Cancer Causes Control (2009) 20:67–74
DOI 10.1007/s10552-008-9218-6

ORIGINAL PAPER

A cluster of vulvar cancer and vulvar intraepithelial neoplasia in young Australian Indigenous women

John R. Condon · Alice R. Rumbold · Jane C. Thorn · Margaret M. O'Brien · Margaret J. Davy · Ibrahim Zardawi

Received: 7 October 2007 / Accepted: 31 July 2008 / Published online: 3 September 2008

Abstract
Objective To describe the epidemiological features of a possible disease cluster of vulvar cancer and pre-cancers in Australian Indigenous women living in the Northern Territory (NT) of Australia.
Methods We identified NT-resident women with a confirmed histological diagnosis of vulvar cancer or high-grade vulvar intraepithelial neoplasia (VIN) between 1 January 1996 and 31 December 2005.
Results Seventy-one women were identified; 32 diagnosed with vulvar cancer and 39 with high-grade VIN. Most women diagnosed were Indigenous, aged less than 50 years and living in remote communities in the East Arnhem (EA) district, on the north-east coast of the NT. The age-adjusted incidence rate of vulvar cancer in EA Indigenous women aged 0–49 years was 31.1 per 100,000 (95% CI 13.1–49.1), over 50 times higher than the national Australian rate (0.4 per 100,000, 95% CI 0.4–0.5) for the same age-group. In the age-group of 0–49 years, the age-adjusted incidence rate of VIN for EA Indigenous women was 34.7 per 100,000 (95% CI 15.2–54.3), compared with 6.7 per 100,000 (95% CI 2.0–11.4) for Indigenous women living elsewhere in the Top End of the NT.
Conclusion These data provide evidence of a geographic cluster of vulvar cancer in remote Indigenous communities in northern Australia.

Keywords Vulvar neoplasms · Ethnology · Incidence

J. R. Condon · A. R. Rumbold (✉)
Services, Systems and Society Division, Menzies School of Health Research, PO Box 41096, Casuarina, NT 0811, Australia
e-mail: alice.rumbold@menzies.edu.au

J. R. Condon · A. R. Rumbold
Institute of Advanced Studies, Charles Darwin University, Darwin, Australia

J. C. Thorn
Department of Obstetrics and Gynaecology, Flinders Medical Centre, Adelaide, Australia

M. M. O'Brien
Department of Obstetrics and Gynaecology, Cairns Base Hospital, Cairns, Australia

M. J. Davy
Department of Gynecologic Oncology, Royal Adelaide Hospital, Adelaide, Australia

I. Zardawi
Hunter Area Pathology Service, John Hunter Hospital, New Lambton, Australia

Introduction

Cancer of the vulva is a rare malignancy. In 1993–1997, the age-adjusted incidence rate ranged from 0.1 to 2.7 per 100,000 women in countries throughout the world [1]; the total Australian incidence rate was 1.4 per 100,000 women, with an average of 207 cases diagnosed each year [2]. The majority of cases of vulvar cancer occur in older women (83% in Australian women aged 50 years and above in 1993–1997) [2], however, increases in the incidence of vulvar cancer in younger women have been reported in the recent decades [3, 4].

Like cervical cancer, pre-malignant cellular changes called vulvar intraepithelial neoplasia (VIN) can be found in the vulvar epithelium. VIN are graded into three categories from lesser to more severe abnormality (VIN 1, 2, or 3); however, this histological rating system does not necessarily infer a biological continuum [5]. VIN 1 is the viral cytopathic effect of a human papillomavirus (HPV)

infection expressed in tissues; it is not considered as a cancer precursor. In contrast, VIN 2 and 3 (high-grade VIN) represent the pre-neoplastic lesion of vulvar squamous cell cancer.

VIN and vulvar cancer occur in two distinctive clinicopathological groups [6, 7]. In younger women (35–55 years of age), VIN and vulvar cancer are associated with persistent infection with oncogenic genotypes of HPV [8]. HPV-related VIN is undifferentiated, often multifocal, with a highly variable clinical outcome and associated with invasive basaloid or warty squamous cell carcinoma. In contrast, in older predominantly post-menopausal women (55–85 years of age), vulvar cancer and VIN develop in areas of vulvar skin affected by Lichen Sclerosus; a chronic dermatological condition of unknown (possibly autoimmune) cause that occurs more commonly in older women. VIN resulting from Lichen Sclerosus is differentiated and strongly associated with keratinising squamous cell carcinoma.

In recent years, gynecologists in the Northern Territory (NT) of Australia have diagnosed and treated vulvar cancer and VIN in an excessive number of younger Aboriginal women from remote communities in Arnhem Land, particularly the East Arnhem district, which is in the north-eastern part of the NT. A review of vulvar biopsies taken between 1989 and 2002 by the Department of Pathology at the Royal Darwin Hospital (RDH), the primary referral center in the NT, confirmed that the majority of women diagnosed with high-grade VIN and vulvar cancer were Aboriginal women from this region [9]. Although this review was not primarily an epidemiologic investigation, these findings confirmed the gynecologists' clinical suspicion. The objective of the present study was to undertake a full epidemiological investigation to confirm the existence and document the epidemiological features of this possible cluster of vulvar neoplastic disease.

Materials and methods

Study population

The NT is a sparsely populated region in the northern part of Australia (Fig. 1); just over 200,000 people live in the region and just under half (46%) live in small remote communities. Twenty-nine percent of the NT population is Indigenous (mainly Aboriginal), a far greater proportion than in any other Australian state or territory [10]. The NT capital, Darwin, is a city of approximately 100,000 people. Specialist medical services in the "Top End" (the northern half of the NT, including East Arnhem Land) are provided from Darwin, while the southern half (termed Central Australia) is serviced from Alice Springs. The Gynaecology Outreach Service (GOS), established in 1996, provides visiting obstetric and gynecological services to remote communities and regional hospitals in the Top End; its operation has been described previously [11]. In Central Australia, a similar program known as the Medical Specialist Outreach Assistance Program has been implemented offering visiting obstetric and gynecology services.

In the East Arnhem district (Fig. 1) there are approximately 13,966 people, of whom 8,813 (63%) are Indigenous (Table 1) and living in small remote communities; the remainder are non-Indigenous people, most of whom live in two mining towns [12]. The proportion of Indigenous residents in other NT districts is listed in Table 1. The cluster of vulvar neoplastic disease has been noted to occur in remote Aboriginal communities in the East Arnhem district and communities bordering that district.

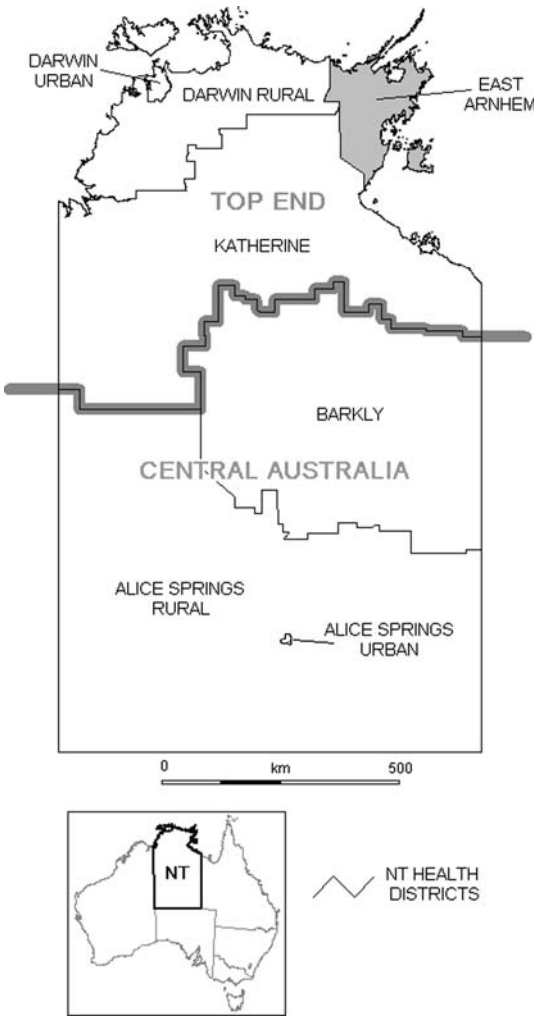

Fig. 1 The Northern Territory (NT) showing NT Government administrative health districts

Table 1 Estimated resident population figures for Northern Territory government administrative health districts, 2001

Health district	% Indigenous persons[a]	% of Indigenous female population aged < 50 years[b]	% of non-Indigenous female population aged < 50 years[c]
Top End			
Darwin Urban	10	89	83
Darwin Rural	74	90	89
Barkly	60	90	82
Katherine	50	90	86
East Arnhem	63	90	89
Central Australia			
Alice Springs Urban	19	88	83
Alice Springs Rural	78	87	84

[a] From Ref. [12]

[b] % of total Indigenous female population in each district

[c] % of total non-Indigenous female population in each district

Data sources

Four data sources were available to identify NT-resident women diagnosed with vulvar cancer (ICD-10 code C51) or high-grade VIN: the NT Cancer Register; the Colposcopy Database maintained by the GOS and RDH, which contains details (including results) of all colposcopies performed by the GOS and public gynecology services in the Top End since 1996; a database of anogenital cancer histology results maintained by the RDH Pathology Department and a separate database of women with vulvar disease developed retrospectively from GOS and other clinical records by GOS gynecologists in 2004. The Colposcopy Database includes almost all colposcopies performed for Indigenous women in the Top End, with the exception of those provided by two private gynecologists in Darwin, who treat a few Indigenous women, and very few from remote communities. All four sources were used to identify women diagnosed with vulvar cancer; all except the Cancer Register were used to identify women diagnosed with high-grade VIN. The Cancer Register and the Pathology Department database included women diagnosed prior to 1996, but the Colposcopy Database and GOS vulvar disease database commenced only from 1996.

Case definition

Vulvar cancer: All women with a confirmed histological diagnosis of vulvar cancer between 1 January 1996 and 31 December 2005 and resident in the NT at the time of diagnosis were included.

High-grade VIN: All women with a confirmed histological diagnosis of VIN grade 2 or 3 between 1 January 1996 and 31 December 2005, and resident in the Top End (which includes the Darwin Urban, Darwin Rural, Katherine, and East Arnhem NT government administrative health districts) at the time of diagnosis were included. Only women in the Top End of the NT were included in the analyses of VIN because the Colposcopy Database, the primary source of data about women diagnosed with VIN, does not include data for Central Australia. This is because the MSOAP service in Central Australia did not maintain a data collection for VIN.

Histology reports confirming the diagnosis of all identified cases were obtained from the NT Cancer Register; the NT Public Pathology Laboratory information system and client medical records at NT public hospitals. Histology slides for all cases of vulvar cancer were referred to the gynecological oncology pathologist at the Institute of Medical and Veterinary Science in Adelaide, South Australia for a second opinion to confirm the histological diagnosis. This was undertaken to ensure eroding ulcers of the vulva caused by donovanosis (an ulcerating disease caused by infection with *Klebsiella granulomatis*) were not misdiagnosed as vulvar cancer [13]. Donovanosis is a rare infection in most parts of Australia, but is more common among Indigenous people in remote areas of northern Australia [14].

Demographic information, medical history, and clinical data for all cases were obtained by checking the hospital medical records, the GOS Colposcopy Database, the NT Cancer Register, and the client master index of the NT public hospitals' patient administration system. Data were also collected about neoplastic or pre-neoplastic lesions of the vagina, cervix, or anus.

Women's usual place of residence was classified according to NT government administrative health district (Darwin Urban, Darwin Rural, Katherine, East Arnhem, Barkly, Alice Springs Urban, or Alice Springs Rural district) (Fig. 1). Incidence rates were calculated for women based on the district of residence, not individual Aboriginal communities, as reliable population data are only available for NT government administrative health districts.

Statistical analysis

The age-standardized incidence rate of vulvar cancer and high-grade VIN was calculated for Indigenous and non-Indigenous women, based on the age-group (<50 or ≥50 years) and the residential district. Analyses compared the incidence of vulvar cancer in the East Arnhem district with the incidence elsewhere in the Top End (Darwin Urban, Darwin Rural, and Katherine districts) and Central Australia (Alice Springs Urban, Alice Springs Rural, and Barkly districts), respectively. For high-grade VIN, the incidence in the East Arnhem district was compared with the incidence elsewhere in the Top End. Population estimates (by sex, five-year age-group, Indigenous status, and district) were obtained from the NT Department of Health and Community Services, based on the estimated resident population data produced by the Australian Bureau of Statistics. Data were age-standardized to the age distribution of the world standard population [15]. All analyses were performed using STATA software (version 8; StataCorp, College Station, Tex, USA).

This study was approved by the Human Research Ethics Committee of the Menzies School of Health Research and the NT Department of Health and Community Services.

Results

Initial searches of all data sources identified 112 women with a recorded diagnosis of either VIN 2 or 3 or invasive vulvar cancer. After further investigation, 41 of these 112 women were excluded for the following reasons: no evidence of diagnosis with VIN 2, VIN 3, or invasive cancer could be found, in clinical or histological records (25 women); diagnosis was made on clinical indications alone with no histological investigation (3); diagnosis occurred prior to 1 January 1996 (10); diagnosis occurred prior to the woman becoming an NT resident (2); and high-grade VIN diagnosis was made in Central Australia, not the Top End (1).

Seventy-one women were identified who fitted the case definition; 32 had a confirmed diagnosis of vulvar cancer (with or without high-grade VIN) and 39 had a confirmed diagnosis of high-grade VIN alone.

Vulvar cancer

Thirty-two women were diagnosed with vulvar cancer in the NT between 1996 and 2005, 21 (66%) were Indigenous and 10 (31%) non-Indigenous; for one woman Indigenous status could not be confirmed.

The total age-adjusted incidence rate for Indigenous women in the NT was 8.3 per 100,000 (95% CI 4.5–12.0), higher than the total incidence rate for non-Indigenous women in the NT (2.0 per 100,000, 95% CI 0.7–3.4) and the total Australian rate in 1996–2001 (1.5 per 100,000, 95% CI 1.5–1.6).

Thirteen (62%) of the Indigenous women diagnosed were residents of the East Arnhem district (Table 2), which includes only 15% of the total NT Indigenous female population [12]; only one of these women was aged above 50 years.

In the age-group of 0–49 years, the age-adjusted incidence rate for East Arnhem Indigenous women was 31.1 per 100,000 (95% CI 13.1–49.1) when compared with 2.7 per 100,000 (95% CI 0.0–5.7) and 3.2 per 100,000 (95% CI 0.0–7.7) for Indigenous women living elsewhere in the Top End and Central Australia, respectively; and 0.4 per 100,000 (95% CI 0.4–0.5) for the total Australian population of the same age-group in 1996–2001 (Fig. 2). In non-Indigenous women in the 0–49 age-group, the age-adjusted incidence rate in East Arnhem was zero (i.e., no cases identified), compared with 0.5 per 100,000 (95% CI 0.0–1.0), for women living elsewhere in the Top End and 0.8 per 100,000 (95% CI 0.0–2.3) for non-Indigenous women living in the Central Australia.

Table 2 Total number of women diagnosed with vulvar cancer and high-grade VIN, 1996–2005, by Indigenous status, district of residence, and age

	Indigenous			Non-Indigenous		
	<50 years	Total		<50 years	Total	
	n	*n*	%	*n*	*n*	%
Invasive vulvar cancer[a]						
East Arnhem district	12[b]	13	62	0	0	0
Other Top End districts[c]	3	4	19	3	8	80
Central Australia[d]	2	4	19	1	2	20
Total		**21**	**100**		**10**	**100**
High-grade VIN						
East Arnhem district	13[e]	13	54	0	0	0
Other Top End districts[b]	8	11	46	11	15	100
Total		**24**	**100**		**15**	**100**

[a] For one vulvar cancer case from the other Top End districts, Indigenous status could not be confirmed

[b] Break down of cases by age-group includes: 25–29 years (six cases); 30–34 years (two cases); 35–39 years (two cases); 40–44 years (zero cases); and 45–49 years (two cases)

[c] Includes the Darwin Urban, Darwin Rural, and Katherine districts

[d] Includes the Alice Springs Urban, Alice Springs Rural, and Barkly districts

[e] Break down of cases by age-group includes: 25–29 years (four cases); 30–34 years (four cases); 35–39 years (one case); 40–45 years (two cases); and 45–49 years (two cases)

VIN, vulvar intraepithelial neoplasia

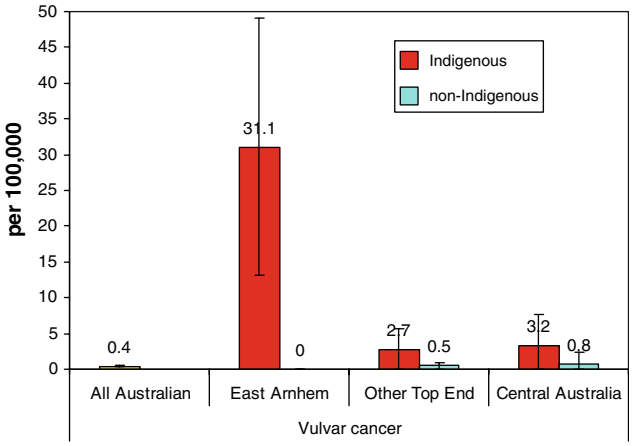

Fig. 2 Age-adjusted incidence rate of vulvar cancer in the age-group 0–49 years for Australian women (1996–2001) and NT women by Indigenous status and district (1996–2005)

In the age-group of 50 years and above, there was no clear evidence of a difference between districts. The age-adjusted incidence rate for Indigenous women in the East Arnhem district was 15.4 per 100,000 (95% CI 0.0–45.7) when compared with 6.1 per 100,000 (95% CI 0.0–18.1) elsewhere in the Top End and 16.5 (95% CI 0.0–39.5) in the Central Australia and 8.0 per 100,000 (95% CI 1.5–14.5) for non-Indigenous women in the NT. All were higher than the national rate for the same age-group (5.2 per 100,000), but the differences were not statistically significant, and caution must be taken in their interpretation as the number of Indigenous cases above 50 years of age was small.

High-grade VIN

Thirty-nine women were diagnosed with high-grade VIN in the Top End of the NT between 1996 and 2005; 24 (62%) Indigenous and 15 (38%) non-Indigenous.

The total age-adjusted incidence rate for Top End Indigenous women was 13.1 per 100,000 (95% CI 7.6–18.5) compared with 2.4 per 100,000 (95% CI 1.1–3.7) for non-Indigenous women. Total Australian incidence rates for high-grade VIN are not available.

Thirteen (54%) of the Indigenous women diagnosed with high-grade VIN were residents of the East Arnhem district (Table 2); the oldest aged 47 years when diagnosed. There were no cases of high-grade VIN in non-Indigenous women in the East Arnhem district.

In the age-group of 0–49 years, the age-adjusted incidence rate for East Arnhem Indigenous women was 34.7 per 100,000 (95% CI 15.2–54.3) when compared with 6.7 per 100,000 (95% CI 2.0–11.4) for Indigenous women living elsewhere in the Top End and 1.9 per 100,000 (95% CI 0.8–3.1) for non-Indigenous women in the Top End.

In the age-group of 50 years and above, the age-adjusted incidence rate for East Arnhem Indigenous women was zero (i.e., no cases were identified) when compared with 16.5 per 100,000 (95% CI 0.00–35.2) for Indigenous women elsewhere in the Top End and 4.2 per 100,000 (95% CI 0.0–8.7) for non-Indigenous women in the Top End.

Other anogenital neoplasia

For NT Indigenous women diagnosed with either vulvar cancer or high-grade VIN, just under half (49%) had previously been or were subsequently diagnosed with a neoplastic or pre-neoplastic lesion of the cervix, vagina, or anus. High-grade cervical lesions were the most common lesions (42% of all Indigenous cases). For Indigenous women in the East Arnhem district, over half (58%) had previous or subsequent other anogenital disease; most often high-grade cervical lesions (50% of all East Arnhem Indigenous cases). Nevertheless, despite the high proportion of East Arnhem cases with high-grade cervical lesions, in the 0–49 age-group, the age-adjusted incidence of cervical cancer in East Arnhem Indigenous women was 13.5 per 100,000 (95% CI 0.1–26.9); similar to the rate for Indigenous women living elsewhere in the NT (8.9 per 100,000, 95% CI 4.4–13.5), and the rate for non-Indigenous women in the NT (6.9 per 100,000, 95% CI 4.8–8.9).

Discussion

This study has confirmed a geographical cluster of vulvar cancer and vulvar intraepithelial neoplasia in younger Indigenous women in the East Arnhem district of the NT. In the age-group of 0–49 years, the incidence of vulvar cancer is more than 50 times higher for East Arnhem Indigenous women than for other Australian women. The incidence of high-grade VIN was also substantially higher in East Arnhem Indigenous women than in non-Indigenous women in the Top End of the NT. There are insufficient data available prior to the time period of this study to determine whether this is a recent or long-term phenomenon.

Data on the incidence of high-grade VIN are not available for the total Australian population, but has been reported for Norway [3]. Between 1988 and 1992, the total age-adjusted incidence of any vulvar intraepithelial squamous cell neoplasia in the Norwegian population was 1.4 per 100,000 women and 33% of affected women were younger than 40 years of age [3]. In the present study, the total age-adjusted incidence of high-grade VIN for non-Indigenous women in the Top End was similar (2.2 per 100,000), with 47% of cases aged below 40 years; although

the rate for non-Indigenous women is an under-estimate because data were not available for some women diagnosed with high-grade VIN by the two private gynecologists in Darwin.

Donovanosis, which causes vulvar ulcers that can be mistaken as vulvar cancer [13], has previously been relatively common in remote Indigenous communities in Australia; however, the number of new cases of donovanosis has fallen dramatically in Australia over the time period of this study [14]. Misdiagnosis of donovanosis as vulvar cancer could be one reason for the excess of vulvar cancer cases, but all cases included in this study have been histologically diagnosed by pathologists experienced in the diagnosis of donovanosis and independently verified. In addition, there is an excess of high-grade VIN, which is not easily confused with donovanosis, in the same region. Misdiagnosis of donovanosis has played minimal, if any, role in this cluster.

The excess of vulvar pathology in the East Arnhem region appears to be limited to women aged less than 50 years; there were no women aged 50 or above diagnosed with high-grade VIN, and only one with vulvar cancer. The cause of excess vulvar pathology in younger Indigenous women is unclear. Possibilities include: a very high prevalence of infection with oncogenic HPV genotypes; presence of a highly virulent variant of an oncogenic HPV genotype; genetic susceptibility to oncogenic effects of HPV; genetic susceptibility to another cause of vulvar cancer; high prevalence of immunosuppressive conditions such as diabetes, human immunodeficiency virus (HIV), or human T-cell lymphotropic virus-1 (HTLV-1) infection, that increase susceptibility to the oncogenic effects of HPV; very high prevalence of smoking, which is associated with vulvar cancer risk; or a combination of these factors.

Chronic infection with oncogenic HPV genotypes is now recognized as an essential component in the etiology of cancer of the cervix [16]. There is evidence that the same HPV genotypes, especially genotype 16, play a causative role in the development of vulvar neoplasia in young women [17]. The excess of vulvar cancer and high-grade VIN seen in this study is restricted to women aged below 50 years; in this age-group vulvar cancer is associated with HPV infection, suggesting that persistent HPV infection plays a causal role in the etiology of this cluster. The prevalence of oncogenic HPV infection in East Arnhem Indigenous women is currently unknown; this needs to be determined urgently.

Variants of HPV 16 exist in different parts of the world, and it has been suggested that some variants may be more oncogenic than others [18]. Furthermore, in vulvar carcinoma, there is evidence of a correlation between HPV-16 intratypic variation and ethnicity [19]. Therefore, it is possible that a variant strain of HPV genotype 16 may be present in the East Arnhem district, a variant that is much more virulent at causing vulvar malignancy.

Cigarette smoking is associated with a fivefold increase in the risk of vulvar cancer [20]. Smoking is more common in Top End Indigenous women than in other Australian women, over 50% of Top End Indigenous women smoke compared with approximately 20% of all Australian women [10, 21]. However, the high prevalence of smoking amongst Indigenous women occurs across districts in the Top End; the proportion of female smokers is similar in the East Arnhem, Darwin Urban, and Darwin Rural districts [21]. Therefore, smoking is unlikely to completely explain why the very high incidence of vulvar cancer is restricted to the East Arnhem district.

Immunosuppression increases the risk of vulvar neoplasia [22]. This is likely to be an HPV-dependent mechanism, where declining immunity is associated with increased HPV DNA proliferation, resulting in an increased risk of HPV-related cancers. There is evidence that immunosuppressive conditions such as diabetes, infection with HIV, or HTLV-1 increase the risk of lower genital tract neoplasia [23–25].

Diabetes is more common in Indigenous Australians when compared with other Australians, with the highest prevalence reported in Indigenous people living in the remote areas [10]. Data on diabetes prevalence is available for the largest Aboriginal community in the East Arnhem district; the prevalence in 2002 was 12.0%, which is higher than the prevalence reported among NT Indigenous women overall (8.3%) and the total Australian population (3.5%) [26–28]. Although the prevalence of diabetes is higher in Indigenous populations in the remote areas, this is unlikely to completely explain the extraordinarily high incidence of vulvar cancer in the East Arnhem region, which is in the order of 50 times the national rate. However, in conjunction with the high prevalence of smoking in Indigenous populations, it may explain why overall, the rate of vulvar cancer and VIN is higher in NT Indigenous women when compared with non-Indigenous women.

The prevalence of HIV infection in the East Arnhem district is unknown. In the NT, the proportion of HIV notifications is lower in Indigenous than non-Indigenous people; in 1996–2005, there were 136 cases of newly diagnosed infection, 16 (12%) occurred in Indigenous people [29], who represent 29% of the total NT population. In the present study, we found evidence of HIV testing in 18% of women with vulvar lesions; all women tested were found to be HIV negative. Testing of all women diagnosed with vulvar pathology for HIV is a priority; however, given the small case numbers and the lower proportion of HIV diagnoses among NT Indigenous people, it seems unlikely that HIV infection is a key factor in this cluster. Similarly, HTLV-1 infection is endemic in remote Indigenous

communities in Central Australia but not in the East Arnhem district, where seroprevalence is close to zero [30]; therefore, HTLV-1 infection is also unlikely to be a contributory factor.

Other possibilities are the presence of heritable genetic risk factors in this population, either associated with susceptibility to HPV infection or the ability to clear HPV and avoid persistence, or susceptibility to an HPV-independent cause of vulvar carcinogenesis. There is evidence of inherited genetic factors in the development of cervical cancer, for example, human leukocyte antigen (HLA) polymorphisms have been associated with HPV-positive cervical neoplasia [31]. Although there have been limited investigations of genetic susceptibility to vulvar cancer, there may be similar immunogenetic contributions, with polymorphisms in genes encoding HLA also detected in vulvar neoplasia [32].

Indigenous women in the East Arnhem district suffer a high burden of disease; other anogenital lesions were present in over half of all women diagnosed with vulvar lesions, and recurrence of vulvar and other lesions was common. This is not surprising as vulvar cancer and VIN share common etiologies, namely HPV infection, with disease at other anogenital sites [16, 17, 33]. The high prevalence of other anogenital lesions in this population supports the suggestion that oncogenic HPV infection is a key causal factor. However, although the incidence of cervical cancer is higher in NT Indigenous women when compared with non-Indigenous women [27], the incidence of cervical cancer is similar amongst Indigenous women in the East Arnhem district and elsewhere in the NT. This is unexpected if HPV 16 is the primary oncogenic subtype in this population. The cause of this disparity in incidence of vulvar and cervical cancer in affected communities is unclear; it may suggest a different subtype of HPV (other than HPV-genotype 16 or 18) is present. It is also possible that the cause of the cluster involves a complex interplay of a number of risk factors, where smoking, diabetes, and genetic susceptibility act as co-factors in the pathogenesis of HPV-related cancer in this population.

Further investigation of the cause of this cluster is a clear priority for future research; equally important is an effective and timely disease control response. A control program has commenced based on the early detection of vulvar lesions during routine cervical screening and antenatal care, coupled with modification of existing training and treatment protocols for practitioners involved in the care of Aboriginal women in remote communities.

This study has confirmed an excess of vulvar cancer in Indigenous communities in the East Arnhem district of the NT. This cluster warrants immediate investigation to identify the cause(s) and to better inform a disease control strategy. If oncogenic HPV infection is found to be a primary cause, the HPV vaccines may be an effective preventive strategy; the recent success of the quadrivalent HPV vaccine in preventing anogenital cancerous lesions provides encouragement in this regard [34]. In the mean time, modification of existing health programs to diagnose and treat affected women as early as possible is our only available control measure. Unfortunately, the recurring nature of the disease and the progressive excisions required by many affected women make this a less than perfect response. Identifying the cause of the problem, and possibly a preventive strategy, would be a far more satisfactory response.

Acknowledgment We are grateful to Dr. Steve Guthridge, Ms. Debbie Taylor-Thomson, and staff of the Health Gains Planning Branch of the Northern Territory Department of Health and Community Services (NTDHCS), and Northern Territory Hospitals for advice and assistance during data collection and analysis. We thank Dr. Tom Dodds, Institute of Medical and Veterinary Science, Adelaide, for providing a second opinion of cases of vulvar cancer. Financial support: Funding for this study was provided by the NT DHCS. Alice Rumbold and John Condon were supported by a National Health and Medical Research Council Capacity Building Grant #236235.

Conflicts of interest We are not aware of any financial or other conflicts of interest.

References

1. Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB (eds) (2002) Cancer incidence in five continents, vol VIII. International Agency for Research on Cancer, Lyon, FRA
2. National Cancer Statistics Clearing House (2003) Interactive cancer data. Australian Institute of Health and Welfare, Canberra, Australia
3. Iversen T, Tretli S (1998) Intraepithelial and invasive squamous cell neoplasia of the vulva: trends in incidence, recurrence and survival rate in Norway. Obstet Gynecol 91:969–972. doi:10.1016/S0029-7844(98)00101-X
4. Jones RW, Ranayai JU, Stables S (1997) Trends in squamous cell carcinoma of the vulva: the influence of vulvar intraepithelial neoplasia. Obstet Gynecol 90:448–452. doi:10.1016/S0029-7844(97)00298-6
5. Sideri M, Jones RW, Wilkinson EJ et al (2005) Squamous vulvar intraepithelial neoplasia: 2004 modified terminology, ISSVD Vulvar Oncology Subcommittee. J Reprod Med 50:807–810
6. Giles GG, Kneale BL (1995) Vulvar cancer: the Cinderella of gynaecological oncology. Aust N Z J Obstet Gynaecol 35:71–75. doi:10.1111/j.1479-828X.1995.tb01835.x
7. Scurry JP, Vanin K (1997) Vulvar squamous cell carcinoma and lichen sclerosus. Australas J Dermatol 38:S20–S25
8. Crum CP, Burkett BJ (1989) Papillomavirus and vulvovaginal neoplasia. J Reprod Med 34(8 Suppl):566–571
9. Zardawi I, Kattampallil J, Rode J (2004) Vulvar precancers and cancers in the Northern Territory of Australia. Pathology 36:87–89. doi:10.1080/00313020310001643589
10. Australian Bureau of Statistics and Australian Institute of Health and Welfare (2005) The health and welfare of Australia's Aboriginal and Torres Strait islander peoples. Australian Bureau

of Statistics and Australian Institute of Health and Welfare, Canberra, Australia
11. Gruen RL, Bailie RS, d'Abbs PH, O'Rourke IC, O'Brien MM, Verma N (2001) Improving access to specialist care for remote Aboriginal communities: evaluation of a specialist outreach service. Med J Aust 174:507–511
12. Chondour R, Guthridge S (2006) Population data in the Northern Territory. Department of Health and Community Services, Darwin, Australia
13. Hart G (1997) Donovanosis. Clin Infect Dis 25:24–30. doi:10.1086/514495
14. Bowden FJ (2005) National Donovanosis Eradication Advisory Committee Donovanosis in Australia: going, going…. Sex Transm Infect 81(5):365–366. doi:10.1136/sti.2004.013227
15. Ahmad OB, Boschi-Pinto C, Lopez AD, Murray CJL, Lozano R, Inoue I (2006) Age standardization rates: a new WHO standard (Discussion paper on the internet). World Health Organisation; GPE Discussion Paper Series: No. 31 (cited 20 Dec 2006). Available from: http://www.emro.who.int/ncd/publications/WHO_pop_standard.pdf
16. Clifford GM, Smith JS, Plummer M, Franceschi S (2003) Human papillomavirus types in invasive cervical cancer worldwide: a meta-analysis. Br J Cancer 88:63–73. doi:10.1038/sj.bjc.6600688
17. van Beurden M, ten Kate FJ, Smits HL et al (1995) Multifocal vulvar intraepithelial neoplasia grade III and multicentric lower genital tract neoplasia is associated with transcriptionally active human papillomavirus. Cancer 75:2879–2884. doi:10.1002/1097-0142(19950615)75:12<2879::AID-CNCR2820751214>3.0.CO;2-W
18. Tornesello ML, Duraturo ML, Salatiello I et al (2004) Analysis of human papillomavirus type-16 variants in Italian women with cervical intraepithelial neoplasia and cervical cancer. J Med Virol 74:117–126. doi:10.1002/jmv.20154
19. de Koning MN, Quint WG, Pirog EC (2008) Prevalence of mucosal and cutaneous human papillomaviruses in different histologic subtypes of vulvar carcinoma. Mod Pathol 21(3):334–344. doi:10.1038/modpathol.3801009
20. Daling JR, Sherman KJ, Hislop G et al (1992) Cigarette smoking and the risk of anogenital cancer. Am J Epidemiol 135:180–189
21. Cunningham J (1997) Occasional paper: cigarette smoking among Indigenous Australians. Australian Bureau of Statistics, Canberra, Australia
22. Carter J, Carlson J, Fowler J et al (1993) Invasive vulvar tumors in young women—a disease of the immunosuppressed? Gynecol Oncol 75:2879–2884
23. O'Mara BA, Byers T, Schoenfeld E (1985) Diabetes mellitus and cancer risk: a multisite case–control study. J Chron Dis 38:435–441. doi:10.1016/0021-9681(85)90139-0
24. Korn AP, Abercrombie PD, Foster A (1996) Vulvar intraepithelial neoplasia in women infected with human immunodeficiency virus-1. Gynecol Oncol 61:384–386. doi:10.1006/gyno.1996.0161
25. Strickler HD, Rattray C, Escoffery C et al (1995) Human T-cell lymphotropic virus type I and severe neoplasia of the cervix in Jamaica. Int J Cancer 61:23–26. doi:10.1002/ijc.2910610105
26. Brimblecombe J, Mackerras D, Garnggulkpuy J et al (2006) Leanness and type 2 diabetes in a population of Indigenous Australians. Diabetes Res Clin Pract 72:93–99. doi:10.1016/j.diabres.2005.09.014
27. Jones C, Zhang X, Dempsey K et al (2005) The health and wellbeing of Northern Territory women: from the desert to the sea. Department of Health and Community Services, Darwin, Australia
28. Australian Bureau of Statistics (2006) National health survey: summary of results, Australia 2004–05. Australian Bureau of Statistics, Canberra, Australia
29. National Centre in HIV Epidemiology and Clinical Research (2006) HIV/AIDS, viral hepatitis and sexually transmissible infections in Australia Annual Surveillance Report 2006. National Centre in HIV Epidemiology and Clinical Research, The University of New South Wales and the Australian Institute of Health and Welfare, Canberra, Australia
30. Bastian I, Hinuma Y, Doherty RR (1993) HTLV-I among Northern Territory aborigines (see comments). Med J Aust 159:12–16
31. Apple RJ, Erlich HA, Klitz W, Manos MM, Becker TM, Wheeler CM (1994) HLA DR-DQ associations with cervical carcinoma show papillomavirus-type specificity. Nat Genet 6:157–162. doi:10.1038/ng0294-157
32. Davidson EJ, Davidson JA, Sterling JC, Baldwin PJ, Kitchener HC, Stern PL (2003) Association between human leukocyte antigen polymorphism and human papillomavirus 16-positive vulval intraepithelial neoplasia in British women. Cancer Res 63:400–403
33. Daling JR, Madeleine MM, Johnson LG et al (2004) Human papillomavirus, smoking, and sexual practices in the etiology of anal cancer. Cancer 101:270–280. doi:10.1002/cncr.20365
34. Garland SM, Hernandez-Avila M, Wheeler CM et al for the Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) I Investigators (2007) Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N Engl J Med 356:1928–1943. doi:10.1056/NEJMoa061760