Frisch, 1994

American Journal of Epidemiology
Copyright © 1994 by The Johns Hopkins University School of Hygiene and Public Health
All rights reserved

Vol. 140, No. 1
Printed in U.S.A.

ORIGINAL CONTRIBUTIONS

Malignancies that Occur before and after Anal Cancer: Clues to Their Etiology

Morten Frisch,[1,2] Jørgen H. Olsen,[2] and Mads Melbye[1]

With the use of two different approaches to study multiple primaries in anal cancer patients, the authors sought clues to the etiology of anal cancer. Based on data from the Danish Cancer Registry for 1943–1989, previous cancers in 831 anal cancer patients were compared with cancers in 12,376 matched population controls, and subsequent cancers in 955 anal cancer patients were compared with expected numbers based on population rates. Overall, previous cancers were in excess among anal cancer patients (odds ratio (OR) = 1.7, 95% confidence interval (CI) 1.3–2.1). Elevated risks were observed especially for the vulva/vagina (OR = 15.4, 95% CI 4.9–48.0), cervix (OR = 4.3, 95% CI 2.7–6.9), and lymphoma/leukemia (OR = 3.9, 95% CI 1.5–10.4). Subsequent cancers were also in excess (relative risk (RR) = 1.4, 95% CI 1.1–1.7), particularly for the lung (RR = 2.3, 95% CI 1.3–3.7), bladder (RR = 2.3, 95% CI 1.0–4.6), breast (RR = 2.0, 95% CI 1.2–3.3), vulva/vagina (RR = 12.3, 95% CI 4.0–28.7), and small intestine (two cases) (RR = 10.8, 95% CI 1.2–39.0). Colorectal cancers were reduced (RR = 0.3, 95% CI 0.1–0.9). The data support a multifactorial etiology for anal cancer, in which an infectious agent and smoking may be involved. The association with lymphatic/hematopoietic cancers may indicate a possible role for immunodeficiency in anal cancer development. Multiple cancers occurred predominantly in patients diagnosed with anal cancer at a young age (<60 years), which raises the possibility of a genetic predisposition for some cases. The authors recommend that, in future hypothesis generating and hypothesis testing multiple cancer studies of rare malignancies, the combined study of cancer events both prior to and following an index cancer should be considered. *Am J Epidemiol* 1994;140:12–19.

anus neoplasms; immunosuppression; neoplasms, multiple primary; risk factors; smoking

Anal cancer has increased in incidence during the past 20–30 years (1–3). This trend has been most marked among women and residents of large cities, but considerable evidence has also linked anal cancer with male homosexual behavior (1, 3–10). The epithelium of the anal region also appears to be susceptible to factors of importance for cancers of the lower female genital tract (11, 12). Sexually transmitted agents, especially human papillomaviruses, are

Received for publication July 26, 1993, and in final form April 8, 1994.

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; RR, relative risk; SMR, standardized morbidity ratio.

[1] Epidemiology Research Unit, Danish Epidemiology Science Centre, State Serum Institute, Copenhagen, Denmark.

[2] Danish Cancer Society, Research Centre, Division for Cancer Epidemiology, Copenhagen, Denmark.

Reprint requests to Dr. Morten Frisch, Epidemiology Research Unit, Danish Epidemiology Science Centre, State Serum Institute, 5 Artillerivej, 2300 Copenhagen S, Denmark.

strongly suspected to be involved in the etiology (13–18). Recently, cigarette smoking has been suggested as another common risk factor for the anogenital epidermoid cancers (6, 7, 19), and the observation of a significant increase in lung cancers following anal cancer supports this hypothesis (20). To extend the study of these and other potential associations, we investigated multiple primaries prior and subsequent to a diagnosis of anal epidermoid carcinoma in a well-monitored, unselected population.

MATERIALS AND METHODS

National incidence data on all cancers have been collected in the Danish Cancer Registry since 1943 (21). A total of 970 invasive epidermoid anal cancer patients diagnosed during 1943–1989 were identified from the registry files as described previously (1). Patients with other cancers in the anorectal region (adenocarcinomas and melanomas) were not included, because there is no evidence to suggest a shared etiology with epidermoid anal cancer. Vital and migration statuses as of December 31, 1989 were obtained for every person under study by linkage to the Central Population Register.

Previous cancers

Among anal cancer patients, we investigated cancers diagnosed during the period from January 1, 1943 (or date of birth for persons born later) until one month before the anal cancer diagnosis. To evaluate the expected cancer incidence, we designed a matched case-control study. Controls were drawn from the Central Population Register, which was initiated on April 1, 1968. Of the 970 anal cancer patients, 831 were alive on that date. For each case, 15 sex- and age-matched (± one day) population controls were chosen who were alive on the date of diagnosis of the anal cancer in the case. Consequently, corresponding cases and controls had exactly the same time at risk prior to the anal cancer diagnosis. Out of 12,465 controls, 89 (0.7 percent) were excluded from the analysis because they had emigrated or were lost to follow-up (0.04 percent) before the date of diagnosis of the index anal cancer. Left in the study of previous cancers were 831 anal cancer cases (264 men and 567 women) and 12,376 controls (3,922 men and 8,454 women). All recorded invasive cancers in the Danish Cancer Registry that occurred among cases and controls were identified. By means of conditional logistic regression analysis for matched data, odds ratios adjusted for sex and marital status were calculated as indicators of the relative risk (22).

Subsequent cancers

Of the 970 anal cancer patients, 15 patients who died within one month after diagnosis were excluded, leaving 955 patients (323 men and 632 women) in the study of subsequent primaries. The period of follow-up for cancer occurrence was calculated from the month following the date of diagnosis of the anal cancer to the date of death, emigration, or December 31, 1989, whichever came first. The age-, sex-, and period-specific national incidence rates were applied to the appropriate person-years under observation to obtain the number of cancers expected had the anal cancer patients experienced the same cancer incidence as prevailed in the general population of Denmark. We used the ratio of observed to expected cancers as a measure of the relative risk, and 95 percent confidence intervals were calculated using Byars limits (23), assuming a Poisson distribution of the observed cancer events. To test if zero observed second cancers in a specific site was significantly below the expected, one-sided exact 95 percent confidence intervals were calculated as: (0.0; $-\ln(0.05)$/expected number).

RESULTS

Previous cancers

Among men, 21 anal cancer patients had 22 previous cancers compared with 200 controls with 212 cancers. Among women, 59

anal cancer patients had 62 previous cancers compared with 560 controls with 603 previous cancers. An overall 1.7-fold risk (95 percent confidence interval (CI) 1.3–2.1) of a previous cancer was observed in anal cancer patients of both sexes (table 1). Men diagnosed with anal cancer at a younger age (<60 years) had previous cancers diagnosed much more frequently than did controls (odds ratio (OR) = 8.9, 95 percent CI 4.1–19.3) (table 2). In men above age 60 years, the corresponding odds ratios were not significantly elevated. In women, no significant excess risk of previous cancers was apparent in younger anal cancer patients (<60 years).

Women with anal cancer had a marked excess of previous gynecologic cancers (OR = 3.1, 95 percent CI 2.1–4.6). In particular, patients with cancers of the vulva and vagina were at risk of developing anal cancer (OR = 15.4, 95 percent CI 4.9–48.0), but cervical cancer patients also had an increased risk (OR = 4.3, 95 percent CI 2.7–6.9) (table 3). The number of previous cancers of the uterine corpus and ovary did not differ significantly from the number expected.

More anal cancer patients than controls had previous lymphoma/leukemia (OR = 3.9, 95 percent CI 1.5–10.4) (table 1). Three men were diagnosed in 1961, 1975, and 1982 with a non-Hodgkin's lymphoma (OR = 7.1, 95 percent CI 1.8–27.6), whereas two women had a chronic lymphatic leukemia and multiple myeloma prior to the anal cancer (OR = 2.5, 95 percent CI 0.6–11.1). The number of previous respiratory cancers (larynx, $n = 1$; lung, $n = 2$) appeared high as well, but this finding was not statistically significant (OR = 2.3, 95 percent CI 0.7–7.6).

Subsequent cancers

After the anal cancer, 323 men were followed for 1,655 person-years and 632 women for 3,531 person-years. In total, we observed 36 subsequent cancers in 36 men and 57 subsequent cancers in 51 women (relative risk (RR) = 1.4, 95 percent CI 1.1–1.7) (table 4).

Men had 2.2 and women 3.1 times more respiratory system cancers than expected (95 percent CI 1.1–3.9 and 1.4–5.9, respectively). Lung cancer (RR = 2.3, 95 percent CI 1.3–3.7) constituted the majority of these cases ($n = 16$), but even higher relative risks were found for second cancers of other parts of the respiratory tract: nasal cavity and

TABLE 1. Odds ratios (OR) for previous cancers in various organ systems in 831 anal cancer patients and 12,376 matched population controls, Denmark, 1943–1989

Site of previous cancer	No. of previous cancers						Men and women OR (95% CI)
	Men			Women			
	Cases*	Controls†	OR‡ (95% CI§)	Cases	Controls	OR (95% CI)	
All malignancies‖	21	200	1.7 (1.1–2.8)	59	560	1.6 (1.2–2.2)	1.7 (1.3–2.1)
Lip, mouth, pharynx	1	13	1.3 (0.2–10.0)	0	13	0	0.6 (0.1–4.2)
Digestive organs	5	39	2.2 (0.8–5.6)	3	75	0.6 (0.2–1.9)	1.1 (0.5–2.2)
Respiratory system	2	12	2.6 (0.6–12.1)	1	8	1.9 (0.2–15.3)	2.3 (0.7–7.6)
Breast	0	1	0	10	154	1.0 (0.5–1.9)	1.0 (0.5–1.8)
Female genital organs				35	177	3.1 (2.1–4.6)	
Male genital organs	2	33	0.9 (0.2–3.9)				
Urinary system	4	41	1.5 (0.5–4.1)	1	23	0.7 (0.1–4.9)	1.2 (0.5–2.9)
Skin	4	61	1.0 (0.4–2.8)	8	112	1.0 (0.5–2.1)	1.0 (0.6–1.9)
Lymphoma/leukemia	3	7	7.1 (1.8–27.6)	2	12	2.5 (0.6–11.1)	3.9 (1.5–10.4)
Other	0	4	0	2	23	1.3 (0.3–5.5)	1.1 (0.3–4.7)

* Anal cancer patients.
† Population controls matched by sex and age (± one day).
‡ Odds ratios adjusted for sex and marital status.
§ CI, confidence interval.
‖ The odds ratios for the category "All malignancies" were calculated based on *persons* with previous cancer diagnoses irrespective of the number of cancers in the individual patients. One male case and 7 controls (1 man and 6 women) had two distinct previous cancers within the same organ system. Each counted only once in the odds ratio calculations for the respective organ system.

TABLE 2. Odds ratios (OR) by age and sex for previous cancers in 831 anal cancer patients and 12,376 matched population controls, Denmark, 1943–1989

Age (years)	No. of previous cancers						Men and women OR (95% CI)
	Men			Women			
	Cases*	Controls†	OR‡ (95% CI§)	Cases	Controls	OR (95% CI)	
<60‖	11	21	8.9 (4.1–19.3)	11	98	1.7 (0.9–3.3)	2.9 (1.8–4.7)
60–69	5	40	2.0 (0.7–5.2)	23	172	2.2 (1.3–3.4)	2.1 (1.4–3.2)
≥70	5	139	0.6 (0.2–1.4)	25	290	1.3 (0.9–2.0)	1.1 (0.7–1.6)
Total	21	200	1.7 (1.1–2.8)	59	560	1.6 (1.2–2.2)	1.7 (1.3–2.1)

* Anal cancer patients.
† Population controls matched by sex and age (± one day).
‡ Odds ratios adjusted for sex and marital status.
§ CI, confidence interval.
‖ Age at diagnosis of anal cancer in cases or corresponding age in controls.

TABLE 3. Odds ratios (OR) for previous gynecologic cancers and relative risks (RR) for subsequent gynecologic cancers in women with anal cancer and population controls, Denmark, 1943–1989

Site of cancer	No. of previous cancers before anal cancer*			No. of subsequent cancers after anal cancer†		
	Cases	Controls	OR‡ (95% CI§)	Observed	Expected	RR‖ (95% CI)
Vulva and vagina	6	6	15.4 (4.9–48.0)	5	0.4	12.3 (4.0–28.7)
Uterine cervix	23	82	4.3 (2.7–6.9)	2	1.6	1.3 (0.1–4.5)
Uterine corpus	3	65	0.7 (0.2–2.2)	1	2.2	0.5 (0.0–2.5)
Ovary	3	25	1.9 (0.6–6.2)	1	1.9	0.5 (0.0–2.9)
Total	35	177¶	3.1 (2.1–4.6)	9	6.1	1.5 (0.7–2.8)

* Previous gynecologic cancers among 567 female anal cancer patients and 8,454 sex- and age-matched (± one day) controls.
† Subsequent gynecologic cancers among 632 female anal cancer patients compared with the entire Danish female population.
‡ Odds ratios adjusted for marital status.
§ CI, confidence interval.
‖ Relative risk estimated as the ratio of observed to expected numbers.
¶ One control had two previous gynecologic cancers.

paranasal sinuses (n = 1) (RR = 7.9, 95 percent CI 0.1–43.9), larynx (n = 2) (RR = 4.4, 95 percent CI 0.5–15.8), and pleura (n = 1) (RR = 6.0, 95 percent CI 0.1–33.1). Numbers were too small, however, to be significantly elevated.

Women had 2.6 and men 1.7 times the expected incidence of urinary system tumors (95 percent CI 1.0–5.7 and 0.5–3.9, respectively). Bladder tumors (including one urethral tumor) were the most frequent urinary system tumors (n = 8; RR = 2.3, 95 percent CI 1.0–4.6). Cancer of the kidney was diagnosed in three patients (RR = 1.6, 95 percent CI 0.3–4.7).

A significantly increased risk of acquiring a subsequent breast cancer was found in women with anal cancer (RR = 2.0, 95 percent CI 1.2–3.3).

Five cancers of the vulva and vagina were observed compared with 0.4 expected (RR = 12.3, 95 percent CI 4.0–28.7) (table 3). We found more cancers of the vulva/vagina and cervix than expected (RR = 3.5, 95 percent CI 1.4–7.2) but fewer than expected cancers of the uterine corpus and ovary (RR = 0.5, 95 percent CI 0.1–1.8). Six out of seven male genital cancers occurred in the prostate (RR = 1.6, 95 percent CI 0.6–3.5). One case of penile cancer was observed compared with 0.1 expected.

Only 12 cancers of the digestive organs were observed compared with 19.7 expected (RR = 0.6, 95 percent CI 0.3–1.1): stomach cancer in two patients (RR = 0.5, 95 percent CI 0.1–1.7), colorectal cancer in three patients (RR = 0.3, 95 percent CI 0.1–0.9), and cancer of the small intestine (both carcinoid tumors) in two patients (RR = 10.8, 95 percent CI 1.2–39.0).

Patients diagnosed with anal cancer at an earlier age (<60 years) had a high incidence of subsequent cancers (RR = 2.1, 95 percent CI 1.6–2.7), whereas older patients did not experience such an excess (table 5). The anatomic distribution of subsequent cancers

TABLE 4. Relative risks (RR) for subsequent cancers in various organ systems in 955 anal cancer patients, Denmark, 1943–1989

Site of subsequent cancer	No. of subsequent cancers						Men and women RR (95% CI)
	Men			Women			
	Observed*	Expected†	RR‡ (95% CI§)	Observed	Expected	RR (95% CI)	
All malignancies	36	27.3	1.3 (0.9–1.8)	57	41.2	1.4 (1.0–1.8)	1.4 (1.1–1.7)
Lip, mouth, pharynx	1	0.7	1.4 (0.0–8.0)	0	0.5	0 (0.0–5.9)	0.8 (0.0–4.6)
Digestive organs	6	8.1	0.7 (0.3–1.6)	6	11.6	0.5 (0.2–1.1)	0.6 (0.3–1.1)
Respiratory system	11	5.0	2.2 (1.1–3.9)	9	2.9	3.1 (1.4–5.9)	2.5 (1.5–3.9)
Breast	0	0.0		16	7.8	2.0 (1.2–3.3)	2.0 (1.2–3.3)
Female genital organs				9	6.1	1.5 (0.7–2.8)	
Male genital organs	7	3.9	1.8 (0.7–3.7)				
Urinary system	5	3.0	1.7 (0.5–3.9)	6	2.3	2.6 (1.0–5.7)	2.1 (1.0–3.7)
Skin	4	3.6	1.1 (0.3–2.8)	5	5.3	0.9 (0.3–2.2)	1.0 (0.5–1.9)
Lymphoma/leukemia	2	1.6	1.3 (0.1–4.5)	2	2.1	0.9 (0.1–3.4)	1.1 (0.3–2.8)
Other	0	1.3	0 (0.0–2.3)	4‖	2.6	1.6 (0.4–4.0)	1.0 (0.3–2.7)

* Observed numbers of subsequent cancers in 955 anal cancer patients (323 men and 632 women).
† Expected numbers of subsequent cancers based on population rates.
‡ Relative risk estimated as the ratio of observed to expected numbers.
§ CI, confidence interval.
‖ Three cases of brain cancer and one thyroid cancer.

TABLE 5. Relative risks (RR) by age and sex for subsequent cancers in 955 anal cancer patients, Denmark, 1943–1989

Age (years)	No. of subsequent cancers						Men and women RR (95% CI)
	Men			Women			
	Observed*	Expected†	RR‡ (95% CI§)	Observed	Expected	RR (95% CI)	
<60‖	16	9.7	1.7 (0.9–2.7)	36	15.2	2.4 (1.7–3.3)	2.1 (1.6–2.7)
60–69	9	7.0	1.3 (0.6–2.4)	8	12.2	0.7 (0.3–1.3)	0.9 (0.5–1.4)
≥70	11	10.5	1.0 (0.5–1.9)	13	13.8	0.9 (0.5–1.6)	1.0 (0.6–1.5)
Total	36	27.3	1.3 (0.9–1.8)	57	41.2	1.4 (1.0–1.8)	1.4 (1.1–1.7)

* Observed numbers of subsequent cancers in 955 anal cancer patients (323 men and 632 women).
† Expected numbers of subsequent cancers based on population rates.
‡ Relative risk estimated as the ratio of observed to expected numbers.
§ CI, confidence interval.
‖ Age at diagnosis of anal cancer.

in the younger age group did not differ from that in the patient population as a whole, but associations were generally stronger (respiratory system cancers, RR = 3.9; bladder cancer, RR = 3.3; breast cancer, RR = 3.2; vulval/vaginal cancer, RR = 31.9; and lymphoma/leukemia (one woman with non-Hodgkin's lymphoma and two men with leukemia), RR = 2.3).

DISCUSSION

Subsequent cancers have been widely studied to generate and examine risk factor hypotheses (24). The basic idea is that new malignancies that occur in non-random excess following an index cancer may have one or more risk factors in common with the index cancer. A measure often used is the standardized morbidity ratio (SMR) (23), in which expected numbers of cancers are calculated on the basis of rates in a reference population weighted according to the age distribution in the patient group under study (indirect standardization). The ratio between observed and expected cancers is an estimate of the relative risk of subsequent malignancies.

It seems reasonable to assume that studies of previous cancers are as informative and hypothesis generating as studies of second cancers. This view, however, has not gained general acceptance among researchers. One reason is probably that it is not possible to

apply the SMR method in studies of previous cancers. The composition of previous cancers in any patient group is skewed in favor of malignancies with a relatively good prognosis compared with cancer experiences in the general population. Therefore, population rates do not serve as a proper means to calculate expected numbers for the SMR. We have overcome this problem by using a matched case-control design, in which cases and controls were matched on sex, age, and vital status on the date of anal cancer diagnosis in the case. In this way, we have adjusted for the survivor status of the case group, which otherwise could introduce a serious selection bias toward a reduced relative risk for lethal cancers.

Patients diagnosed with anal cancer at a younger age were particularly at increased risk of other malignancies both before and after the anal cancer. Apart from a possible overlap in external risk factors between these malignancies, a case for an increased underlying genetic susceptibility should be considered. Recent laboratory investigations have detected an overexpression of identical oncogene products in different cancers, including epidermoid anal cancer (25), which theoretically could contribute to the observed associations with other malignancies.

A recent study of cancers after anal neoplasms (20) revealed associations essentially identical to those presented here, even though both in-situ and non-epidermoid lesions were included in the study. We observed a 4.3-fold risk of cervical cancer prior to the diagnosis of anal cancer, which supports previous findings of a link between anal and cervical cancer (11, 12). Interestingly, the association was less obvious with respect to cervical cancer *after* a diagnosis of anal cancer (RR = 1.3). A similar result was observed by Rabkin et al. (20). The high risk of cervical cancer before but not after anal cancer probably reflects the much younger age distribution for patients with cervical cancer (11). Furthermore, increased cervical smear screening activity in anal cancer patients may to some extent have lowered the number of subsequent invasive cervical cancers. A clearer association (12- to 15-fold risk) appeared with vulval/vaginal cancer both prior to and after anal cancer. This strongly argues for overlapping risk factors.

Theoretically, the risk of anal and lower gynecologic cancers could be influenced by previous radiotherapy. Of the subsequent cancers of the vulva, vagina, and cervix that occurred at a median time period of 7.2 years (range 30–402 months) after anal cancer, only one patient (14 percent) had received radiotherapy for the anal carcinoma. Likewise, of 29 anal cancer patients who had a lower genital organ cancer at a median time period of 17.9 years earlier (range 1–486 months), only 15 (52 percent) had received radiotherapy for the gynecologic malignancy (one of six with vulval cancer; 14 of 23 with cervical cancer). Therefore, it is unlikely that radiotherapy has played an important role in the observed close association between anal and lower gynecologic cancers.

Case-control studies have found an increased risk of anal cancer in heavy smokers (6, 7, 19, 26). We found a significant excess of subsequent respiratory system cancers in both sexes (RR = 2.5). The corresponding relative risk *before* anal cancer was of the same magnitude (OR = 2.3), but this estimate was statistically unstable, probably because of the few long-term survivors from lung cancer. The risk of another smoking-associated cancer, bladder cancer, was similarly elevated after (RR = 2.3), but not prior to, anal cancer. The possible influence of radiotherapy should be taken into consideration here as well. However, only one of eight subsequent bladder tumor patients had received radiation therapy for the anal cancer. Rather than reflecting an effect of radiotherapy, it seems plausible that the excess risk of lung and bladder cancers mirrors overlapping risk factors.

Immunologic dysfunction may promote anogenital carcinogenesis. We (14) and others (27–29) have previously documented a strong positive correlation between reduced immune status and the presence of anal in-

traepithelial abnormalities in homosexual/bisexual men infected with human immunodeficiency virus (HIV), and immunosuppressed renal transplant patients have been found to be at elevated risk of anal and other anogenital cancers (30). If our present finding of a nearly four times increased occurrence of previous lymphoma/leukemia reflects a real association, it might either be explained by a common risk factor or by the hypothesis that lymphoma/leukemia increases the risk of anal cancer. The observed lymphomas (all in men) were diagnosed in 1961, 1975, and 1982, i.e., 8, 9, and 3 years before the anal cancer, respectively, and although all were of the non-Hodgkin's type, they are unlikely to represent a strong association with HIV. Only one of these lymphomas was diagnosed in an unmarried man after the introduction of the acquired immunodeficiency syndrome epidemic in Denmark (31). All other men with previous cancers had married and were statistically at low risk of HIV. We speculate whether immunodeficiency caused by lymphoma or leukemia per se or by the cytotoxic or radiation therapy of these malignancies somehow facilitates the carcinogenic process in anal lesions. However, although the association appears rather strong, data are too sparse to reach any firm conclusions. Similarly, further studies are needed to determine whether the observed sex difference is real.

Only three cases of subsequent colorectal cancers were observed compared with 10.1 expected (RR = 0.3), giving no support for etiologic parallels between these tumors. By contrast, the number of observed cases of cancer of the small intestine was above the expected. Prior to the diagnosis of anal cancer, one patient had this rare malignancy (OR = 15.0, 95 percent CI 0.9–239.4), and after anal cancer diagnosis, two patients were diagnosed with cancer of the small intestine compared with 0.2 expected (RR = 10.8, 95 percent CI 1.2–39.0). Previously, cancer of the small intestine has been reported (20) to be in excess among survivors from cervical cancer. Although these observations are limited, the data raise the possibility of shared risk factors for small intestine and anogenital cancers.

To our knowledge, our observation that breast cancer occurred in excess after, but not prior to, the diagnosis of anal cancer has not been observed before. Recent advances in molecular biology have revealed identical gene alterations in breast cancer and anal cancer tissue (32, 33). Thus, if the observed association represents a real link, it might be explained by genetic predisposition. Alternatively, the carcinogenic agents responsible for anal and breast cancer might operate by causing the same somatic mutations in anal and breast tissue.

Our results and those of other investigators suggest a multifactorial etiology of anal cancer. We confirmed previous findings of a strong link between anal cancer and lower gynecologic cancers, particularly cancers of the vulva and vagina. The excess risks of cancers of the lung and bladder support the hypothesis that smoking plays a role in anal cancer pathogenesis. It is hypothesized that immunologic dysfunction several years prior to the diagnosis of anal cancer may play some role, but this association and the finding of a high risk of multiple cancers in young patients with anal cancer need further study. Finally, we believe that future multiple cancer studies, particularly of rare malignancies, could benefit from the investigation of both previous and subsequent cancer experiences, since in such studies it is important to use optimally the total cancer experience in each of the few patients available.

ACKNOWLEDGMENTS

Supported by grant no. 90–7620 from The Danish Cancer Society.

The authors thank Andrea Meersohn and Bendix Carstensen of The Danish Cancer Society for computer assistance and comments on statistical analyses.

REFERENCES

1. Frisch M, Melbye M, Møller H. Trends in incidence of anal cancer in Denmark. BMJ 1993; 306:419–22.

2. Goldman S, Glimelius B, Nilsson B, et al. Incidence of anal epidermoid carcinoma in Sweden 1970–1984. Acta Chir Scand 1989;155:191–7.
3. Melbye M, Rabkin C, Frisch M, et al. Changing patterns of anal cancer incidence in the United States, 1940–1989. Am J Epidemiol 1994;139: 772–80.
4. Daling JR, Weiss NS, Klopfenstein LL, et al. Correlates of homosexual behavior and the incidence of anal cancer. JAMA 1982;247:1988–90.
5. Austin DF. Etiological clues from descriptive epidemiology: squamous carcinoma of the rectum or anus. Natl Cancer Inst Monogr 1982;62: 89–90.
6. Daling JR, Weiss NS, Hislop TG, et al. Sexual practices, sexually transmitted diseases, and the incidence of anal cancer. N Engl J Med 1987; 317:973–7.
7. Holly EA, Whittemore AS, Aston DA, et al. Anal cancer incidence: genital warts, anal fissure or fistula, hemorrhoids, and smoking. JNCI 1989;81:726–31.
8. Scholefield JH, Thornton Jones H, Cuzick J, et al. Anal cancer and marital status. Br J Cancer 1990;62:286–8.
9. Wexner SD, Milsom JW, Dailey TH. The demographics of anal cancer are changing. Dis Colon Rectum 1987;30:942–6.
10. Peters RK, Mack TM. Patterns of anal carcinoma by gender and marital status in Los Angeles County. Br J Cancer 1983;48:629–36.
11. Melbye M, Sprøgel P. Aetiological parallel between anal cancer and cervical cancer. Lancet 1991;338:657–9.
12. Scholefield JH, Sonnex C, Talbot IC, et al. Anal and cervical intraepithelial neoplasia: possible parallel. Lancet 1989;2:765–9.
13. Daling JR, Sherman KJ. Relationship between human papillomavirus infection and tumors of anogenital sites other than the cervix. In: Muñoz N, Bosch FX, Shah KV, et al, eds. The epidemiology of cervical cancer and human papillomavirus. IARC scientific publications no. 119. Lyon: International Agency for Research on Cancer, 1992:223–41.
14. Melbye M, Palefsky J, Gonzales J, et al. Immune status as a determinant of human papillomavirus detection and its association with anal epithelial abnormalities. Int J Cancer 1990;46:203–6.
15. Beckmann AM, Daling JR, Sherman KJ, et al. Human papillomavirus infection and anal cancer. Int J Cancer 1989;43:1042–9.
16. Scholefield JH, McIntyre P, Palmer JG, et al. DNA hybridization of routinely processed tissue for detecting HPV DNA in anal squamous cell carcinomas over 40 years. J Clin Pathol 1990; 43:133–6.
17. Scholefield JH, Kerr IB, Shepherd NA, et al. Human papillomavirus type 16 DNA in anal cancers from six different countries. Gut 1991;32: 674–6.
18. zur Hausen H. Papillomaviruses in anogenital cancer as a model to understand the role of viruses in human cancers. Cancer Res 1989;9: 4677–81.
19. Daling JR, Sherman KJ, Hislop TG, et al. Cigarette smoking and the risk of anogenital cancer. Am J Epidemiol 1992;135:180–9.
20. Rabkin CS, Biggar RJ, Melbye M, et al. Second primary cancers following anal and cervical carcinoma: evidence of shared etiologic factors. Am J Epidemiol 1992;136:54–8.
21. Storm HH. The Danish Cancer Registry, a self-reporting national cancer registration system with elements of active data collection. In: Jensen OM, Parkin DM, Maclennan R, et al, eds. Cancer registration principles and methods. IARC scientific publications no. 95. Lyon: International Agency for Research on Cancer, 1991: 220–36.
22. Breslow NE, Day NE. Statistical methods in cancer research. Vol 1. The analysis of case-control studies. IARC scientific publications no. 32. Lyon: International Agency for Research on Cancer, 1980:248–79.
23. Breslow NE, Day NE. Statistical methods in cancer research. Vol 2. The design and analysis of cohort studies. IARC scientific publications no. 82. Lyon: International Agency for Research on Cancer, 1987:65–71.
24. Boice JD, Storm HH, Curtis RE, et al. Introduction to the study of multiple primary cancers. In: Boice JD, Storm HH, Curtis RE, et al, eds. Multiple primary cancers in Connecticut and Denmark. National Cancer Institute monograph 68. NIH publication no. 85–2714, Bethesda, MD: National Cancer Institute, 1985:3–9.
25. Ogunbiyi OA. Scholefield JH, Rogers K, et al. C-myc oncogene expression in anal squamous neoplasia. J Clin Pathol 1993;46:23–7.
26. Holmes F, Borek D, Owen-Kummer M, et al. Anal cancer in women. Gastroenterology 1988; 95:107–11.
27. Caussy D, Goedert JJ, Palefsky J, et al. Interaction of human immunodeficiency virus and papillomaviruses: association with anal epithelial abnormality in homosexual men. Int J Cancer 1990;46:214–19.
28. Frazer IH, Medley G, Crapper RM, et al. Association between anorectal dysplasia, human papillomavirus, and human immunodeficiency virus infection in homosexual men. Lancet 1986;2: 657–60.
29. Palefsky JM, Holly EA, Gonzales J, et al. Natural history of anal cytologic abnormalities and papillomavirus infection among homosexual men with group IV HIV disease. J Acquir Immune Defic Syndr 1992;5:1258–65.
30. Penn I. Cancers of the anogenital region in renal transplant recipients. Cancer 1986;58:611–16.
31. Melbye M, Biggar RJ, Ebbesen P, et al. Seroepidemiology of HTLV-III antibody in Danish homosexual men: prevalence, transmission, and disease outcome. BMJ 1984;289:573–5.
32. Escot C, Theillet C, Lidereau R, et al. Genetic alteration of the c-myc protooncogene (MYC) in human primary breast carcinomas. Proc Natl Acad Sci USA 1986; 83:4834–8.
33. Crook T, Wrede D, Tidy J, et al. Status of c-myc, p53 and retinoblastoma genes in human papillomavirus positive and negative squamous cell carcinomas of the anus. Oncogene 1991;6:1251–7.