

Short CommunicationAlcoholism and Risk for Cancer of the Cervix Uteri, Vagina, and Vulva¹

Elisabete Weiderpass,² Weimin Ye, Rulla Tamimi, Dimitrios Trichopoulos, Olof Nyren, Harri Vainio, and Hans-Olov Adami

International Agency for Research on Cancer, Lyon, France [E. W., H. V.]; Department of Medical Epidemiology, Karolinska Institutet, Stockholm, Sweden [E. W., W. Y., D. T., O. N., H-O. A.]; Department of Epidemiology, Harvard School of Public Health, Harvard University, Boston, Massachusetts [R. T., D. T., H-O. A.]; and Department of Clinical Epidemiology, Södersjukhuset, Stockholm, Sweden [O. N.]

Abstract

We conducted a population-based cohort study to analyze the risk of developing cancers of the female genitals among 36,856 patients with a hospital discharge diagnosis of alcoholism (ICD-7: 307, 322; ICD-8: 291, 303; ICD-9: 291, 303, 305A) in Sweden between 1965 and 1995. The follow-up was done by linkages of national registries. Standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) were computed based on nationwide specific cancer rates. The first year of follow-up was excluded from all analyses to minimize the impact of selection bias.

We found that alcoholic women had excess risks for *in situ* cervical cancer (SIR, 1.7; 95% CI, 1.6–1.9), for invasive cervical cancer (SIR, 2.9; 95% CI, 2.4–3.5), and for cancer of the vagina (SIR, 4.6; 95% CI, 2.2–8.5) but not for cancer of the vulva (SIR, 1.0; 95% CI, 0.4–2.0). The fact that alcoholics had an excess risk also for the *in situ* cancer suggests that the observed excess in invasive cervical cancer may not only be attributable to less use of Pap smear screening among them. The alcoholic women may be at higher risk for the progression from human papillomavirus infection to a malignant lesion for lifestyle-related reasons (promiscuity, smoking, use of contraceptive hormones, and dietary deficiencies). We conclude that alcoholic women are at high risk for *in situ* and invasive cervical cancer and for cancer of the vagina.

Introduction

The few published studies on the association between alcohol consumption and risk of cancers of the cervix uteri, vulva, and vagina presented contradictory or inconclusive results (1–5). We conducted a large retrospective cohort study among women

with alcoholism in Sweden aiming to compare the incidence of these cancers among alcoholics and the general population.

Materials and Methods

Our methods have been described in detail previously (6). We identified our cohort in the Swedish Inpatient Register, held by the National Board of Health and Welfare since 1964. In Sweden, there is virtually no private inpatient treatment; thus hospital-provided medical services are population based and referable to the county in which the patient lives. In addition to national registration numbers (unique personal identifiers assigned to all Swedish residents), each record contains administrative and medical data, such as hospital department and discharge diagnoses. The diagnoses are coded according to the seventh revision of the ICD³ (ICD-7) through 1968, the eighth revision (ICD-8) until 1987, and the ninth revision (ICD-9) thereafter. The number of hospitals delivering data to the register has increased steadily; the register covered 60% of the Swedish population in 1969, 75% in 1978, and 85% by the end of 1983 (7). From 1987, the register attained complete nationwide coverage.

After exclusion of records with erroneous national registration numbers and patients with a prevalent cancer, our cohort consisted of 36,856 women, registered at least once with a hospital discharge diagnosis of alcoholism (ICD-7: 307, 322; ICD-8: 291, 303; ICD-9: 291, 303, 305A) between 1965 and 1994. Record linkage of this cohort to the nationwide registers of Causes of Death, Emigration and Cancer, allowed complete follow-up through 1995. We calculated the expected number of cancers by multiplying the observed number of person-years in 5-year age and calendar year strata with stratum-specific cancer incidence rates in Sweden and subsequently the corresponding SIRs and 95% CIs. We excluded the person-time and events during the first year of follow-up to avoid bias attributable to increased likelihood of hospitalization for alcoholism in the presence of a yet undetected malignancy (8).

Results

The women's mean age at enrolment was 42.7 years, and the mean duration of follow-up was 9.4 years. We found a moderate excess risk for *in situ* cervical cancer and for invasive cervical cancer (Table 1) and a marked excess risk for cancer of the vagina (Table 2). This increased risk was fairly constant during the entire follow-up. For cancer of the vagina, and to a lesser extent cancer of the cervix, the SIRs increased with age at follow-up (that means, age at cancer diagnosis). Among the vaginal cancers, one was an adenocarcinoma (SIR, 4.1; 95% CI, 0.1–22.9), 8 were squamous cell cancers (SIR, 4.7; 95% CI, 2.0–9.2), whereas 1 had unknown histology. Vulvar cancer was

Received 12/1/00; revised 4/27/01; accepted 5/11/01.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

¹ This study was supported by a grant from the Swedish Cancer Society.

² To whom requests for reprints should be addressed, at International Agency for Research on Cancer, Unit of Field and Intervention Studies, 150, Cours Albert Thomas, F-69372 Lyon Cedex 08 France. Phone: 33-4-7273-8049; Fax: 33-4-72738345; E-mail: Weiderpass@iarc.fr.

³ The abbreviations used are: ICD, International Classification of Diseases; SIR, standardized incidence ratio; CI, confidence interval; HPV, human papillomavirus.

Table 1 SIR with 95% CI of developing cancer of the cervix during 1–28 years of follow-up among 36,856 women who were hospitalized between 1965 and 1994 for alcoholism in Sweden

	Cervix, <i>in situ</i>			Cervix, invasive ICD-7 code 171		
	Observed	SIR	95% CI	Observed	SIR	95% CI
Total	502	1.7	1.6–1.9	129	2.9	2.4–3.5
Age at follow-up ^a						
<35	180	1.5	1.3–1.8	16	3.2	1.8–5.2
35–49	246	1.8	1.6–2.0	40	2.4	1.7–3.2
50–59	55	2.4	1.8–3.1	35	3.7	2.6–5.2
60+	21	2.7	1.7–4.2	38	2.9	2.1–4.0

^a Age at cancer diagnosis.

detected among 8 women, all of them squamous cell cancers, yielding an overall SIR of 1.0 (Table 2).

For *in situ* cervical cancer, the SIRs increased with increased age at follow-up. This trend of increasing SIRs with age at follow-up was not evident for invasive cervical cancer (Table 1).

Discussion

To our knowledge, this is the largest prospective study on alcoholism and cancer of the cervix, vagina, and vulva published to date. In our population-based, prospective cohort study design, selection and information bias, as well as differential misclassification of the alcoholism diagnosis, are unlikely. If misclassification occurred, it should have been non-differential (for patients that develop cancer and those who do not) and, therefore our point estimates could have been biased toward the unit.

The incidence of reported cancer *in situ* in Sweden increased rapidly during 1958–1967, and since then it has been quite stable (9). Although we cannot measure the completeness of registration of cancer *in situ* of the cervix (*i.e.*, the proportion of occurring *in situ* cancers that are actually detected and registered), it is known that the registration of detected and diagnosed cancers *in situ* is >90% (10). To assess whether we had variations in the registration of *in situ* lesions during the study period, we performed a stratified analysis by age and calendar year at diagnosis. We observed no remarkable differences in the association between alcoholism and *in situ* cervical cancer over time or by age groups (data not shown).

Among women alcoholics, the excess risk for invasive cervical cancer may not arise only because they get fewer Pap smears, because we found also an excess of carcinoma *in situ*, an asymptomatic lesion detected by screening. These alcoholic women may be at a higher risk for progression from HPV infection to a malignant lesion for lifestyle-related reasons, such as promiscuity and early initiation of sexual intercourse (11, 12). Alcoholic women are likely to have smoked more than women in general. Women who smoke have a significantly increased risk of cervical cancer compared with nonsmokers, even when adjusting for HPV infections (13). Tobacco-specific carcinogens are present in the mucus of the female genital tract (14). It is apparent that the HPV infection alone is not sufficient for the development of cervical cancer, and several possible cofactors have been proposed including exposure to smoking-related carcinogens, coexisting microbial/viral infections, contraceptive hormones, and dietary deficiencies (13). The current understanding is that HPV infection is an “initiating” event and

Table 2 SIR with 95% CI of developing cancer of the vagina and vulva during 1–28 years of follow-up among 36,856 women who were hospitalized between 1965 and 1994 for alcoholism in Sweden

	Vulva ^a ICD-7 code 176.0			Vagina ICD-7 code 176.1		
	Observed	SIR	95% CI	Observed	SIR	95% CI
Total	8	1.0	0.4–2.0	10	4.6	2.2–8.5
Age at follow-up ^b						
<50	0	—	—	1	2.5	0.1–14.1
50+	8	1.2	0.5–2.4	9	5.1	2.3–9.7

^a Using expected rates specifically for vulva squamous cell carcinoma, the overall SIR was 1.1 (95% CI, 0.5–2.2).

^b Age at cancer diagnosis.

that additional somatic alterations with one or more cofactors are necessary to support malignant transformation.

The high risk of cancer of the vagina among alcoholics has been suggested by earlier, less powerful, and somewhat more limited epidemiological studies (15, 16). The similarly increased risks in the two genital tumors, of the cervix and vagina, are not surprising from the biological point of view. Smoking is a strong confounder for noncervical genital cancers. Tobacco carcinogens have been detected in the mucus of the female genital tract (14), which makes the direct contact possible between the carcinogens and the cervical and vulvar tissues.

Cancer of the vagina and vulva are assumed to have similar etiological profiles (17). Smoking and HPV are the known risk factors in vulvar cancer as well (18). It is somewhat puzzling, therefore, that smoking did not seem to have exerted a confounding effect in the findings for cancer of the vulva; however, because of its rarity, the number of vulvar cancers was small. Alcoholics may possess higher circulating estrogen levels (19, 20), and the vaginal epithelium may be more estrogen responsive than vulvar tissue, which could explain the difference in cancer response.

References

- Martin, P. M., and Hill, G. B. Cervical cancer in relation to tobacco and alcohol consumption in Lesotho, southern Africa. *Cancer Detect. Prev.*, 7: 109–115, 1984.
- Licciardone, J. C., Wilkins, J. R., Brownson, R. C., and Chang, J. C. Cigarette smoking and alcohol consumption in the aetiology of cervical cancer. *Int. J. Epidemiol.*, 18: 533–537, 1989.
- Adelstein, A., and White, G. Alcoholism and mortality. *Popul. Trends*, 6: 7–13, 1976.
- Glade, M. J. Food, Nutrition and the prevention of cancer: a global perspective. American Cancer Institute for Cancer Research/World Cancer Research Fund, American Institute for Cancer, 1997. *Nutrition*, 15: 523–526, 1999.
- Williams, R. R., and Horm, J. W. Association of cancer sites with tobacco and alcohol consumption and socioeconomic status of patients: interview study from the Third National Cancer Survey. *J. Natl. Cancer Inst.*, 58: 525–5247, 1997.
- Kuper, H., Ye, W., Weiderpass, E., Ekblom, A., Trichopoulos, D., Nyren, O., and Adami, H.-O. Alcohol and breast cancer risk: the alcoholism paradox. *Br. J. Cancer*, 83: 949–951, 2000.
- Nyrén, O., McLaughlin, J. K., Gridley, G., Ekblom, A., Johnell, O., Fraumeni, J. F., Jr., and Adami, H. O. Cancer risk after hip replacement with metal implants: a population-based cohort study in Sweden. *J. Natl. Cancer Inst.*, 87: 28–33, 1995.
- Berkson, J. Limitations of the application of the fourfold table analysis to hospital data. *Biomet. Bull.*, 2: 47–53, 1946.
- Bergstrom, E., Sparen, P., and Adami, H. O. Trends in cancer of the cervix uteri in Sweden following cytological screening. *Br. J. Cancer*, 81: 159–166, 1999.

10. Bergstrom, R., Adami, H. O., Gustafsson, L., Ponten, J., and Sparen, P. Detection of preinvasive cancer of the cervix and the subsequent reduction in invasive cancer. *J. Natl. Cancer Inst.*, 85: 1050–1057, 1993.
11. Ylitalo, N., Sorensen, P., Josefsson, A. M., Magnusson, P. K., Andersen, P. K., Ponten, J., Adami, H.-O., Gyllensten, U. B., and Melbye, M. Consistent high viral load of human papillomavirus 16 and risk of cervical carcinoma *in situ*: a nested case-control study. *Lancet*, 24: 2194–2198, 2000.
12. International Agency for Research on Cancer (IARC). Human Papilloma Viruses. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 64. Lyon, France: IARC, 1995.
13. Kjellberg, L., Hallmans, G., Ahren, A. M., Johansson, R., Bergman, F., Wadell, G., Angstrom, T., and Dillner, J. Smoking, diet, pregnancy and oral contraceptive use as risk factors for cervical intra-epithelial neoplasia in relation to human papillomavirus infection. *Br. J. Cancer*, 82: 1332–1338, 2000.
14. Chen, C., Cook, L. S., Li, X. Y., Hallagan, S., Madeleine, M. M., Daling, J. R., and Weiss, N. S. CYP2D6 genotype and the incidence of anal and vulvar cancer. *Cancer Epidemiol. Biomark. Prev.*, 8: 317–321, 1999.
15. Sigvardsson, S., Hardell, L., Przybeck, T. R., and Cloninger, R. Increased risk among Swedish female alcoholics. *Epidemiology*, 7: 140–143, 1996.
16. Pukkala, E., and Saarni, H. Cancer incidence among Finnish seafarers, 1967–92. *Cancer Causes Control*, 7: 231–239, 1996.
17. Daling, J. R., and Sherman, K. J. Cancers of the vulva and vagina. *In*: D. Schottenfeld and J. F. Fraumeni (eds.), *Cancer Epidemiology and Prevention*, Ed. 2, pp. 1117–1129. Oxford: Oxford University Press, 1996.
18. Levi, F., Randimbison, L., and La Vecchia, C. Descriptive epidemiology of vulvar and vaginal cancers in Vaud, Switzerland, 1974–1994. *Ann. Oncol.*, 9: 1229–1232, 1998.
19. Hankinson, S. E., Willett, W. C., Manson, J. E., Hunter, D. J., Colditz, G. A., Stampfer, M. J., Longcope, C., and Speizer, F. E. Alcohol, height, and adiposity in relation to estrogen and prolactin levels in postmenopausal women. *J. Natl. Cancer Inst.*, 87: 1297–1302, 1995.
20. Reichman, M. E., Judd, J. T., Longcope, C., Schatzkin, A., Clevidence, B. A., Nair, P. P., Campbell, W. S., and Taylor, P. R. Effects of alcohol consumption on plasma and urinary hormone concentrations in premenopausal women. *J. Natl. Cancer Inst.*, 85: 722–727, 1993.

BLOOD CANCER DISCOVERY

Alcoholism and Risk for Cancer of the Cervix Uteri, Vagina, and Vulva

Elisabete Weiderpass, Weimin Ye, Rulla Tamimi, et al.

Cancer Epidemiol Biomarkers Prev 2001;10:899-901.

Updated version Access the most recent version of this article at:
<http://cebp.aacrjournals.org/content/10/8/899>

Cited articles This article cites 18 articles, 1 of which you can access for free at:
<http://cebp.aacrjournals.org/content/10/8/899.full#ref-list-1>

Citing articles This article has been cited by 1 HighWire-hosted articles. Access the articles at:
<http://cebp.aacrjournals.org/content/10/8/899.full#related-urls>

E-mail alerts [Sign up to receive free email-alerts](#) related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, use this link
<http://cebp.aacrjournals.org/content/10/8/899>.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.