months or who developed a second primary cancer within the first two months following their initial cancer diagnosis were excluded, leaving 364,857 persons with a single cancer and 15,084 persons with a second primary cancer available for study. A total of 551 third and fourth primary cancers occurred in these individuals but were not considered in this study. These 379,941 eligible patients, 171,749 men and 208,192 women, were on average followed for five years and accumulated 1,706,736 person-years of observation. Second primary cancers developed in 4.2 percent of the women and 3.7 percent of the men. In persons with multiple tumors, approximately 92 percent of the first and 85 percent of the second primary cancers were verified histologically. Only 4 percent of the second primary cancers were known to the Registry solely from death certificates.

Calculation of Relative Risks

Person-years at risk were calculated from the date of diagnosis of the first primary cancer (i.e., date of first hospital admission) until the date of diagnosis of a second primary cancer, death, or December 31, 1980, whichever occurred first. The expected numbers of second cancers were estimated by applying sex and site-specific incidence rates for the general population in Denmark to the corresponding person-years of observation, using a modified version of the program developed by Monson [20]. The relative risk (RR) was taken as the ratio of observed to expected incident cancers and approximate 95 percent confidence intervals (CI) of the RR were computed, assuming a Poisson distribution of the observed cancers as described by Rothman and Boice [21].

RESULTS AND DISCUSSION

All Cancers

For both sexes combined, 16,580 second primary cancers were expected, yielding a deficit of approximately 1,500 cancers (RR = 0.91; 95 percent CI = 0.90–0.92), as shown in Table 1. The risk of second primary cancer increased significantly with the time, since diagnosis of the first primary ($p < .001$ for trend), from RR = 0.9 in short-term survivors to RR = 1.1 among those living 30 or more years after their initial primary cancer (Table 2). The present finding corresponds to an annual average incidence of 8.8 second cancers per 1,000 persons (7.8/1,000 women; 10.9/1,000 men). These findings agree well with other results [22,23,24]; however, a significant 31 percent increased RR of second cancer in Connecticut [3] was not matched by a similar increase in our investigation. Differences in registration· procedures may explain some of the discrepant results between Denmark and Connecticut.

The overall deficit of cancers occurred mainly during the first five years of follow-up [4]. During this early follow-up period, both the notifying physician and the Registry would be hesitant to accept and record a new primary cancer, as a large proportion of such tumors would likely be regarded as misdiagnosed metastases. In Connecticut, no similar deficit was observed [3]; in fact the 30 percent excess is present throughout all time intervals since first primary diagnosis. If the observed and expected second

TABLE 1

Observed (O) and Expected (E) Crude and Adjusted Numbers of Second Primary Cancers Among Both Sexes in Connecticut (1935–1982) and Denmark (1943–1980)

Adjustment		Connecticut[a]	Denmark[b]	Denmark[c]
None	O	16,727	15,084	18,523
	E	12,797	16,580	16,580
	O/E	1.31	0.91	1.12
Excluding				
site of	O	12,831	13,231	16,247
initial	E	10,428	13,113	13,113
cancer	O/E	1.23	1.01	1.24

[a]From [3]
[b]From [4]
[c]Adjusted for possible underreporting

TABLE 2

Relative Risk of Second Primary Cancer Following Any Primary Cancer in Denmark, 1943–1980

Year Since First Primary	Uncorrected			Corrected		
	O	E	RR	O[a]	E	RR[a]
1–9	8,399	8,979.6	0.94	9,710	8,979.6	1.08
10–19	3,458	3,504.0	0.99	4,257	3,504.0	1.22
20–29	1,158	1,187.3	0.98	1,470	1,187.3	1.24
30+	190	167.6	1.13	236	167.6	1.41

[a]Number corrected for estimated degree of underreporting

cancers of the same site as the index cancer were subtracted, and when excluding cancers of buccal cavity following a cancer of lip, tongue, and mouth; colorectal cancers after a colorectal; female genital after an initial female genital; urinary following another urinary; and a hematological malignancy following a primary hematological cancer [3], the RR increased to 1.01 in Denmark and was not significantly different from unity, while the RR in Connecticut decreased from 1.31 to 1.23 (Table 1).

The change of the RR in opposite directions in Connecticut and Denmark indicates different attitudes to recording of multiple tumors by these two cancer registries, overreporting of multiple primary cancers may thus take place in Connecticut, in contrast to Denmark, where underreporting may be equally important. It has been possible to evaluate reporting of multiple cancers in Denmark. A similar evaluation of other Registry data, including Connecticut's, has to our knowledge not been undertaken.

Table 3 shows the results of a linkage study among cancer patients known both to the Cancer Registry and to the LPR [17]. According to the LPR, 6.8 percent of the cancer patients admitted to hospitals in 1977 had multiple primary cancers, whereas the Cancer Registry 1943–80 observed 4.0 percent. However, it is important to emphasize that the LPR is not a cancer registry. This registry holds all discharge diagnoses (20 possible) for every single hospital admission linked to the personal identifying number provided all Danish inhabitants. If a patient had more hospital admissions, no attempt was made to link the discharge information from the various admissions and thus to avoid duplications and errors if a diagnosis was revised. Consequently the LPR had to be edited to simulate a Cancer Registry, and the computerized editing process may have allowed for too many multiple cases [17]. For example, a patient with a cancer in

TABLE 3

Frequency of Multiple Primary Cancers in Denmark Estimated from the Danish Cancer Registry 1943–80 (CRG), National Patient Discharge Registry 1977 (LPR), and Cervix Cancer Cohort 1943–82 (CCC)

Cancer Case	CRG	(%)	LPR	(%)	CCC	(%)
Single	364,857	(96.0)	15,342	(93.2)	22,779	(91.2)
Multiple	15,084	(4.0)	1,126	(6.8)	2,191[a]	(8.8)
All	379,941	(100)	16,468	(100)	24,970	(100)

[a]Estimated, based on scrutiny of 7.5 percent sample of all notified single cervix cancer cases and 35 percent sample of all notified second primaries after cervix cancer

the sigmoid colon, with a primary discharge diagnosis of colon cancer, may, at a later admission, have been discharged as a rectal cancer case and thus calculated as a multiple primary case. If the patient later was admitted with lung metastasis, and the discharge diagnosis in error stated lung cancer, this too would give rise to a multiple primary case. The validity of the cancer discharge diagnoses in the LPR is currently under evaluation.

On the other hand, some second primary cancers are not reported to the Registry, as was demonstrated in a study of second primary cancer within a cohort of 24,970 cervix cancer patients [19]. Diagnostic information on 627 cases with a known second primary cancer and 1,705 matched controls, with no knowledge of any other cancer but the cervix cancer, were evaluated by thorough scrutiny of all hospital and pathology records available from the date of cervix cancer diagnosis until death or December 1982. Based on these results, 8.8 percent of all cancer patients should have a second primary cancer, which is more than twice as many as reported to the Registry (Table 3).

In order to evaluate the upper limit of possible underreporting, we applied these results from the cervix cancer study on the Cancer Registry cohort of single cancer cases, taking account of time elapsed between the first and second primary cancer (Table 4). No account of the influence of overreporting of multiple primary cancers was taken, as the influence would be minor. The largest proportion (7.2 percent of total 18.6 percent) of unreported second primaries (1,337) was observed within the first five years of observation (the mean observation time of the Cancer Registry cohort). The total estimated number of unreported second primaries would be 3,439 cases, which would increase the number of second primary cancers from 15,084 to 18,523. When applying these corrected observed numbers, the overall RR changes from 1.01 to 1.24, which is similar to the observed RR (1.23) in Connecticut (Table 1), while the RR by time since first primary increases from 1.1 to 1.4, 30 years or more after the first cancer (Table 2).

TABLE 4

Possible Underreporting of Multiple Primary Cancer in Denmark 1943–80, Based on Scrutiny of Sample of Notified Single Cervix Cancer Cases (CCC)

	Time Elapsed Since First Tumor (years)					
	0–4	5–9	10–19	20–29	30+	Total
CCC "Single"						
No. starting interval	1,705	1,629	1,405	802	237	1,705
Unreported second primary	6	6	26	19	4	65
% unreported	0.4	0.6	1.9	2.4	1.7	3.8
Cancer Registry						
No. single cases starting interval	379,941	102,664	56,430	18,121	3,699	379,941
Reported second primary	6,831	3,447	3,458	1,158	190	15,084
Unreported second primary	1,337	567	1,044	429	62	3,439
Estimate no. second primary	8,168	4,014	4,502	1,587	252	18,523
Underreporting of Second Primary						
% in interval	16.4	14.1	23.2	27.0	24.6	18.6
% of total	7.2	3.1	5.6	2.3	0.3	18.6

It must be borne in mind that these figures represent the upper limit of underreporting. Furthermore, it is unknown whether they are applicable to the entire Registry material, as they were derived from underreporting observed in following only one site, cervix. Differences in registration procedures [16,25] and probably definitions of second primary cancers between the registries in Denmark and Connecticut thus are an important factor in evaluation of discrepant results. In view of the underreporting of multiple cancer, the significant elevated RRs of second primary cancers in Denmark may be regarded as minimum figures, whereas an insignificant elevated RR or decreased RR is difficult to interpret.

RELATIONSHIPS BETWEEN SITES OF FIRST AND SECOND PRIMARY CANCERS

The overall risk of a new primary cancer among all cancer patients is composed of excesses and deficits of various second tumors after different first primary cancers [6–14]. Thus the constellation of multiple tumors that occurs in individuals with the same first primary cancer may provide clues to factors that influence risk.

When bidirectional associations appear to be independent of intervals between

TABLE 5
Significant Associations Between Smoking-Related Cancers, Both Sexes, in
Denmark, 1943–80

First Primary	Second Primary	O/E	95% CI
Lip	Mouth	2.4	1.1–4.8
	Larynx	0.1	0.0–0.6
Tongue	Mouth	12.0	2.4–35.0
	Lung	2.5	1.4–4.1
Mouth	Lip	6.3	2.5–12.9
	Tongue	20.8	6.7–48.6
	Esophagus	5.3	2.3–10.5
	Lung	2.4	1.6–3.4
Pharynx	Larynx	5.1	1.0–14.9
	Lung	1.9	1.1–3.2
Larynx	Lung	2.6	2.2–3.1
	Pancreas	1.7	1.0–2.6
Lung	Larynx	3.1	2.0–4.7
	Kidney	2.7	2.0–3.6
	Bladder	1.6	1.2–2.0
Kidney	Bladder	7.1	6.0–8.4
Bladder	Lung	1.6	1.4–1.8
	Kidney	3.2	2.7–3.8
Pancreas	Kidney	2.7	1.1–5.6
Cervix	Esophagus	2.0	1.2–3.0
	Lung	2.8	2.4–3.2
	Kidney	1.4	1.1–1.8
	Bladder	3.0	2.5–3.5

tumor diagnosis, common etiologic factors are suspected. Tobacco smoking appears to underlie the associations between cancers of the oral cavity and pharynx, esophagus, respiratory system, urinary tract, pancreas, and cervix [26–31] (Table 5). Not only do smokers have an increased risk of developing cancer of these sites, but persons who develop one of these cancers have an increased risk of yet another smoking-related tumor [4,6,7,8,10,12]. One-third of all 481 second tumors seen in lung cancer patients could be considered to be related to smoking, which explains the 20 percent excess of second primary cancer among lung cancer patients [6].

For cancers of the oral cavity and pharynx, the elevated RR of cancer of adjacent sites can be attributed to tobacco (and alcohol), and the same applies to the reciprocal associations between kidney and bladder cancer. However, it is difficult for us to rule out the influence of misdiagnosis and misclassification of metastatic spread on the risk estimates for tumors arising from the same organ system, and host factors may play an important role in promoting multifocal tumors and predisposing to the influence of environmental risk factors. The associations between tobacco-related sites and cancer of the cervix may be confounded by socioeconomic and other characteristics associated both with smoking and cervical cancer [32].

Nutritional and hormonal factors probably affect the reciprocal associations observed between cancers of the large bowel, breast, and female genital organs (Table 6). Although the associations are weak and misdiagnosis of metastatic spread in the abdominal cavity could bias results, cancers of the colon, rectum, biliary tract, pancreas, breast, endometrium, ovary, and prostate may have similar dietary and nutritional determinants, such as fat intake [33]. However, the biologic mechanisms involved are not clear, and the suggested relationship with fat for many of these sites is based mainly on evidence from international correlations [34]. Some of these cancers evolve in hormone-dependent organs, particularly cancers of the breast, corpus uteri, and ovary, and it has been suggested that the risk for females developing colon cancer may also be related to endocrine factors [35]. Thus, an association in both directions between cancer of the colon and cancers of the endometrium and ovary is interesting. The overall absence of strong bidirectional associations between cancers of these sites may be due to a weak association with fat [1,22,23], little variation in the diet of the Danish population, or a possible underreporting of multiple primary cancers.

Obesity has been associated with cancers of the endometrium and breast [29], possibly due to the increased production of endogenous estrogens [36]. Several studies show an association between the use of estrogen unopposed by progesterone and

TABLE 6

Reciprocal Associations (RR) Between Cancers of Hormone-Dependent Organs and the Colon among Females in Denmark, 1943–1980

First Primary	Second Primary	RR	95% CI	First Primary	Second Primary	RR	95% CI
Breast	Colon	1.1	1.0–1.2	Colon	Breast	0.9	0.8–1.1
Colon	Corpus uteri	1.8	1.3–2.3	Corpus uteri	Colon	1.5	1.3–1.7
Colon	Ovary	2.6	2.1–3.1	Ovary	Colon	1.7	1.3–2.2
Corpus uteri	Breast	1.2	1.1–1.4	Breast	Corpus uteri	1.0	0.9–1.2
Ovary	Breast	1.1	0.9–1.3	Breast	Ovary	1.3	1.1–1.4
Corpus uteri	Ovary	0.8[a]	0.6–1.0	Ovary	Corpus uteri	2.3	1.7–3.0

[a]The RR = 2.7 when allowing for hysterectomies (and thus possible oophorectomies) in calculation of risk.

endometrial cancer [37]. Some evidence indicates that estrogens may cause breast tumors, particularly in high-risk individuals [38]. Ovarian cancer has also been linked to estrogens [39]. In our study, we observed excesses of breast cancer following endometrial cancer, and an increased risk of ovarian cancer following endometrial cancer (Table 6). These data are consistent with the hypothesis that hormonal factors, including endogenous estrogens, may influence tumor development for these cancer sites.

Ionizing radiation [40] and certain chemotherapeutic drugs [41] used in the treatment of cancer are known carcinogens. To evaluate the possible influence of irradiation on second cancer development, we classified index cancer sites as irradiated if 50 percent or more received radiation, and not irradiated if 10 percent or less were irradiated (Table 7). Significant risks of solid tumors ten years or more after the initial cancer diagnosis and the risk of subsequent ANLL during the one- to nine-year follow-up interval are presented, as radiogenic leukemias are known to appear early, contrary to solid tumors.

A 2.7-fold and a 1.6-fold increased risk of thyroid and breast cancers, respectively, was observed following head and neck cancer. The thyroid gland is known to be

TABLE 7

Relative Risks for Solid Tumors in Long-Term Survivors (10+ Years) and Risk of Acute Non-Lymphocytic Leukemia (ANLL) among 1–9 Years' Survivors Following Frequently and Infrequently Irradiated First Primary Cancer in Denmark, 1943–1980

First Primary Site, % Irradiated	Second Primary Cancer	Irradiated[a]		Not Irradiated[b]	
		RR	95% CI	RR	95% CI
Head and neck,[c] 76%	Thyroid	2.7	1.0–6.0	0.8	0.1–2.8
	Female breast	1.6	1.0–2.2	1.0	0.8–1.4
	ANLL	1.1	0.4–2.5	1.1	0.6–1.8
Genital organs,[d] 65%	Colon	1.2	1.0–1.4	1.0	0.8–1.3
	Rectum	1.5	1.2–1.8	1.4	1.1–1.9
	Bladder[e]	2.6	2.2–3.2	0.8	0.5–1.2
	Connective tissue	2.5	1.2–4.6	0.7	0.0–3.8
	ANLL	1.9	1.1–3.1	1.1	0.6–1.8
Female breast, 69%	Salivary gland	3.2	1.3–6.5	0.8	0.0–4.7
	Esophagus	1.7	1.0–2.9	1.0	0.4–2.1
	Lung	1.7	1.3–2.1	1.0	0.7–1.3
	Ovary	1.5	1.2–1.9	0.5	0.2–1.1
	Connective tissue	4.2	2.1–7.6	0.7	0.0–3.8
	ANLL	2.7	1.9–3.9	1.1	0.6–1.8
Hodgkin's and NHL 64%	Lung	1.8	1.0–2.9	1.0	0.7–1.3
	Female breast	2.1	1.1–3.5	1.0	0.8–1.4
	Bladder	2.6	1.3–4.7	0.8	0.5–1.2
	ANLL	8.4	4.0–15.5	1.1	0.6–1.8

[a]50 percent or more initial cancers irradiated
[b]10 percent or less (average 4 percent) received irradiation (primary sites: stomach, small intestine, colon, liver, gallbladder, and pancreas).
[c]Includes cancers of the lip, tongue, salivary glands, gum, mouth, pharynx, larynx, and nasal cavities
[d]Includes cancers of testis, cervix, and corpus uteri
[e]Includes bladder papillomas

sensitive to radiation, and increased cancer risks have previously been described following X-rays to the head and neck region [42], treatment for tinea capitis [43], and among atomic bomb survivors [44]. The breast cancer excess is unlikely to be attributable to radiation of the head and neck region because in most instances the breast would not be in or near the therapeutic fields. The same argument would apply to head and neck cancers following breast irradiation. A bidirectional association between salivary gland tumors and breast cancer has been described [45,46], but this was only suggested among long-term survivors in our study [6,9]. However, the elevated risk of salivary gland tumors following a breast cancer indicates that these sites share some common etiology.

The relative risks of cancers of the colon (1.2), rectum (1.5), bladder (2.6), and connective tissue (2.5) following a frequently irradiated genital cancer were not unexpected, as all these organs are close to the radiation fields used to treat genital cancers [47]. The RRs for colon and rectal cancer are compatible with those seen for other irradiated populations, e.g., patients with ankylosing spondylitis and metropathia hemorrhagica [48,49]. However, common risk factors for genital and gastrointestinal cancers or misdiagnosed metastases may account for some of the increased risks.

The increased risks of cancers of the esophagus and lung following breast cancer are consistent with a radiation effect which has been seen in studies of atomic bomb survivors [50]. It is unlikely that the increased risk of ovarian cancer following breast cancer is related to castration radiotherapy because only 6 percent of Danish breast cancer patients received such treatment [51].

Solid tumors were also in excess among long-term survivors with malignant lymphoma, in particular cancers of the lung, female breast, and bladder (Table 7). Radiation may have increased the risk of second cancers in some instances, such as following the inverted Y irradiation for Hodgkin's disease that exposes a large proportion of the body trunk. Common etiologies and misdiagnoses of lymphatic infiltrations could also be involved.

Significantly increased RR of ANLL was noted during the first ten years of follow-up among patients with initial cancers of the genital organs (1.9), female breast cancer (2.7), and malignant lymphoma (8.4) (Hodgkin's disease, 20.6; NHL, 3.5). Interestingly, the RR of ANLL remained significantly elevated among long-term survivors of breast cancer (2.3) [9] and malignant lymphoma (Hodgkin's disease, 14.3; NHL, 7.1) [14].

The induction of acute leukemia, especially ANLL, is a well-known consequence of radiation [52–54]. The pattern of increased risk of ANLL within the first ten years after exposure is consistent with previous reports [55] and different from that observed for solid tumors. The late excesses of ANLL ten years or more after initial diagnosis may be related to treatment of recurrent disease. For Hodgkin's disease and NHL, chemotherapy undoubtedly contributed to the increased risk of leukemia as reported by others [52,56–58]. Our present findings do not allow us to state whether radiation, chemotherapy, or both are associated with ANLL, but previous studies have indicated that alkylating agents are much more likely to be responsible for the increased leukemia risk than is radiotherapy [59].

CONCLUSION

Many factors influence the results from our study on multiple primary cancers in Denmark. Utilization of Cancer Registry data is subject to differences in reporting and

coding practices during the years of operation. Medical surveillance, specificity of diagnostic methods, and local interest as well as changes in risk factors may over the years modify the risk. Nonetheless, the usefulness of a population-based cancer registry in a well-defined population for evaluation and quantification of the risk of second primary cancers is demonstrated. The long period of follow-up allows consideration of time trends in risk even for rare cancers.

Even if the overall risk of a person developing a second cancer at a different site from the first may be slightly underestimated, this study shows that a RR above 1.3 may be ruled out when possible underreporting is taken into account. Our results suggest that cancer patients overall are not at high risk of developing new malignant tumors. Conversely, the occurrence of one cancer does not appear to protect against the development of a new tumor in another organ.

Elevated rates may occur for particular combinations of sites, especially those related to common risk factors. No specific risk factor could be examined in the present descriptive study, but several etiologic leads have been suggested or confirmed, i.e., cigarette smoking, hormonal and nutritional factors, radiation, and chemotherapy.

Studies of multiple primary neoplasms provide researchers with a strategy to investigate the exogenous and endogenous determinants of cancer. To increase the value of the survey data, staffs of population-based cancer registries must give attention to improvements in registration of multiple cancers in the same individual and agree to rules that facilitate international comparisons. This is important with a view to future etiologic studies and to the identification of high-risk cancer patients who should be monitored closely for the early detection and management of second primary cancers.

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