COLORECTAL CANCER

Elevated anal squamous cell carcinoma risk associated with benign inflammatory anal lesions

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Background: The association between benign anal lesions and anal cancer is still unclear. Few data from large cohort studies are available.

Methods: We conducted a register based retrospective cohort study including 45 186 patients hospitalised for inflammatory anal lesions (anal fissures, fistulas, and perianal abscesses) as well as 79 808 haemorrhoid patients, from 1965 to 2002. Multiple record linkages identified all incident anal (squamous cell carcinoma only) and colorectal cancers through to 2002. Relative risk was estimated by standardised incidence ratio (SIR), the ratio of observed number of cases divided by that expected in the age, sex, and calendar year-matched general Swedish population.

Results: There was a distinct incidence peak in the first three years of follow up among patients with inflammatory lesions. SIR then levelled off at around 3 and remained at this level throughout follow up (SIR during years 3–37 of follow up was 3.3 (95% confidence interval 1.8–5.7)). A similar initial incidence peak was observed among haemorrhoid patients but was confined to the first year; SIR was 2.8 in the second year, and then it decreased further and was close to unity in the following years (SIR during years 3–37 was 1.3 (95% confidence interval 0.7–2.1)). Among inflammatory lesion and haemorrhoid patients, a significantly increased risk of colorectal cancer was observed only in the first year after hospitalisation.

Conclusions: Inflammatory benign anal lesions are associated with a significantly increased long term risk of anal cancer. In contrast, haemorrhoids appear not to be a risk factor for this malignancy.

Anal cancer is an uncommon disease in the heterosexual population, with an incidence of 1 per 100 000. However, the incidence is much higher in men who regularly practice anal receptive intercourse (approximately 35 per 100 000).¹ Apart from a strong link to sexual promiscuity and human papillomavirus (HPV) infection, suspected risk factors include genital warts, herpes simplex virus type 2, and smoking.^{2–6}

In 1863 the first connection between inflammation and cancer was made by Rudolf Virchow.⁷ Since then several types of cancer have been associated with infection and inflammation,⁷ and different mechanisms have been hypothesised. Local inflammation may contribute to ovarian cancer⁸; ulcerative colitis increases the risk of colorectal cancer^{9–10}; infection by *Helicobacter pylori* increases the risk of distal stomach cancer¹¹; hepatitis B virus and hepatitis C virus infection are well recognised risk factors for hepatocellular carcinoma¹²; and tumour necrosis factor, a protein mediating inflammation, has been suggested to be involved in the progression and spread of cancer.¹³

The possible association of benign anal lesions, including fissures, fistulas, perianal abscesses, and haemorrhoids, with anal cancer has long been debated.^{2–3 14 15} In a case control study, a significantly increased risk of anal cancer was found in patients treated for anal fissures, fistulas, or with more than 12 episodes of haemorrhoids.² Constant irritation, chronic inflammatory changes, and repeated epithelial regeneration were hypothesised as explanations for the association.² This was supported by another case control study in which a significantly increased risk of anal cancer was reported in patients with severe haemorrhoids, and a weak association was also observed between anal cancer and other infections and inflammations in the anogenital area.¹⁵ A third case control study found an association with haemorrhoids and non-specific anal irritation among men but not among women.¹⁶ Case control studies may be subject

to recall bias and thus a cohort study design is favourable although few cohort studies are available due to the rarity of anal cancer. In the only two cohort studies, a null association was reported.^{14 17}

Given the contradictory results from case control studies and the rarity of cohort studies, we investigated the association between benign anal lesions and anal cancer using a large cohort with a long follow up.

METHODS

Identification of the cohort

The Swedish National Board of Health and Welfare established the inpatient register in 1964 to document individual hospital discharges. Each inpatient register record corresponds to one inpatient episode and contains: (a) the patient's national registration number—a unique identifier assigned to all Swedish residents; (b) dates of hospital admission and discharge; and (c) up to eight discharge diagnoses coded according to the 7th version of the International Classification of Diseases (ICD-7) until 1968, the 8th version (ICD-8) from 1969 to 1986, the 9th version (ICD-9) from 1987 to 1996, and the 10th version (ICD-10) thereafter. The national registration number permits unambiguous linkage across all national registers in Sweden.

All records in the inpatient register with a diagnosis of benign anal lesion, including fissure (ICD7: 574.00, ICD8: 565.00, ICD9:565.A, ICD10:K60.1, K60.2, K60.3), fistula (ICD7: 574.10, ICD8: 565.10, ICD9:565.B, ICD10:K60.3, K60.4, K60.5), perianal abscess (ICD7: 575.00, ICD8:566.00, ICD9:566, ICD10:K61.0), and haemorrhoid (ICD7: 461.99, ICD8: 455.99, ICD9: 455, ICD10:I84) from January 1965 to December 2002 were initially selected. We identified 135 276

Abbreviations: HPV, human papillomavirus; SIR, standardised incidence ratio; NO, nitric oxide

Table 1 Characteristics of the 124 994 patients hospitalised for benign anal lesions and their follow up

	Benign anal lesions		
	Inflammatory lesions*	Haemorrhoids	Total
No of subjects	45 186	79 808	124 994
Men	29 057	42 168	71 225
Women	16 129	37 640	53 769
Total No of person years	555 646	1 022 543	1 578 189
Men	350 194	537 228	887 422
Women	205 452	485 314	690 766
Mean follow up duration (y)	12.3	12.8	12.6
Men	12.0	12.7	12.5
Women	12.7	12.9	12.8
Mean age at entry (y)	42.2	52.6	48.8
Men	41.9	52.2	48.0
Women	42.7	53.1	49.9
No of hospitalisations (%)			
1	77.7	90.3	
2+	22.2	9.7	
Presence of Crohn's disease (%)	3.5	0.1	1.3
No of anal cancers	26	27	53
Age at diagnosis of anal cancer (y)†	59.5 (15.0)	65.0 (14.6)	62.3 (14.9)

*Including fissure, fistula, and perianal abscess.

†Mean (SD).

unique national registration numbers with hospital admissions for benign anal lesions during the period studied.

Follow up/record linkage

In order to obtain correct dates for censoring, our dataset was first linked to the nationwide registers of total population, migration, and causes of death. National registration numbers which could not be found in any of these registers ($n = 316$, 0.23% of the identified records) were deemed to be erroneous and the corresponding records were removed as a correct national registration number is a prerequisite for record linkage and thus for follow up. The National Cancer Register, founded in 1958 and estimated to be 98% complete,¹⁸ was used to ascertain all incident cancers diagnosed in the cohort before and from the start of follow up, until 31 December 2002. The Cancer Register has coded malignant neoplasm according to the ICD-7 classification scheme during the entire period of the study, and used a pathology code to identify histological type. To restrict our outcome to first primary tumours, we further excluded all patients with a cancer diagnosis preceding index hospitalisation ($n = 7090$). We excluded an additional 2876 subjects because of observed inconsistencies among data from the registers. Hence the final cohort comprised 124 994 patients. As we hypothesised that inflammatory lesions (fissures, fistulas, and perianal abscesses) and haemorrhoids may be differentially associated with anal cancer risk, the total cohort was broken down into two subcohorts. Patients who had been hospitalised for both were allocated to the inflammatory lesion subcohort. The haemorrhoid and inflammatory lesion subcohorts consisted of 79 808 and 45 186 patients, respectively. The latter was further divided into three non-overlapping subcohorts—that is, anal fissure ($n = 11 696$), fistula ($n = 13 847$), and perianal abscess ($n = 19 643$), according to the diagnosis of their first hospitalisation (index hospitalisation).

Statistical analysis

Individual person time was calculated from the day of the index hospitalisation until first cancer diagnosis, death, emigration, or 31 December 2002, whichever came first. In order to avoid possible ascertainment bias due to differential autopsy rates in the study cohort and in the general population, we did not count anal cancers found incidentally

at autopsy. To minimise the possibility of misclassification, we limited our analyses to anal squamous cell carcinomas only. The standardised incidence ratio (SIR)—the observed number of anal cancer occurrences divided by the expected—expressed relative risk among the cohort members. The expected number of anal cancers was calculated by multiplying age, sex, and calendar year specific incidence rates in the general population by the corresponding stratum specific person time accrued in the cohort. In the calculation of expected rates, we counted only the first primary cancer and excluded individuals in the general population with prevalent cancer in the calculation of person time. We calculated 95% confidence intervals (CIs) for SIR under the assumption that the observed events follow a Poisson probability distribution.¹⁹ Stratified analyses were performed by follow up duration, sex, age at index hospitalisation, or calendar periods of index hospitalisation. To assess the effect of treatment, we also performed stratified analyses by number of hospitalisation for inflammatory benign anal lesions or haemorrhoids. Person years accrued before second hospitalisation was attributed to the only one hospitalisation stratum. All *p* values presented in this report are two sided and the results were considered to be statistically significant at $p < 0.05$.

RESULTS

The cohort members were followed for a mean of 12.5 years, with more than 1.5 million person years accumulated. Mean age at entry (the first (index) hospitalisation for a benign anal lesion) was close to 49 years (table 1). Mean follow up duration was similar in the inflammatory lesion and haemorrhoid subcohorts but members in the latter were, on average, hospitalised at an older age than the latter. There were no significant sex differences with regard to mean follow up duration or mean age at entry. Patients with inflammatory anal lesions were more likely to be hospitalised more than once than those with haemorrhoids (22.2 v 9.7%). Crohn's disease was more common in patients with inflammatory benign anal lesions (3.5%) than in patients with haemorrhoids (0.1%). In total, 53 incident anal cancer cases (squamous cell carcinoma) were observed during follow up (26 and 27 in the inflammatory lesion and haemorrhoid subcohorts, respectively). Mean age at anal cancer diagnosis was 62 years (table 1).

Table 2 Standardised incidence ratios (SIRs) and their 95% confidence intervals (CI) for anal and colorectal cancer among patients with benign inflammatory anal lesions and haemorrhoids, by duration of follow up

	Inflammatory lesions*				Haemorrhoids			
	Anal cancer		Colorectal cancer†		Anal cancer		Colorectal cancer†	
	Obs	SIR (95% CI)	Obs	SIR (95% CI)	Obs	SIR (95% CI)	Obs	SIR (95% CI)
<1 y	6	24.0 (8.8–52.3)	71	3.9 (3.0–4.9)	11	14.9 (7.5–26.7)	200	3.6 (3.1–4.1)
1–4 y	8	8.3 (3.6–16.3)	88	1.3 (1.0–1.6)	2	0.7 (0.1–2.5)	228	1.1 (0.9–1.2)
1 y	4	16.3 (4.4–41.7)	21	1.2 (0.7–1.8)	2	2.8 (0.3–9.9)	68	1.3 (1.0–1.6)
2 y	3	12.3 (2.6–36.1)	22	1.3 (0.8–1.9)	0	–	55	1.0 (0.8–1.3)
3–4 y	1	2.1 (0.05–11.7)	45	1.4 (1.0–1.8)	0	–	105	1.0 (0.8–1.2)
5–9 y	6	5.4 (2.0–11.7)	97	1.3 (1.0–1.5)	6	1.8 (0.7–3.9)	243	1.0 (0.9–1.1)
10+ y	6	2.6 (1.0–5.7)	180	1.1 (0.9–1.3)	8	1.3 (0.6–2.5)	509	1.1 (1.0–1.1)
10–14 y	2	2.2 (0.3–7.9)	75	1.2 (0.9–1.5)	3	1.1 (0.2–3.3)	189	1.0 (0.8–1.1)
15–19 y	2	2.9 (0.4–10.6)	56	1.2 (0.9–1.5)	4	2.2 (0.6–5.6)	145	1.0 (0.9–1.2)
20+ y	2	2.8 (0.3–10.2)	49	0.9 (0.7–1.2)	1	0.6 (0.01–3.0)	175	1.2 (1.0–1.4)
3–37 y	13	3.3 (1.8–5.7)	322	1.2 (1.1–1.3)	14	1.3 (0.7–2.1)	857	1.0 (1.0–1.1)

*Benign inflammatory anal lesions included anal fissure, fistula, and perianal abscess.

†Excluding anal cancer.

Obs, observed.

Table 2 shows SIRs by follow up duration. Among patients with inflammatory lesions, we observed six anal cancer cases compared with 0.25 expected, entailing an SIR of 24.0 (95% CI 8.8–52.3) in the first year of follow up. Over eightfold excess risk was still noted 1–4 years after hospitalisation which was mainly attributed to the highly significant excess risks in the second and third years of follow-up. The excess risks decreased somewhat, but were still significant, in the following years (SIR 5.3 (95% CI 2.0–11.7) for 5–9 years after hospitalisation; SIR 2.6 (95% CI 1.0–5.7) for 10 or more years after hospitalisation, respectively). The observed six cases of anal cancer after 10 years of follow up were evenly distributed throughout the observation period (SIRs 2.2, 2.9, and 2.8 for 10–14, 15–19, and 20 or more years after hospitalisation, respectively). After excluding the first three years of observation, SIR during years 3–37 was 3.3 (95% CI 1.8–5.7), based on 13 observed anal cancer cases. We observed a similarly significant excess risk for anal cancer in the first year of follow up among haemorrhoid patients. However, relative risk dropped to approximately 3 in the second year of follow up, and was close to unity thereafter (SIR during years 3–37 1.3 (95% CI 0.7–2.1)). Significant excess risks for colorectal cancers (excluding anal cancer) were noted only in the first year of follow up in both the

inflammatory lesion and haemorrhoid cohorts. During years 3–37 there was an approximate 30% excess risk for lung cancer among patients with inflammatory lesions (SIR 1.3 (95% CI 1.1–1.4)).

Among patients with inflammatory lesions, stratified analyses (first three years excluded) showed no conspicuous variation in relative risks for anal or colorectal cancer by sex, age at index hospitalisation, calendar period of index hospitalisation, or number of hospitalisations for inflammatory anal lesions (table 3). Absence of any strong association with anal or colorectal cancer was evident across different strata in patients with haemorrhoids (table 3).

Table 4 lists results for the three subtypes of inflammatory lesions. After the first three years of follow up, we observed five cases of anal cancer among fissure patients, corresponding to an approximate fourfold excess risk (95% CI 1.3–9.2). Excess risk was also noted for patients with perianal abscesses (n = 6; SIR 5.3), but less obvious for patients with anal fistulas (n = 2; SIR 1.3). Stratified analyses by sex and follow up duration showed similar results in most strata, except that for perianal abscess patients where excess risk was noted only among women (SIR 9.7 for women v 1.6 for men).

For sensitivity analysis, after excluding patients with a history of Crohn's disease, human immunodeficiency virus

Table 3 Standardised incidence ratios (SIRs) and their 95% confidence intervals (CIs) for anal and colorectal cancer among patients with benign inflammatory anal lesions and haemorrhoids, by sex, age at entry, periods at entry, or number of hospitalisations*

	Inflammatory lesions†				Haemorrhoids			
	Anal cancer		Colorectal cancer‡		Anal cancer		Colorectal cancer‡	
	Obs	SIR (95% CI)	Obs	SIR (95% CI)	Obs	SIR (95% CI)	Obs	SIR (95% CI)
Sex								
Men	4	2.2 (0.6–5.7)	223	1.2 (1.0–1.4)	6	1.5 (0.5–3.2)	489	1.0 (0.9–1.1)
Women	9	4.3 (2.0–8.2)	99	1.1 (0.9–1.4)	8	1.1 (0.5–2.3)	368	1.1 (1.0–1.2)
Age at entry (y)								
<50	6	2.9 (1.1–6.3)	101	1.1 (0.9–1.3)	3	0.7 (0.2–2.1)	218	1.1 (0.9–1.2)
50+	7	3.8 (1.5–7.9)	221	1.2 (1.1–1.4)	11	1.6 (0.8–2.9)	639	1.0 (0.9–1.1)
Period at entry (year)								
1965–1986	9	3.2 (1.5–6.1)	244	1.2 (1.0–1.3)	9	1.1 (0.5–2.1)	671	1.1 (1.0–1.2)
1987–2002	4	3.7 (1.0–9.4)	78	1.2 (0.9–1.4)	5	1.6 (0.5–3.8)	186	0.9 (0.8–1.1)
No of hospitalisations								
1	10	3.3 (1.6–6.1)	241	1.1 (1.0–1.3)	14	1.4 (0.8–2.4)	774	1.0 (1.0–1.1)
2 or more	3	3.4 (0.7–9.9)	81	1.3 (1.1–1.6)	0	–	83	1.0 (0.8–1.2)

*Person years and anal cancer cases accrued during the first three years of follow up were excluded.

†Benign inflammatory anal lesions included anal fissure, fistula, and perianal abscess.

‡Excluding anal cancer.

Obs, observed.

Table 4 Standardised incidence ratios (SIRs) and their 95% confidence intervals (CIs) for anal cancer among patients with anal fissure, fistula, or perianal abscess*

	Fissure			Fistula			Perianal abscess		
	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI
Overall	5	3.9	1.3–9.2	2	1.3	0.2–4.9	6	5.3	1.9–11.5
Sex									
Men	2	4.7	0.6–16.9	1	1.3	0.03–7.4	1	1.6	0.04–9.0
Women	3	3.6	0.7–10.4	1	1.4	0.04–7.6	5	9.7	3.1–22.6
Follow up duration (y)									
3–9	3	5.9	1.2–17.3	0	–	–	4	7.1	1.9–18.3
10+	2	2.6	0.3–9.4	2	2.1	0.3–7.5	2	3.5	0.4–12.5

*Person years and anal cancer cases accrued during the first three years of follow-up were excluded.
Obs, observed.

disease, condylomata acuminata, cervix cancer in situ, or organ transplantation, 42 857 inflammatory anal lesion patients remained. Overall SIR during years 3–37 was somewhat attenuated but still statistically significant ($n = 10$; SIR 2.7 (95% CI 1.3–5.0)), and the excess risk persisted after 10 years of follow up ($n = 5$; SIR 2.3 (95% CI 0.7–5.3)).

DISCUSSION

This retrospective cohort study showed an increased risk of anal cancer for both male and female patients hospitalised for inflammatory benign anal lesions, including anal fissures, fistulas, and perianal abscesses. In contrast, haemorrhoids did not appear to be associated with any increased risk for anal cancer.

Although there were marked incidence peaks for anal cancer in all subcohorts during the first 2–3 years of follow up, suggesting some initial misclassification of anal cancer as benign anal lesions, such misclassification cannot explain the observed long term excess risk of anal cancer among patients hospitalised for anal fissures, fistulas, or perianal abscesses, as the excess risk persisted after 10 years or more of follow up. Confounding by smoking is another potential explanation, as smoking has been suggested as one risk factor for anal cancer.²⁰ However, the incidence of lung cancer—a marker of the smoking prevalence in our cohort—was increased by no more than 30%. Accordingly, smoking cannot explain the observed threefold excess risk for anal cancer. Furthermore, confounding by HPV and human immunodeficiency virus infection may also partly explain the observed excess anal cancer risk. Previous organ transplantation can lead to perianal abscess, and organ transplantation has been found to increase the risk of anal cancer.²¹ However, sensitivity analyses by excluding subjects with these comorbid diseases or organ transplantation revealed essentially unchanged results.

Our finding of an increased risk associated with benign inflammatory anal lesions was consistent with the results from two previous case control studies^{2–15} which asked about any past medical history of anal fissures, fistulas, infection, inflammation, or itching in or around the anus. The association with previous anorectal disease was less clear in another case control study among women.⁴ Somewhat conflicting results among men and women emerged in a fourth case control study; an increased risk of anal cancer was observed among women with a previous history of anal abscesses but the risk in men was linked to haemorrhoids and unspecific irritation.¹⁶ In the above mentioned two case control studies,^{2–15} an increased risk of anal cancer has been found among subjects who self reported severe haemorrhoids, which was in conflict with our finding. All of these case control studies had to rely on self reports, and misclassification of the lesion or recall bias may be

quantitatively important. A previous cohort study from Denmark, of a similar design as ours but with fewer observed cancer cases, found a comparable incidence peak shortly after index hospitalisation but did not observe any anal cancer cases in patients with anal fissures or fistulas, and a statistically non-significant excess risk among perianal abscess patients based on two observed cases after five or more years of follow up.¹⁴ The authors concluded that their data did not support a causal link between benign anal lesions and anal cancer but the study was clearly underpowered. A considerably larger American cohort study in male veterans showed a fourfold increased risk after 5–9 years among African Americans but no clear corresponding excess among Caucasians.¹⁷ As inflammatory lesions and haemorrhoids were counted together, it is impossible to tell whether racial differences reflected differences in the case mix.

The strengths of our study include the essentially population based cohort, the virtually complete and thus practically bias free follow up, and the restriction to first and squamous cell carcinomas only. However, the relatively small observed number of anal cancers limited our ability for detailed stratified analyses by sex or specific type of inflammatory benign anal lesions, and made estimates in some strata unstable. Moreover, the possibility of ascertainment or detection bias cannot be completely ruled out, and the limited availability of information on potential confounding factors, notably smoking and HPV infection, is an important caveat. Patients with benign anal lesions are usually treated in the outpatient setting. Thus hospitalised patients may represent a subgroup of more severe lesions. If severity of disease is associated with anal cancer risk, our results may overestimate the true relative risk. On the other hand, patients hospitalised for benign anal lesions usually have their lesions cured before discharge, especially for haemorrhoids. Thus our results may underestimate the true association, especially in haemorrhoid patients. However, the fact that no obvious excess anal cancer risk was observed among patient with recurrent haemorrhoids may somewhat allay such a concern.

Anal fissures and fistulas are typically infected, and chronic inflammation is common. Perianal abscesses are, per definition, infected. On the other hand, haemorrhoids is not an inflammatory disease. It is thus reasonable to postulate that the association between anal fissures, fistulas, perianal abscesses, and anal cancer can be explained by prolonged inflammation. This conclusion is also supported by our findings. Almost 25% of patients treated for benign inflammatory anal lesions were hospitalised more than once for their lesion, suggesting that surgical treatment was not able to eradicate all inflammatory tissue. Patients with relapsing infections had an increased risk of anal cancer compared with patients treated only once. The similarly

elevated risk of anal cancer was not seen among patients with recurrent haemorrhoids. Inflammation and chronic activation of the immune system have been proposed to cause cancer. In chronic inflammation, macrophages, lymphocytes, and plasma cells infiltrate the damaged tissue, and persistent pathological activation of macrophages can result in continuous tissue damage.²² Macrophages release a number of powerful substances, among them nitric oxide (NO). NO seems to directly damage DNA, inhibit DNA repair enzymes, inhibit caspase activity leading to inhibited apoptosis, and stimulate angiogenesis, which may promote tumour growth.²³ The inflammatory process also generates inflammatory cytokines and prostaglandins which repress cell mediated immune responses and favour angiogenesis.²⁴ Moreover, carcinogenic substances, as reactive oxygen species and metabolites, may be produced in sites with chronic inflammation. Ulcerative colitis is a well established risk factor for colon cancer.^{9 10 25}

HPV is considered to play a central role in the aetiology of anal cancer.²⁰ Epidemiological studies have also found that the presence of genital warts (condylomata acuminata) is linked to an elevated risk of anal cancer.^{2 3 6 15} Thus it is conceivable that benign inflammatory anal lesions might either act as a cofactor to promote HPV initiated carcinogenesis or facilitate access of HPV to the epithelium, or serve as a marker of infection of high risk HPV.¹⁶

We conclude that benign inflammatory anal lesions are associated with a moderately increased long term risk of anal cancer. Whether this association is due to inflammation or to facilitated infection with HPV warrants further investigation. Clinicians who are responsible for treatment of benign anal lesions should be aware of the high possibility of misdiagnosis of anal cancer. Given the relative rarity of anal cancer and the only moderate excess long term risk, however, regular surveillance for anal cancer among patients with benign inflammatory anal lesions is not justifiable.

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REFERENCES

- 1 Clark MA, Hartley A, Geh JI. Cancer of the anal canal. *Lancet Oncol* 2004;5:149–57.
- 2 Holly EA, Whittemore AS, Aston DA, et al. Anal cancer incidence: genital warts, anal fissure or fistula, hemorrhoids, and smoking. *J Natl Cancer Inst* 1989;81:1726–31.
- 3 Frisch M, Glimelius B, van den Brule AJ, et al. Sexually transmitted infection as a cause of anal cancer. *N Engl J Med* 1997;337:1350–8.
- 4 Holmes F, Borek D, Owen-Kummer M, et al. Anal cancer in women. *Gastroenterology* 1988;95:107–11.
- 5 Daling JR, Sherman KJ, Hislop TG, et al. Cigarette smoking and the risk of anogenital cancer. *Am J Epidemiol* 1992;135:180–9.
- 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 Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? *Lancet* 2001;357:539–45.
- 8 Ness RB, Cottreau C. Possible role of ovarian epithelial inflammation in ovarian cancer. *J Natl Cancer Inst* 1999;91:1459–67.
- 9 Ekblom A, Helmick C, Zack M, et al. Ulcerative colitis and colorectal cancer. A population-based study. *N Engl J Med* 1990;323:1228–33.
- 10 Karlen P, Lofberg R, Brostrom O, et al. Increased risk of cancer in ulcerative colitis: a population-based cohort study. *Am J Gastroenterol* 1999;94:1047–52.
- 11 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Schistosomes, liver flukes and *Helicobacter pylori*. Lyon, 7–14 June 1994. *IARC Monogr Eval Carcinog Risks Hum* 1994;61:1–241.
- 12 Lotz G, Kiss A, Novak PK, et al. Hepatitis viruses and hepatocarcinogenesis. *J Physiol Paris* 2001;95:417–22.
- 13 Balkwill FR. Tumour necrosis factor and cancer. *Prog Growth Factor Res* 1992;4:121–37.
- 14 Frisch M, Olsen JH, Bautz A, et al. Benign anal lesions and the risk of anal cancer. *N Engl J Med* 1994;331:300–2.
- 15 Tseng HF, Morgenstern H, Mack TM, et al. Risk factors for anal cancer: results of a population-based case–control study. *Cancer Causes Control* 2003;14:837–46.
- 16 Frisch M, Glimelius B, van den Brule AJ, et al. Benign anal lesions, inflammatory bowel disease and risk for high-risk human papillomavirus-positive and -negative anal carcinoma. *Br J Cancer* 1998;78:1534–8.
- 17 Lin AY, Gridley G, Tucker M. Benign anal lesions and anal cancer. *N Engl J Med* 1995;332:190–1.
- 18 Mattsson B, Wallgren A. Completeness of the Swedish Cancer Register. Non-notified cancer cases recorded on death certificates in 1978. *Acta Radiol Oncol* 1984;23:305–13.
- 19 Breslow NE, Day NE. *The design and analysis of cohort studies*. IARC Scientific Publications No 82. Lyon: International Agency for Research on Cancer, 1987.
- 20 Daling JR, Madeleine MM, Johnson LG, et al. Human papillomavirus, smoking, and sexual practices in the etiology of anal cancer. *Cancer* 2004;101:270–80.
- 21 Adami J, Gabel H, Lindelof B, et al. Cancer risk following organ transplantation: a nationwide cohort study in Sweden. *Br J Cancer* 2003;89:1221–7.
- 22 Macarthur M, Hold GL, El-Omar EM. Inflammation and cancer II. Role of chronic inflammation and cytokine gene polymorphisms in the pathogenesis of gastrointestinal malignancy. *Am J Physiol Gastrointest Liver Physiol* 2004;286:G515–20.
- 23 Jaiswal M, LaRusso NF, Gores GJ. Nitric oxide in gastrointestinal epithelial cell carcinogenesis: linking inflammation to oncogenesis. *Am J Physiol Gastrointest Liver Physiol* 2001;281:G626–34.
- 24 O'Byrne KJ, Dalgleish AG. Chronic immune activation and inflammation as the cause of malignancy. *Br J Cancer* 2001;85:473–83.
- 25 Kornfeld D, Ekblom A, Ihre T. Is there an excess risk for colorectal cancer in patients with ulcerative colitis and concomitant primary sclerosing cholangitis? A population based study. *Gut* 1997;41:522–5.