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Correlation between Vulvar Symptoms Stratification and Vulvar Cancer Detection: Prospective Cohort Observational Study

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Abstract

Background: The incidence of cancer vulva is increasing. 50% of cases are occurring at younger age especially the type related to Human Papilloma Virus infection. Cancer vulva can be prevented. Awareness of cancer vulva is deficient among women and healthcare providers. In this study we looked for a correlation between the most significant vulval symptoms to be associated with cancer vulva in order to educate women and to provide guidance for the health care providers. **Methods:** 569 women were enrolled in this observational cohort study. The patients were stratified according to their symptoms into 5 groups. Biopsy from the vulva, unless the lesion is obviously benign. **Results:** Vulvar lesion, as a symptom (mass-ulcer), was significantly associated with detection of vulvar cancer ($P \leq 0.001$). 100% of those women presented with vulvar lesions (mass or ulcer) had cancer. Positive predictive value (PPV) of vulvar lesion alone was 1.25% but the probability of detection of a cancer dramatically increased when the lesion was accompanied with bleeding 35.2% or pain 26.9% respectively. **Conclusion:** Presenting symptoms other than a lesion in the vulva as for example, soreness, irritation or bleeding was rarely associated with detection of cancer.

Keywords

Cancer, Vulva, Soreness, Lesion, Bleeding

1. Introduction

Cancer of the vulva is considered rare; there are around 1300 new vulval cancer cases in the UK every year, that's more than 3 every day in 2015 until 2017. Since the early 1990s, vulval cancer incidence rates have increased by around a seventh

(15%) in females in the UK. There are around 440 vulval cancer deaths in the UK every year, that's more than 1 every day. 69% of vulval cancer cases in the UK are preventable. In the United States, vulvar cancer accounts for nearly 6% of cancers of the female reproductive organs and 0.7% of all cancers in women. The American Cancer Society estimates that about 1350 women will die of this cancer [1].

The risk of cancer vulva increases when women get older. It was estimated that 20% of cases occur at ages less than 50, and 50% occur in women older than 70. Vulvar intraepithelial neoplasia (VIN) and other preinvasive lesions may start 20 years before invasive cancer to develop [2].

In about 50% of cases human papillomavirus (HPV) infection is considered the etiological factor in vulvar cancers. And usually this type is associated with other areas of vulvar intraepithelial neoplasia (VIN). Most of the victims of this type are younger and smokers [3].

In the other 50% of cancer vulva, there is no association to HPV infection. It affects older women above 55 years. These women may have lichen sclerosis and may also have the differentiated type of VIN. DNA testing in this group usually shows mutations of the *p*53 tumor suppressor gene [4].

There is an agreement that there is lack of specific clinical picture for cancer vulva and preinvasive lesions. There are also suggested factors that delay detection of cancer vulva; some of them are: lack of awareness of vulvar cancer, women usually feel ashamed to seek medical advice and they try to self-treat for longer time [5].

Limited studies had explored factors affecting the delay for presentation of patients with vulvar cancer and the specification of red flag signs for the disease [6] [7].

In this study we are looking for a correlation between the most significant vulval symptoms to be associated with cancer vulva in order to health educate women and to provide guidance for the health care providers.

2. Materials and Methods

Study type: observational cohort study.

Sample size [8]:

$$\text{Sample size} = \frac{Z^2_{1-\alpha/2}\, p(1-p)}{d_2}$$

$Z^2_{1-\alpha/2}$ = standard normal variate at 1% type 1 error $P < 0.01$, it is 2.58.

p = expected proportion in population based on previous studies.

d = absolute error or precision.

So at least the sample size should be = $\frac{2.580^2 \times 0.15(1-0.15)}{0.04^2}$ = 530 women.

Study Design: Allocation: consecutive patients have been sequentially investigated.

Primary Purpose: diagnosis.

The present prospective observational trial was conducted in Hai Jamma hospital. The protocol was approved by institutional research committee.

Eligibility: 569 women were recruited from the gynecology outpatient clinic in the duration from November 2015 until May 2019 were recruited from the gynecology outpatient clinic. The present study was conducted in accordance with the Declaration of Helsinki and a written informed consent was obtained from all the participants.

Inclusion criteria:

- Females who were presented with vulvar symptoms, the patients were stratified according to their symptoms into 5 groups:

  1) Vulvar soreness or pain

  2) Vulvar soreness and bleeding

  3) Vulvar lesion (ulcer or mass)

  4) Vulvar lesion with bleeding

  5) Vulvar lesion with pain

Exclusion criteria:

- Coagulopathy
- Clinically unfit patient who cannot receive anesthesia
- Previous history of vulvar biopsy
- History of vulvar radiotherapy

Primary outcome:

Correlation between specified vulvar symptoms and detection of cancer vulva.

Secondary outcome:

Positive predicative value of each of the above mentioned vulvar symptoms as an indicator of cancer vulva.

Enrollment:

Every patient met the selection criteria was undergone.

- History and physical examination;
- Characterization of vulvar symptoms according to the previously mentioned 5 groups;
- Biopsy from the vulva, Unless the lesion is obviously benign e.g.: sebaceous inclusion cyst; urethral diverticulum or clitoral inclusion cyst.

Categorical data were analyzed by Chi-squared or Fisher exact tests. Continuous nonparametric data were analyzed by Kruskal-Wallis or Mann-Whitney tests, with Dunn's correction for multiple comparisons, where appropriate, and a P value of <0.05 was considered statistically significant. Median and range are represented, where indicated.

3. Results

A total 569 women with specified vulvar symptoms were checked in the gynecologic outpatient clinics between 1st November 2015, and 15th May 2019. The median age of the patients was 53 years. The median age of women whose biopsies

tested positive for cancer was higher (65 years [range 48.1 - 90.2]) than that for women whose biopsies were negative for cancer (59 years [range 25.5 - 88.9] but with no significance statistically: P = 0.072). Statistical analysis of the median age of each of the symptom groups showed no significant differences between them as shown in Table 1.

Nonspecific vulvar inflammatory conditions (others) were the most common diagnoses (55.1%) followed by lichen sclerosus 25% with 21 cases of lichen planus (3.7%). Cancer was detected in 53 women (9.3%) patients. A pre-invasive lesion like usual type vulvar intraepithelial neoplasia [VIN(u)] or differentiated vulvar intraepithelial neoplasia [VIN(d)] or Paget's disease was diagnosed in 37 women (6.1%).

Cancer was not detected in any of the women in group (1 & 2) (Table 2). Only one patient in group (2) had vulvar intra-epithelial neoplasia of differentiated type. Also 90 out of 226 (39%) of women in group (1 & 2) were diagnosed to have lichen sclerosus or lichen planus or lichen sclerosus atrophicus.

Vulvar lesion, as a symptom (mass-ulcer), was significantly associated with detection of vulvar cancer ($P \leq 0.001$). 100% of those women presented with vulvar lesions (mass or ulcer) had cancer. Positive predictive value (PPV) of vulvar lesion alone was 1.25% but the probability of detection of a cancer dramatically increased when the lesion was accompanied with bleeding 35.2% or pain 26.9% respectively (Table 3).

Table 1. Shows the demographic data of all patients of the study (n = 569).

	Group (1)	Group (2)	Group (3)	Group (4)	Group (5)	*P*
Age (year)	56 ± 2.1	55 ± 4.3	58 ± 1.2	64 ± 4.1	65 ± 2.3	0.072
Number of smokers	19	4	14	2	13	0.081
Body Mass Index (BMI) kg/m^2	29 ± 2.5	31 ± 1.7	30 ± 2.7	30 ± 2.9	31 ± 1.2	0.065
Number of total patients	199	27	159	17	167	

Table 2. Distribution of women presenting with vulvar symptoms according to the histopathological results.

Presenting symptoms	Cancer	VIN(U)	VIN(D)	Paget's	LS/LP/LSA	Others	Total
Group (1)	0	0	0	0	79	120	199
Group (2)	0	0	1	0	11	16	27
Group (3)	2	3	1	2	35	116	159
Group (4)	6	1	0	1	4	5	17
Group (5)	45	17	5	6	37	57	167
% of total patients	9.3	3.7	1.2	1.6	29.1	55.1	100

LSA: lichen sclerosus atrophicus; LP: lichen planus; LS: lichen simplex; VIN(u): vulvar intra-epithelial neoplasia, usual type; VIN(d): vulvar intra-epithelial neoplasia differentiated (normally associated with LSA).

Table 3. Positive predictive value (PPV) of each symptom group for detection of cancer.

Symptom group	+ve patients for cancer (n: 53)	−ve patients for cancer (n: 516)	PPV % for cancer detection
Group (1)	0	199	0
Group (2)	0	27	0
Group (3)	2	157	1.25
Group (4)	6	11	35.2
Group (5)	45	122	26.9

4. Discussion

The incidence of cancer vulva is increasing in younger age groups especially the type related to HPV infection. So, larger cohort studies are needed to stratify risk of cancer vulva by age. Health care providers should be cautious not to miss cancer vulva cases due to age discrepancy [9].

Cancer vulva was detected in 53 women out of 569 (9.3%). Preinvasive lesions were detected in 37 women (6.5%). 100% of cancer vulva presented with symptoms related to presence of a lesion in the vulva either mass or ulcer. Presence of pain or bleeding accompanied with the mass raised the probability of cancer detection. Cancer was diagnosed in 6 out of 17 women presented with a lesion associated with bleeding with a positive predictive value 35.2% which was statistically significant.

Presenting symptoms other than a lesion in the vulva as for example, soreness, irritation or bleeding were rarely associated with detection of cancer, Nevertheless these observations are needed to be applied in a larger cohort studies to confirm or nullify our hypothesis.

90 women out of 226 women presented with soreness, irritation with or without bleeding but without a mass had been diagnosed with lichen sclerosus atrophicus, lichen planus or lichen simplex. And the other 136 women in group (1 & 2) were diagnosed to have nonspecific inflammation or normal vulva. Such an observation supports the dermatology guidelines advice not to biopsy patients if they responded to high-potency topical steroids [10].

In this study the incidence of cancer vulva is different from that in the literature [4]. A similar study in the South East of England found a positive predictive value of a cancer diagnosis of 15.4% [11]. The results of this study differed from other study results, where 1105 women were included and 13.6% were diagnosed with a malignancy [12]. This difference could be explained by that those studies included women who were referred to secondary care with suspicious lesions; they did not include all women presented to the clinic with vulval symptoms. Also this study included larger number of biopsies which leaded to more power for statistical analysis.

The strengths of this study were related to the reliability of data, clearness of our stratification symptoms and adherence to the study protocol. The results of

this study will guide primary health care providers whom should be referred to higher levels of care in order to not to miss any case of cancer vulva.

One limitations of this study was that the patient sample did not represent the whole community, because the study included women presented to our institution only. They therefore may be were exposed to similar environmental and social factors. So the results couldn't globalize.

5. Conclusion

Vulvar lesion, as a symptom (mass-ulcer), was significantly associated with detection of vulvar cancer ($P \leq 0.001$). 100% of those women presented with vulvar lesions (mass or ulcer) had cancer.

Recommendations

Training courses should be conducted to general practioner doctors and family medicine doctors to improve their knowledge about the red flag symptoms of cancer vulvae. Also we recommend wide based health education sessions through the media and/or the internet to be established to address women at risk so as to improve their awareness about cancer vulva and to avoid delay in presentation to health care service providers.

Compliance with Ethical Standards and Conflict of Interest

The author declares no conflicts of interest to the contents of this manuscript. The patients were counseled and informed about the trial protocol and a written consent according to declaration of Helsinki was signed. The study protocol was approved by institutional ethics committee.

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