

ORIGINAL ARTICLE

# Risk for anogenital cancer and other cancer among women hospitalized with gonorrhoea

CHRISTOFFER JOHANSEN<sup>1</sup>, LENE MELLEMKJÆR<sup>1</sup>, MORTEN FRISCH<sup>2</sup>, SUSANNE K. KJÆR<sup>1</sup>, GLORIA GRIDLEY<sup>3</sup> AND JØRGEN H. OLSEN<sup>1</sup>

From the <sup>1</sup>Danish Cancer Society, Institute of Cancer Epidemiology, Copenhagen, the <sup>2</sup>Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark and the <sup>3</sup>Epidemiology and Biostatistics Program, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland, USA

Acta Obstet Gynecol Scand 2001; 80: 757–761. © Acta Obstet Gynecol Scand 2001

**Background.** We investigated the relationship between infections with *Neisseria gonorrhoeae* and anogenital and other cancers.

**Methods.** Nationwide and population based register linkage study utilizing prospectively notified information. The observed numbers of cancers among the women were compared with those expected on the basis of national incidence rates.

**Results.** In a cohort of 4440 women hospitalized for gonorrhoea we observed a total of 227 cases of cervical intraepithelial neoplasia grade III (CIN III), with 103 expected (standardized incidence ratio (SIR), 2.2; 95% confidence interval (CI), 1.9–2.5). No significantly increased risk for other anogenital cancers or cancer at other sites was seen.

**Conclusions.** These results support the view that the observed association between gonorrheal infection and subsequent cervical preneoplasia is due mainly to surveillance bias. However, our results also indicate that women hospitalized with a *N. gonorrhoeae* infection will benefit from the compliance with the regular Pap smear screening programs.

**Key words:** cancer; epidemiology; gonorrhoea

Submitted 12 January, 2001

Accepted 27 March, 2001

Gonorrhoea, caused by *Neisseria gonorrhoeae*, is a sexually transmitted disease capable of causing urethritis, endocervicitis, proctitis and pharyngeal infection. Pelvic inflammatory disease caused by ascending inflammation and acute septic arthritis are among the more common complications and are seen more often in women than in men (1). Factors such as sex, age, race and socioeconomic status are all predictive for gonorrheal infection (2). In Denmark (total population in 1988, 5,129,000), the number of cases of gonorrhoea declined from nearly 8000 in 1984 to 500 in 1992, with a concurrent change in the male-female sex

ratio from 1.4 to 1.8, probably indicating an increasing proportion of cases of gonorrhoea acquired by homosexual men (3).

An ecological study of birth cohorts in the United Kingdom suggested that patterns of mortality from cancer of the uterine cervix were associated with sexually transmitted infections, including infections with *N. gonorrhoeae* (4). A more recent Danish case-control study (5) and a larger Latin American case-control study observed that a history of gonorrhoea was significantly associated with the risk of cervical cancer (6). In addition, Frisch et al. (1997) observed an increased risk for anal cancer among women who had had a gonorrheal infection (7).

Little is known about the occurrence of types of cancer other than anogenital malignancies among women with previous gonorrheal infections. The

**Abbreviations:**

HPV: human papillomavirus; RR: relative risk; CI: confidence interval; CIN: cervical intraepithelial neoplasia; HDR: hospital discharge register; SIR: standardized incidence ratio.

purpose of the present study was to assess in a large cohort of women hospitalized with a gonorrhoeal infection the rates of anogenital malignancies, including precancerous lesions labelled cervical intraepithelial neoplasia (CIN), cervical cancer and cancers of the vulva, vagina, anus and other sites, and to compare these rates with the appropriate rates of premalignant and malignant neoplasia in the general population.

### Material and methods

In 1977, the Danish National Board of Health established a population-based Hospital Discharge Register (HDR), which keeps records of nearly all hospital discharges for somatic diseases in Denmark (8). The information on each discharged patient includes the personal identification number, a unique 10-digit number for every Danish resident, which includes a code for sex and six digits for date of birth and permits linkage between registers. Furthermore, the information in the HDR includes date of discharge and up to 20 diagnoses per discharge, classified according to a Danish modification of the *International Classification of Diseases, 8th revision (ICD-8)* (9).

The study population consisted of women discharged from hospital with a diagnosis of gonorrhoea (ICD-8 code 098) during 1977–92. For women who had been discharged more than once with such a diagnosis, the day of the first hospital discharge was used as the date of entry into the cohort; it should be noted, however, that some of the women included may have had gonorrhoea before 1977. Using the personal identification number, linkage was made to the Danish National Death Certificate File to obtain information on vital status and – if deceased – date of death, and to the Danish Cancer Registry, which has been in operation since 1942, to obtain information on incident cancers (10). Registration of CIN grades I and II is considered to be highly incomplete, and these lesions were not included in this study, whereas systematic coverage of all practising gynecologists in Denmark has increased the completeness of registration of CIN grade III (11). Consequently cases of CIN III only were included. Cases of cancer were classified according to a modified version of the ICD-7 (12).

Of 4533 patients with a gonorrhoeal infection initially identified in the HDR, we excluded 59 patients (1.3%) because they were under the age of 15 years at the time of diagnosis. Likewise, 34 patients (0.8%) were excluded because they were not Danish residents or because their identification number was invalid. The remaining 4440 women were followed for cancer occurrence, including

CIN III, from the day of discharge for gonorrhoea until the date of death or the end of 1994, whichever came first.

The observed numbers of cancers were compared with those expected on the basis of national incidence rates divided into strata according to sex, age and calendar time in five-year intervals. Multiplication of the strata-specific person-years under observation by the corresponding incidence rate and subsequent summing up over strata yields the number of cancers that would be expected if women with gonorrhoea experienced the same risk as that prevailing in the general female population of Denmark. Tests for significance and 95% confidence intervals (CIs) for the standardized incidence ratio (SIR), i.e. the ratio of observed-to-expected cancers, were computed on the assumption that the observed number of cancer cases in a specific category follows a Poisson distribution (13, 14).

### Results

The 4440 women included in the study accrued 54,576 person-years of follow-up, with an average of 12.3 years (range, 0–18 years). At the time of discharge from a hospital with gonorrhoea, 1608 (36%) of these women were 15–20 years old, 2172 (49%) were 20–29 years old, 509 (11%) were 30–39 years old, and 151 women (3%) were >40 years of age. The median age at entry into the cohort was 21 years, and a total of 631 women (14%) were discharged with a diagnosis of gonorrhoea more than once. The number of women discharged from a hospital with a diagnosis of gonorrhoea declined from 423 women in 1977 to 25 women in 1992, however, the distribution of discharge diagnoses did not change in the period under study (data not shown).

No significant excess risk was observed for anogenital cancer, on the basis of 11 cases, all confined to the cervix uteri (SIR for all anogenital sites

Table 1. Standardized incidence ratios (SIRs) for anogenital neoplasias among 4440 women hospitalized with gonorrhoea in Denmark, 1977–94

Lesion	Observed	Expected	SIR	95% CI
Cancer of anogenital organs <sup>1</sup>	11	9.4	1.2	0.6–2.1
Vulva	0	0.2	–	0.0–18.4
Vagina	0	0.1	–	0.0–37.0
Anus	0	0.2	–	0.0–18.4
Cervix uteri	11	8.9	1.2	0.6–2.2
CIN III	227	102.6	2.2	1.9–2.5

SIR, ratio of observed to expected; CI, confidence interval; CIN III, cervical intraepithelial neoplasia grade III.

<sup>1</sup>Includes cancers at anogenital sites with a predominant histological subtype of squamous – cell carcinoma.

Table II. Standardized incidence ratios (SIRs) for invasive cancer of cervix uteri and cervical intraepithelial neoplasia grade III (CIN III) by time since discharge among 4440 women hospitalized with gonorrhoea in Denmark, 1977–94

Length of follow-up (years)	Invasive cancers of cervix uteri				CIN III			
	Obs	Exp	SIR	95% CI	Obs	Exp	SIR	95% CI
< 1	0	0.4	–	0.0–9.2	30	4.7	6.5	4.4–9.2
1–4	2	1.9	1.0	0.1–3.7	70	26.3	2.7	2.1–3.4
5–9	6	3.4	1.8	0.6–3.8	76	42.1	1.8	1.4–2.3
10–18	3	3.2	0.9	0.2–2.7	51	29.6	1.7	1.3–2.3

SIR, ratio of observed to expected; CI, confidence interval.

combined, 1.2; Table I). The risk for cervical cancer did not vary significantly with length of follow-up (Table II). The group of CIN III comprised 227 cases. The overall risk for CIN III was significantly increased (SIR, 2.2; 95% CI, 1.9–2.5; Table I). The risk for CIN III was highest within the first year after hospitalization for gonorrhoea (SIR, 6.5; 95% CI 4.4–9.2) and declined during subsequent years; however, the risk for it remained significantly elevated even after 10–18 years of follow-up (SIR, 1.7; 95% CI, 1.3–2.3; Table II). None of the women in this cohort had been discharged more than once with a diagnosis of CIN III (data not shown).

Overall, 46 cancers at sites other than the anogenital organs were observed with 57.2 expected, yielding a moderate but non-significantly decreased risk of 0.8 (95% CI, 0.6–1.1; Table III). The decreased risk was due mainly to moderately reduced risks (statistically non-significant) for breast cancer (SIR, 0.6), non-melanoma skin cancer (SIR, 0.6), cancer of the digestive organs (SIR,

0.7) and brain cancer (SIR, 0.5). For the combination of smoking-related cancer sites, there was no increased risk in women with gonorrhoea as compared with the general female population (SIR, 1.1; 95% CI, 0.4–2.4).

## Discussion

This study shows that women with gonorrhoea have an increased risk for high-grade CIN. We observed, however, no significantly increased risk for invasive cervical cancer or cancers at other sites, including other anogenital sites. As cancers of the anus, vulva and vagina are exceedingly rare in the age groups studied, our finding of no association between a previous gonorrhoeal infection and such cancers should be interpreted cautiously. In addition, we observed no increase in the risks for cancers generally accepted as causally related to cigarette smoking (15).

Women hospitalized with gonorrhoea may have sexual habits characterized by early sexual debut, a large number of partners and a higher prevalence of other sexually transmitted infections, such as those caused by mucosotropic types of HPV. Convincing experimental, clinical and epidemiological evidence now indicates that specific types of HPV, mainly types 16 and 18, are major risk factors for cervical neoplasia and an important etiological factor in other anogenital cancers (cancer of vulva, vagina and anus 7, 16–19). The association between a history of gonorrhoeal infection and cervical and anal cancer observed in previous studies may be explained by the fact that gonorrhoea is an indicator of exposure to HPV (5–7). The previous case-control studies were based on anamnestic information about gonorrhoeal infection from patients and control subjects, however, and recall bias is a possible explanation of the observed association. In contrast, our cohort study relied only on information obtained from population-based registers and all cases of gonorrhoeal infection were determined by culture.

Although we found no significantly increased risk

Table III. Standardized incidence ratios (SIRs) for cancers excluding anogenital cancer among 4440 women hospitalized with gonorrhoea in Denmark, 1977–94

Cancer site	Observed	Expected	SIR	95% CI
All non-anogenital neoplasms <sup>1</sup>	46	57.2	0.8	0.6–1.1
Buccal cavity and pharynx	2	0.6	3.5	0.4–12.4
Digestive organs	3	4.6	0.7	0.1–1.9
Larynx	0	0.1	–	0.0–37.0
Lung	3	2.3	1.3	0.3–3.9
Breast	10	16.4	0.6	0.3–1.1
Corpus uteri	2	1.2	1.7	0.2–6.2
Ovary	5	3.0	1.7	0.5–3.9
Urinary organs	0	1.2	–	0.0–3.1
Melanoma	5	5.8	0.9	0.3–2.0
Other skin	9	13.9	0.6	0.3–1.2
Brain and nervous system	2	3.8	0.5	0.1–1.9
Lymphatic and hematopoietic	5	4.3	1.2	0.4–2.7
Smoking-related cancers <sup>2</sup>	6	5.4	1.1	0.4–2.4

SIR, ratio of observed to expected; CI, confidence interval.

<sup>1</sup>All cancers except anogenital malignancies.

<sup>2</sup>Includes cancers of the mouth, pharynx, esophagus, pancreas, larynx, lung, renal pelvis and urinary bladder.

for cervical cancer, we did find an increased risk for CIN III in this cohort. Closer gynecological surveillance, including more Pap smears, of women with gonorrhea or one of the complications of this infection may have led to a higher rate of detection of CIN III and thus to a reduction in the number of cervical cancers that would otherwise have occurred. Contrary to women with a gonorrheal infection who will present with symptoms of the infection and receive treatment, women who acquire other sexually transmitted infections, e.g., HPV or *C. Trachomatis* may remain asymptomatic and be more likely to develop cervical neoplasia. In addition, almost 15% of the women in the cohort had been discharged more than once with a diagnosis of gonorrhea, indicating that surveillance may have increased the number of CIN III lesions diagnosed. The negative time trend in risk observed for CIN III indicates the presence of this surveillance bias. Although one would expect that closer gynecological surveillance would be followed by a decline in the number of cases of invasive cervical neoplasia, however, we observed 11 cases of this invasive cancer, with nine cases expected. This non-significantly increased risk for invasive cervical neoplasia may be due to co-infection with HPV 16 and 18. The size of the study limits the possibility for establishing a firm explanation for the pattern of cervical neoplasia observed.

In a recently published cohort study, we observed a significant association between hospitalization for condylomata acuminata and cervical cancer (20), which we did not confirm in the present study of women with gonorrhea. Women hospitalized for condylomata acuminata or gonorrhea probably have sexual habits in common that may be associated with an elevated risk for exposure to HPV 16 and 18. In addition, women with condylomata acuminata may be susceptible to infection with HPV 16 and 18 via lesions of the anogenital epithelium. Thus, the association with a history of condylomata acuminata may be a possible sign of co-infection with high-risk HPV types in addition to the HPV types that cause genital warts (usually HPV-types 6 and 11). It is also possible that a history of condyloma is simply a surrogate marker of viral persistence due to the characteristic lesions. This would explain why women hospitalized with condylomata acuminata have an excess risk for anogenital cancer, which we did not observe in women hospitalized with gonorrhea.

On the basis of six cases only, we did not observe increased risk for smoking-related cancers as in our previous study of condylomata acuminata (20), however, we cannot exclude the possibility of an increased SIR for smoking-related cancer up to 2.4 in this cohort of women.

We studied only women who had been admitted to hospital with gonorrhea. These women are likely to be the most serious cases and may also be characterized by complications of the initial infection more often than patients treated as out-patients. In general, women with gonorrhea are treated as out-patients or by their general practitioner, and their risk for cancer may differ from that of women in whom gonorrhea was diagnosed and treated in a hospital. These considerations limit generalization of these findings to all women with gonorrhea. In addition we had no information of the virulence of the gonococcal infection.

In summary, we observed a persistently increased risk for CIN III, but not for invasive cervical cancer, among women hospitalized for *N. gonorrhoeae* infection, which is probably due to an above-average surveillance of the cervix uteri, resulting in diagnoses of cervical neoplasia at an early stage. Besides the normal screening and follow-up for other sexually transmitted diseases such as HIV and syphilis in women hospitalized with gonorrhea, our results indicate that women hospitalized with a *N. gonorrhoeae* infection will benefit from the compliance with Pap smear screening programs, as the risk of CIN III among women hospitalized with gonorrhea relative to the general population of women remained significantly elevated even 10 years after the gonorrhea diagnosis.

### Acknowledgment

The authors want to thank Ms. Andrea Mehrsohn for skilful computer assistance. This study was supported by research grant MAO NO1-CP-85639-04 from the National Cancer Institute, Bethesda, Maryland, USA and the Danish Cancer Society.

### References

1. Holmes KK, Mårdh P-A, Sparling PF, Wiesner PJ (eds). Sexually transmitted diseases, 2nd Ed New York: McGraw-Hill, 1990.
2. Lacey CJN, Merrick DW, Bensley DC, Fairley I. Analysis of the sociodemography of gonorrhoea in Leeds, 1989-93. *BMJ* 1997; 314: 1715-18.
3. Lind I. Gonorrhoea. In: Elsner P, Eichmann A (eds): Sexually transmitted diseases. Advances in diagnosis and treatment. *Curr Probl Dermatol* 1996; 24: 12-19.
4. Beral V. Cancer of the cervix: a sexually transmitted infection? *Lancet* 1974; i: 1037-40.
5. Kjør SK, Dahl C, Engholm G, Bock JE, Lyng E, Jensen OM. Case-control study of risk factors for cervical neoplasia in Denmark. II. Role of sexual activity, reproductive factors, and venereal infections. *Cancer Causes Control* 1992; 3: 339-48.
6. Herrero R, Brinton LA, Reeves WC, Brenes MA, Tenorio F, Britton RC et al. Sexual behavior, venereal diseases, hygiene practices, and invasive cervical cancer in a high-risk population. *Cancer* 1990; 65: 380-6.

7. Frisch M, Glimelius B, van den Brule AJC, Wohlfart J, Meijer CJLM, Walboomers JMM et al. Sexually transmitted infections as a cause of anal cancer. *N Engl J Med* 1997; 337: 1350–8.
8. Danish National Board of Health. The activity in the hospital care system 1979. Copenhagen, 1981. [in Danish].
9. Danish National Board of Health. Classification of diseases (1976). Copenhagen, 1981. [in Danish].
10. Danish National Board of Health. Cancer incidence in Denmark 1994. Statistical information, Copenhagen, 1997 no. 7.
11. Storm HH, Manders T, Friis S, Brandt B. Cancer incidence in Denmark 1990. Copenhagen: Danish Cancer Society, Copenhagen, 1992.
12. 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, Muir CS, Skeet RG. Cancer registration, principles, and methods. IARC Scientific Publication No. 95. Lyon: International Agency for Research on Cancer, 1991: 220–36.
13. Rothman KJ, Boice JD. Epidemiologic analysis with a programmable calculator (DHHS Publication No. (NIH) 79–1649). Washington DC: US Government Printing Office, 1979.
14. Breslow NE, Day NE. Statistical methods in cancer research. Vol. II. The design and analysis of cohort studies. IARC Sci. Pub. No. 82. Lyon: International Agency for Research on Cancer, 1987.
15. IARC. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans vol. 38, tobacco smoking. Lyon: International Agency for Research on Cancer, 1986.
16. zur Hausen H, De Villiers EM. Human papillomaviruses. *Ann Rev Microbiol* 1994; 48: 427–47.
17. ACOG. Genital human papillomavirus infections. ACOG Technical Bulletin No. 19. *Int J Gynaecol Obstet* 1994; 46: 339–45.
18. IARC. IARC monographs on the evaluation of carcinogenic risks to humans, Vol. 64, Human papillomavirus. Lyon: International Agency for Research on Cancer, 1995.
19. Kjær SK, van den Brule AJC, Bock JE, Poll PA, Engholm G, Sherman M et al. Human papillomavirus – the most significant risk determinant of cervical intraepithelial neoplasia. *Int J Cancer* 1996; 65: 601–6.
20. Friis S, Kjær SK, Frisch M, Mellemkjær L, Olsen JH. Cervical intraepithelial neoplasia, anogenital cancer, and other cancer types in women after hospitalization for condylomata acuminata. *J Infect Dis* 1997; 175: 743–8.

*Address for correspondence:*

Christoffer Johansen, M.D., Ph.D.  
 Danish Cancer Society, Institute of Cancer Epidemiology  
 Strandboulevarden 49  
 DK-2100 Copenhagen Ø  
 Denmark  
 e-mail: christof@cancer.dk