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Relative and Attributable Risk for Cervical Cancer: A Comparative Study in the United States and Italy

FABIO PARAZZINI*, ALLAN HILDESHEIM**, MONICA FERRARONI†, CARLO LA VECCHIA*‡, AND LOUISE A BRINTON*

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The attributable risk for invasive cervical cancer in the US and Italian populations has been estimated in relation to main 'aetiological' factors (number of sexual partners, age at first intercourse, parity, oral contraceptive use and smoking) and history of Pap smear using data from two case-control studies conducted in the US (466 cases and 788 controls) and Italy (528 cases and 456 controls). The risk of cervical cancer increased in both studies with multiple sexual partners, decreasing age at first intercourse, higher parity, oral contraceptive use and smoking. Levels of exposure to various risk factors were markedly different in the two countries (ie number of sexual partners, frequency of oral contraceptive use and smoking were greater in the US). Multiple Pap smears and a short interval since last Pap smear strongly reduced risk of cervical cancer in both populations, although screening was much more widespread in the US study population, with only 9% of controls reporting no previous smear versus 38% of the Italian control series.

The combined population attributable risk for the five 'aetiological' risk factors was slightly greater in the US study (76%) than in the Italian one (69%), chiefly because of a higher prevalence of exposure to sexual factors in US study women. A substantially larger proportion of Italian cases were due in part to deficiency in screening (46% in US and 84% in Italy). Thus, further inclusion of the effect of screening programmes (number of Pap smears and time since last Pap) led to an overall proportion of cases attributable to the examined risk factors of 87% in the US and 95% in Italy.

There is extensive epidemiological evidence that invasive cervical cancer is largely due to a number of environmental factors.[1,2] Geographical variations and temporal trends in various countries have been interpreted as differences in exposure to risk factors, chiefly reproductive and sexual habits and availability of cervical cytology screening.[1-5] Thus, comparisons of epidemiological features of cervical cancer in countries with differences in disease rates and lifestyle habits are clearly of major interest, since they may offer direct evidence of the role of environmental factors and important clues in terms of prevention and health planning.

To this aim, we have compared relative and attributable risks for the major known environmental risk factors for invasive cervical cancer in the US and Italy. Within the developed world, these countries provide an interesting opportunity for comparative studies of cervical cancer, since they are characterized by differences in incidence of the disease and lifestyle habits and health care organization. For example the world population standardized incidence rate of invasive cervical cancer was 10.1/100 000 women (median age at diagnosis = 60–64 years) in 1978–82 in the cancer registration area of Varese,[6] a city close to Milan. In comparison, based on unpublished data from the Surveillance, Epidemiology, End Results (SEER) programme, the rate of invasive cervical cancer in the US was 8.4/100 000 women (median age at diagnosis = 50–54 years) in 1980–85.[7]

The availability of comparable data, drawn from two large case-control studies conducted in the US and Italy, has made this comparison of relative and attributable risks possible.

*Istituto di Ricerche Farmacologiche 'Mario Negri' via Eritrea 62, 20157 Milan, Italy.
**Environmental Epidemiology Branch, National Cancer Institute, Bethesda, MD, USA.
†Istituto di Biometria e Statistica Medica, University of Milan, 20133 Milan, Italy.
‡Institute of Social and Preventive Medicine, University of Lausanne, 1005 Lausanne, Switzerland.

SUBJECTS AND METHODS

The design and methods of the American and Italian studies have been described in detail in several publications.[8-12] Briefly, the US study was based on incident

cases of invasive cervical cancer (n = 658) occurring during the period April 1982 to January 1984 among women 20–74 years of age identified in a network of 24 hospitals located in five geographical areas, Birmingham, Chicago, Denver, Miami and Philadelphia. Control subjects were ascertained through random-digit dialling techniques, which involved matching of controls to individual cases on age, race and telephone exchange. After exclusion of women found to have had a hysterectomy, a total of 1114 subjects were eligible as controls. Home interviews were obtained for 481 eligible cases (73.1%) and for 801 controls (71.9%). Refusal (9.7% of cases versus 21.9% of controls) was the major reason for non-response of the study subjects. Other reasons were subjects having moved or not being locatable (3.8% versus 3.4%), death (5.0% versus 0.5%), illness (2.1% versus 1.1%), other problems (1.7% versus 1.1%) and failure to obtain physician consent for interview (4.6% of cases). After elimination of cases and controls for whom information was unknown for at least one of the risk factors of interest (education, number of sexual partners, age at first intercourse, parity, oral contraceptive use, smoking and number of Pap smears), the final group analysed had 466 cases with invasive carcinoma (median age 45, range 21–74) and 788 controls (median age 42, range 19–71).

The Italian study was a hospital-based case-control investigation conducted in the Greater Milan area, Northern Italy, on a total of 528 histologically confirmed invasive cervical cancer cases younger than 75 years of age (median age 54 years, range 22–74) admitted between 1981 and 1987 to the obstetrics and gynaecology clinics of the University of Milan, the National Cancer Institute and the Ospedale Maggiore of Milan (which includes the four largest hospitals in Milan). The comparison group consisted of women younger than 75 years, with acute conditions judged to be unrelated to any of the known or suspected risk factors for cervical cancer, admitted to the same network of hospitals where the cases had been identified (chiefly the Ospedale Maggiore of Milan and several specialized university clinics), and hence from comparable catchment areas to cases. Controls were matched to cases on quinquennia of age and were not included if they were admitted for gynaecological, hormonal or neoplastic diseases or had undergone a total hysterectomy. A total of 456 controls (median age 53 years, range 20–74) were interviewed. Of these, 26% were admitted for traumatic conditions (mostly fractures and sprains), 35% had non-traumatic orthopaedic disorders (mostly lower back pain and disc disorders), 14% surgical conditions (mostly abdominal, such as acute appendicitis or strangulated hernia) and 24% had other illnesses, such as ear, nose and throat or dental disorders. Less than 2% of eligible women (cases and controls) refused to be interviewed.

The age distributions of the American and Italian cases and controls are presented in Table 1. The Italian series was considerably older, the percentage of women aged 60 years or more being 19% in the American study and 31% in the Italian one.

For both studies, information was available on personal characteristics and habits, gynaecological and obstetric data, medical history, general indicators of sexual habits (age at first intercourse, total number of sexual partners) lifelong history of use of oral contraceptives and smoking. Data were also collected on total number of Papanicolau smears in the last ten years before diagnosis and time since last cervical smear, after exclusion of diagnostic cytological tests.

Data Analysis

We estimated the relative risks (RR) of cervical neoplasia together with their 95% confidence intervals (CI)[13] in the US and Italian studies according to sexual and reproductive factors, smoking habits, oral contraceptive use and indicators of Pap smear screening. Maximum likelihood estimates of RRs were obtained after simultaneous allowance for potential confounding effects of age, education and the seven risk factors considered (number of sexual partners, age at first intercourse, parity, oral contraceptive use, ever smoked, number of Pap smears, time since last smear) through unconditional multiple logistic regression equations.[14] The choice of an unconditional logistic regression instead of a conditional one was dictated by the large number of unmatched elements in the US study and the absence of strict age matching in the Italian one. The risk estimates obtained through conditional models were in any case not materially different from those presented.

TABLE 1 *Distribution of cases of invasive cervical cancer and controls according to age in US and Italian studies*

	US		Italy	
	Cases No. (%)	Controls No. (%)	Cases No. (%)	Controls No. (%)
Age (years)				
<30	34 (7.3)	78 (9.9)	17 (3.2)	31 (6.8)
30–39	119 (25.5)	232 (29.4)	69 (13.1)	61 (13.4)
40–49	119 (25.5)	195 (24.7)	117 (22.2)	90 (19.7)
50–59	106 (22.7)	167 (21.2)	164 (31.1)	141 (30.9)
≥60	88 (18.9)	116 (14.7)	161 (30.5)	133 (29.2)
Total	466 (100.0)	788 (100.0)	528 (100.0)	456 (100.0)

Using the multivariate RRs per cent population attributable risks for the American and Italian studies were computed for each separate factor, ie number of sexual partners, age at first intercourse, parity, oral contraceptive use, smoking, number of Pap smears and time since last Pap smear, and for the seven factors combined, using the method described by Bruzzi *et al.*[15] This method provides a summary attributable risk for multiple factors (after allowing for effects of confounding) which requires information only on the joint distribution of the risk factors among cases and on the adjusted RR associated with each factor. Thus, provided that unbiased RR estimates are obtained and that the cases can be assumed to be representative of all cases in the population in terms of exposure distribution, this method can be applied to data from hospital-based case-control studies. The adjusted attributable risk calculation assumes no interaction between the risk factors. Further, whenever risk factors are not mutally exclusive, their combined attributable risk differs from the simple sum of the attributable risk of each factor.

When comparing exposure rates to the various risk factors among the US and Italian control groups, adjustment was made for age.[16] This was done by employing the direct method of adjustment and using the pooled control group from the two studies as the standard population.

RESULTS

The RRs of cervical cancer according to number of sexual partners and age at first intercourse for the American and Italian studies are shown in Table 2. The risk of cervical cancer increased with number of sexual partners and with decreasing age at first intercourse. The levels of exposure were markedly different in the two study groups (ie 49% of US cases had four or more partners versus 6% of Italian cases; 68% of US versus 17% of Italian cases had first intercourse before age 18). Nonetheless, the RR estimates were comparable in the Italian and US series. Compared to women with zero or one partner, the estimated RRs were 2.1 for women with four or more partners in the US series and 3.0 in the Italian one. In relation to age at first intercourse, the RRs for <18 versus ≥22 years were 1.8 in the American and 2.3 in the Italian dataset.

The RRs increased with parity in both studies: compared with nulliparae, US and Italian women with four or more term pregnancies had a RR of invasive cervical cancer of 1.7 and 3.1, respectively. Although the point estimate was higher in Italy, the confidence intervals overlapped considerably (Table 3). Oral contraceptive use and smoking were associated with increased cervical cancer risk in both series, but the association with smoking was not statistically significant in the Italian study, possibly due to the lower smoking prevalence among Italian women.

The number of Pap smears was strongly inversely related to cervical cancer risk in both populations (Table 4), although the procedure was much more widespread in the US population, with only 9% of controls reporting no previous smear versus 38% of the Italian series. Compared with women who reported no prior smear, those who had three or more previous smears had a relative risk of only 0.3 in the US and 0.2 in Italy. Likewise, the time since last smear was shorter in controls than cases; compared with women who had had a Pap smear within two years of interview, the RRs

TABLE 2 *Relative risks of invasive cervical cancer according to number of sexual partners and age at first intercourse in US and Italian studies*

	US		Italy	
	No. of cases	Relative risk* (95% CI)	No. of cases	Relative risk* (95% CI)
Number of sexual partners				
0–1	109	1†	402	1†
2–3	130	1.35 (0.95–1.91)	94	1.81 (1.56–2.83)
≥4	227	2.08 (1.47–2.95)	32	3.01 (1.36–6.67)
X^2_1 trend		18.14 (p = <0.001)		13.02 (p = <0.001)
Age at first intercourse				
≥22	43	1†	215	1†
18–<22	106	1.48 (0.94–2.32)	218	1.51 (1.10–2.08)
<18	316	1.78 (1.40–2.77)	88	2.32 (1.38–4.07)
Never	1	—	7	—
X^2_1 trend		4.27 (p = 0.039)		11.78 (p = <0.001)

* Estimates from multiple logistic regression equation including terms for age, education, smoking, number of Pap smears, oral contraceptive use, parity and the above variables.
† Reference category.

TABLE 3 *Relative risks of invasive cervical cancer according to parity, oral contraceptives use and smoking habits in US and Italian studies*

	US		Italy	
	No. of cases	Relative risk* (95% CI)	No. of cases	Relative risk* (95% CI)
Parity				
0	52	1†	56	1†
1	75	1.23 (0.83–2.15)	107	1.27 (0.74–2.16)
2	79	1.19 (0.68–1.74)	145	1.75 (1.03–2.99)
3	79	1.14 (0.71–1.84)	92	2.62 (1.43–4.79)
≥4	181	1.71 (1.09–2.69)	128	3.08 (1.69–5 62)
X^2_1 trend		4.57 (p = 0 033)		21.93 (p = <0 001)
Oral contraceptives				
Never used	258	1†	464	1†
<5 years	114	1.03 (0.71–1.51)	53	1 67 (0.93–3 00)
≥5 years	94	1.78 (1.19–2.66)	11	2 17 (0.64–7 33)
X^2_1 trend		7.79 (p = 0 005)		4.48 (p = 0.034)
Ever smoked				
No	183	1†	360	1†
Yes	283	1.48 (1 14–1.92)	168	1.28 (0.91–1.80)

* Estimates from multiple logistic regression equation including terms for age, education, number of sexual partners, age at first intercourse, number of Pap smears and the above variables.
† Reference category.

in the US and Italian study increased to 3.1 and 2.9 for women who had their last Pap more than five years before or who never had a Pap smear (Table 4).

The proportion of cases of invasive cervical cancer attributable to the identified risk factors in the two populations is given in Table 5. Attributable risks for sexual factors, smoking and oral contraceptive use were slightly greater in the US population, but the role of parity was greater in Italy.The overall estimates, including the joint effect of the five 'aetiological' factors (number of sexual partners, age at the first intercourse, parity, oral contraceptive use and smoking), was slightly greater in the American study (76%) than in the Italian one (69%). A substantially larger proportion of Italian cases was due to absence of prior screening (84% versus 46%). Therefore, further inclusion of the effect of screening (number of Pap smears and time since last Pap smear) led to a greater proportion of cases attributable to the seven factors considered in Italy (95%) than in the US (87%).

TABLE 4 *Relative risks of invasive cervical cancer according to number of Pap smears and time since last Pap smear in US and Italian studies*

	US		Italy	
	No. of cases	Relative risk* (95% CI)	No. of cases	Relative risk* (95% CI)
Number of Pap smears				
0	117	1†*	366	1†
1–2	106	0.40 (0 26–0.61)	93	0.32 (0.18–0.58)
≥3	243	0.29 (0.15–0.33)	69	0.18 (0.13–0 26)
X^2_1 for trend		58.98 (p = <0.001)		100.5 (p = <0.001)
Time since last Pap smear (years)				
<2	193‡	1†	59	1†
2–5	98	0.88 (0.65–1.19)	64	1.95 (1 13–3.36)
>5 or never	172	3.11 (2.22–4.35)	405	2.88 (1.62–5.13)
X^2_1 for trend		34.42 (p = <0.001)		107.11 (p = 0.001)

* Estimates from multiple logistic regression equation including terms for age, education, number of sexual partners, age at first intercourse, parity, oral contraceptive use and smoking.
† Reference category.
‡ Final group used in this analysis include 463 cases and 783 controls. Subjects who had missing values for education, number of sexual partners, age at first intercourse, parity, oral contraceptive use, smoking or time since last Pap smear were excluded.

TABLE 5 *Per cent population attributable risk of cervical cancer in American and Italian population according to selected risk factors and their combination*

Risk factor	Attributable risk per cent					
	US			Italy		
Sexual partners	32			12		
Age at first intercourse	37			22		
Parity	24	76		43	69	
Oral contraceptive use	9		87	5		95
Ever smoked	20			17		
Inadequate Pap Screening (number and time since last Pap smear)	46			84		

Since it is generally accepted that women at higher risk of cervical cancer are more likely not to make use of screening services,[17] it might not be appropriate from a public health viewpoint to adjust for other risk factors for cervical cancer when computing the attributable risk for screening inadequacy. This concern led us to compare the crude and adjusted RRs for cervical cancer associated with number of Pap smears and interval since last Pap smear. No appreciable differences were noted between the two estimates. Indeed, the attributable risk for inadequate Pap smear screening obtained by using the crude RRs (45% in the US and 82% in Italy) were remarkably similar to those computed using the adjusted risk estimates (Table 5).

DISCUSSION

The present overview indicates that the major 'aetiological' factors for invasive cervical cancer (sexual habits, parity, smoking and oral contraceptive use) explain about 70% of cervical cancer in the two populations under study, and that this percentage may be slightly greater in the US than in the Italian population, chiefly because of a higher prevalence of exposure to sexual factors in US women. The number of sexual partners and age at first intercourse alone, accounted in part for about 55% of incidence in the US versus 30% in Italy. Conversely, deficiencies in the utilization of cervical screening played a major role in Italy, i.e. inadequate screening accounted for 84% of the cancer cases in the Italian study, but only 46% in the US investigation. Thus, the overall attributable risk for the various determinants of cervical cancer considered was 95% in the Italian population and 87% in the US.

In strict terms, the validity of these estimates are limited to the areas under surveillance. However, the population living in the greater Milan area is probably comparable in terms of general lifestyle habits and healthcare utilization to that of northern Italy.[18] In the US study, women were recruited from five areas of the country and are therefore a diverse group. Thus, these estimates may provide interesting clues to understanding differences between the incidence of cervical cancer in the two populations.

Some comment should be made on the design of the two studies and potential biases in the computation of RRs and estimation of population attributable risks. The Italian study was hospital-based with subjects collected from the main general and teaching hospitals in the greater Milan area. Although the study protocol indicated that all new consecutive cases should be interviewed, the design was not strictly population-based, and, hence, it is likely that some subjects did not enter the study (for instance simply because they were not present in the ward at the time of the interviewer's visit). Further, women admitted to general and teaching hospitals are different, for example, from those treated in private ones in relation to socio-demographic characteristics.[18] However, cervical cancer cases treated outside of the survey hospitals represent a limited (although not precisely quantified) percentage of incident cases.

The US study also enrolled hospital-based cases. The referral patterns to the participating hospitals are not well understood and could have potentially biased the estimates of exposure to the factors examined. Also, the response rates in the US study were not optimal, and it is possible that selection bias could somewhat affect the exposure prevalence of various factors and consequently the relative risk estimation. However analyses restricted to subgroups with the highest response rates (younger subjects, white women, and those from Philadelphia and Miami), showed estimated RRs largely similar to those of the entire dataset. Furthermore, the frequency of Pap smears reported by controls in both studies is comparable with estimates from interview surveys conducted on more than 27 000 women in Italy[17] and 5500 in the US.[19]

Most of the estimated relative risks were generally comparable, but the parity-related ones tended to be greater in the Italian series; this difference may reflect residual confounding by social class or genital hygiene (among younger women in Italy, multiparous ones tend to be of lower social class). However chance may also be a possible explanation, since the confidence intervals for the risk estimates overlapped considerably.

In concordance with previous findings,[6] the age distribution of cases with cervical cancer in our two studies varied significantly, with Italian cases being older than US cases. It is interesting to note that this

difference is not accounted for by underlying differences in the age distribution of women in the two populations. In fact, after adjusting for age, the annual incidence rate of invasive cervical cancer in Italy is 20% higher than that in the US.[6,7] The varying incidence of cervical cancer in these two countries might therefore be a reflection of differences in prevalence and timing of exposure to various risk factors, resulting in substantial heterogeneity in the cohort patterns of disease in the two countries.

When the prevalences of exposure to aetiological risk factors for cervical cancer were examined, women from the US were found to have higher rather than lower levels of exposure than Italian women. This was true even after the age differential between the two groups was taken into account. For example, the age-adjusted prevalence of parous women was 81% among Italian controls and 85% among US controls. More importantly, the prevalence of women reporting two or more sexual partners was only 9% among Italian controls and 62% among US controls.

Although the control groups in our studies are not necessarily representative of the general population of the two countries such large differences in exposure rates probably reflect real heterogeneities in risk factor exposures in the two populations. Consequently, a higher prevalence of invasive cervical cancer should be expected in the US but cervical cancer incidence rates are, in fact, higher in Italy.[6] Thus, the frequency of cytological cervical cancer screening in the two countries must be considered when explaining the approximately 20% higher rates observed in Italy.

Overall, the age-adjusted prevalence of women reporting no previous Pap test was 33% in Italy and 10% in the US. The role of Pap smears was more evident when the analysis was conducted in different age strata (data not presented). In women 50 years of age or under, for instance, the population attributable risks for inadequate Pap screening were 78% in the Italian population and only 43% in the US, where more than 90% of younger controls reported at least one Pap smear during their life. In older women (over 50 years) the attributable risks were greater, and less markedly different (87% and 72% respectively in Italy and US). It is, moreover, still possible that these proportions are somewhat underestimated, following some misreporting of screening variables, or non-optimal identification of baseline risk categories.

In summary, we find that 90–95% of invasive cervical cancer is explained either by known risk factors or absence of regular cytological screening. If sexual and reproductive factors are only partially avoidable, the observation that about 45% of invasive cervical cancer in the US and over 85% in Italy is attributable to inadequate screening practices emphasizes the importance of Pap smear screening in preventing the incidence of invasive cervical cancer.

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