

Past cervical intraepithelial neoplasia grade 3, obesity, and earlier menopause are associated with an increased risk of vulval cancer in postmenopausal women

Running title: Risk factors for postmenopausal vulval cancer

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Abstract:

Background: Vulval cancer predominantly affects postmenopausal women. A smaller proportion of vulval cancers, particularly at older ages, are now thought to be associated with human papillomavirus infection than previously reported, but other risk factors have not been well-examined in prospective cohort studies.

Methods: 1.3 million women aged 49-65 were followed for incident vulval cancer (ICD-10 C51). Adjusted Cox regression models were used to examine the relationship between reproductive and lifestyle factors and risk of vulval cancer.

Results: There were 898 vulval cancers registered in the cohort over an average of 14 years of follow-up; 70% were squamous cell carcinomas. Past registration of cervical carcinoma *in situ*, (RR 2.68, 95% CI 1.71-4.18; $p < 0.001$), obesity (RR 1.71, 95% CI 1.44-2.04; $p < 0.0001$), and menopause before the age of 50 (RR 1.52, 95% CI 1.22-1.89; $p < 0.001$) were associated with a significantly increased risk of subsequent vulval cancer.

Interpretation:

Past cervical pre-cancer, obesity, and earlier age at menopause are associated with an increased risk of vulval cancer at older ages.

Key words:

Vulval cancer, obesity, CIN 3, Million Women Study, postmenopausal.

Introduction:

Although vulval cancer accounts for less than 1% of all female cancer, it is the most common anogenital cancer in women over 70 (Figure 1). In 2012, there were 1,052 vulval cancers registered in England, of which 86% (909 cases) were in women aged over 50 years. Its annual incidence increases markedly with age, rising from 2.5 cases per 100,000 women at ages 40-44, to 17.0 per 100,000 at ages 80-84 (Office of National Statistics, 2014).

It has been shown that the risk of vulval cancer is associated with cervical intraepithelial neoplasia (CIN) and that vulval cancer has aetiopathological similarities with high-risk human papillomavirus (HrHPV)-related cancers such as cervical, anal and vaginal cancers (Kalliala *et al*, 2005; Crawford *et al*, 2011). Until recently, it was thought that approximately 40% of vulval cancer cases were attributable to HrHPVs (Chaturvedi, 2010). However, it now seems that a decreasing proportion of vulval cancers are associated with HrHPV as women age; it has been reported that only 15-17% of cases in women 67 years of age and older are associated with HrHPV infection (de Sanjosé *et al*, 2013). Vulval cancers in older women are thought to be more likely to arise in a background of vulval dermatosis (Van De Nieuwenhof *et al*, 2009), and less likely to be HrHPV-driven. In addition, cohort period and age effects relating to HrHPV exposure are likely to play a role (Barlow *et al*, 2015)

Most previous epidemiological studies of risk factors have been small and no consistent findings have emerged (Japaze *et al*, 1977; Newcombe *et al*, 1984; Brinton *et al*, 1990; Parazzini *et al*, 1993; Madsen *et al*, 2008). Some uncontrolled case series suggested a relationship between obesity and vulval cancer risk (Green *et al*, 1958; Franklin & Rutledge, 1972), however a 2013 review concluded that while there may be a relationship between adiposity and vulval cancer, studies had been too small to answer the question definitively (Webb, 2013).

We investigated risk factors for vulval cancer in a large cohort of UK women aged 50 and over, examining associations for vulval cancer overall, and by histological subtype, with obesity, diabetes, and various lifestyle and reproductive risk factors including smoking, parity, past cervical dysplasia, age at menopause, and use of oral contraceptives and of menopausal hormone therapy (HT).

Materials and Methods:

The Million Women Study is a large prospective cohort study, which recruited 1.3 million women invited for routine breast screening via the National Health Service Breast Screening Programme (NHSBSP) between 1996 and 2001 (i.e. women who were born between 1931 and 1945). Full details of the study design and methods are described in further detail elsewhere (Beral *et al*, 2003). Study questionnaires and further details of the data and access policies can be view online at www.millionwomenstudy.org.

Study participants completed a baseline questionnaire providing self-reported information on lifestyle, health and reproductive exposures. Participants were resurveyed twice, approximately four and eight years after recruitment. The study has Multi-Centre Research Ethics Committee approval (MREC 97/01).

The study team are provided with regularly updated information on incident cancers and deaths via the UK National Health Service Central Registers (NHSCR). Cases of incident vulval cancer were identified as “malignant neoplasm of vulva”, International Classification of Diseases version 10 (ICD-10) (World Health Organization 2011) C51. We used self-reported data from the recruitment questionnaire to define most exposures, including menopausal hormone therapy (HT) use. Excellent agreement has been found between HT use as reported by Million Women Study participants and general practice records in a past validation study (Banks *et al*, 2011).

Marital status and history of cervical screening were based on self-reported data from the first resurvey, when information on these exposures was first collected. The Townsend Deprivation Index (Townsend, 1987) was calculated using post-code and 1991 census data. Body mass index was calculated from self-reported weight and height measurements at recruitment, which have been shown to correlate closely with measured variables in Million Women Study participants (Bobrow *et al*. 2012). Women with a registration of CIN grade 3 (CIN 3) prior to recruitment were identified using the information provided by NHSCR.

Vulval cancers were divided into four main histological subtypes: squamous cell carcinomas (SCC), basal cell carcinomas (BCCs), glandular tumours and melanocytic tumours. Histological subtypes were identified using ICDO-3 (International Classification of Diseases for Oncology version 3) morphology codes (Kurman *et al*, 2014; World Health Organization, 2000).

Squamous tumours included the following ICDO-3 codes: M8051/3, M8070/3, M8070/5, M8071/3, M8072/3, M8074/3, M8075/3; and M8076/3. Basal cell carcinomas included: M8090/3, M8091/3, M8094/3, and M8097/3. Glandular tumours (including Paget's disease, Bartholin gland tumours, and adenocarcinomas) were: M8140/3, M8200/3, M8390/3, M8400/3, M8480/3, M8542/3, M8560/3. Finally, melanocytic tumours included: M8720/3, M8721/3, M8743/3, M8744/3 and M8746/3. 'Other' rarer tumour types were excluded from the analysis, and these included unclassified malignancies and sarcomas (see the results section for further enumeration of 'other' tumour histologies).

Statistical analyses:

Participants were excluded from the analyses if they had any invasive cancer registered prior to the start of follow-up, other than non-melanoma skin cancer (ICD-10 C44 according to the International Classification of Diseases, 10th revision, ICD10) (World Health Organisation, 2011). For analyses of all exposures apart from marital status and history of cervical screening, follow-up started on the date of recruitment or at the age of 50 for the small number of women (3%) who were younger than 50 at recruitment. For marital status and history of cervical screening, follow-up started on the date that participants completed the first resurvey. Follow-up continued until the earliest of: the date of registration of any cancer; death; emigration or other loss to follow-up; or 31st of December 2013, the end of follow-up.

We used Cox proportional hazard models with attained age as the underlying time variable to estimate hazard ratios (referred to as relative risks (RRs)) of developing vulval cancer in relation to the following exposures: smoking (never, past, current); alcohol (0-2, 3+ units per week); BMI (normal: <25 kg/m², overweight: 25-29 kg/m², obese: 30+ kg/m²); diabetes (no, yes); oral contraceptive use (never, ever); parity (parous, nulliparous); prior hysterectomy (no, with oophorectomy, without oophorectomy); prior CIN 3 registration (no, yes); deprivation (tertiles); marital status (married/living with a partner, or not); past cervical screening (no,

yes); age at menopause (<50, 50+ years); and HT use (never, past, current).

All analyses were, where possible, mutually adjusted for exposures. In addition, all analyses were stratified by region of residence consisting of 10 geographical areas corresponding to the cancer registry regions: Oxford, East Anglia, South West, Thames, West Midlands, Northern & Yorkshire, Trent, North West (Mersey), North West (Manchester/Lancashire), and Scotland. The assumption of proportional hazards was examined using plots of the Schoenfeld residuals and was found to be reasonable.

In order to avoid distortion by HT use, analyses of age at menopause were restricted to women who reported at baseline that they had never used HT and that they either had a natural menopause or had a bilateral oophorectomy. Analyses of HT use were restricted to women who reported being post-menopausal at baseline.

A subgroup analysis was performed using a competing hazards model to examine the associations between BMI (<30, 30+ kg/m²), smoking (never, ever), age at menopause (<50, 50+ years), and menopausal HT use (never, past, current) and vulval cancer by histological subtype. Results were tested for heterogeneity of effect of these exposures by tumour histological type. We were unable to look at the effect of CIN 3 by histology due to the small number of cases with this exposure within subtype groups.

We performed two sensitivity analyses. In the first, we excluded the first three years of follow-up from the main analysis, to assess the possibility of reverse association. In the second, we assessed the possibility of bias due to changes in exposures over the follow-up period. To do this we censored women who did not respond to a resurvey four years after their previous survey. We then compared an analysis in which exposures were fixed at recruitment to one in which smoking status, alcohol use, BMI, diabetes, and hysterectomy/oophorectomy were updated using self-reported data from the first and second resurveys, and CIN 3 registration was updated using data provided by the NHSCR.

The few women with missing data for adjustment variables (<5% for each variable) were included in a separate category for each variable of interest. Relative risks are reported with 95% confidence intervals. Analyses were performed in Stata 14 (Statacorp, 2014).

Results:

1.3 million women without prior cancer were followed for 18 million person-years (on average 13.8 years per woman), and there were 898 vulval cancers registered in the cohort over that period. Just over half of the cohort were overweight or obese: 34% of women had a BMI of 25 to 29.9, putting them in the overweight range, and 17% were obese with a BMI of 30 or more. Most women were parous, with 89% of participants reporting ever having given birth. Nearly 60% had a history of oral contraceptive use, 46% had ever smoked, with 19% reporting being current smokers. Around half of all participants had ever used menopausal hormone therapy (Table 1).

The exposure with the strongest association with risk of vulval cancer later in life was a registration of CIN 3 prior to recruitment. Women with a CIN 3 registration prior to recruitment had more than a doubling in risk of vulval cancer compared with women who had not had CIN 3, RR 2.68 (95% CI 1.71-4.18, $p < 0.0001$).

Being overweight or obese was associated with an increased risk of vulval cancer compared with women with a normal BMI and risk increased with adiposity. Overweight women (BMI of 25-29) had a 19% increase in risk of incident vulval cancer, with a RR of 1.19 (95% CI 1.02-1.39; $p < 0.0001$), and this rose further in women classed as obese (BMI of 30 and over), who had a RR of 1.71 (95% CI 1.44-2.04; $p < 0.0001$) (Figure 2). After adjustment for BMI and other factors, there was no significant increase in risk associated with a history of diabetes.

There was no association seen between smoking and overall vulval cancer risk; women who reported ever having smoked had a RR of 0.98 (95% CI 0.82-1.17) compared with never smokers. Similarly, no significant increase in risk was seen with alcohol use, age at menarche, oral contraceptive pill use, parity, or tubal ligation.

We examined risk associated with age at menopause in women who had never used menopausal HT and who reported a natural menopause or bilateral oophorectomy. Women with an earlier

age at menopause had an increased risk of vulval cancer later in life. Menopause prior to age 50 was associated with a 50% increase in risk of vulval cancer compared with menopause that occurred after 50; RR 1.52, 95% CI 1.22-1.89; $p < 0.001$. There did not appear to be any further increase in risk associated with age at menopause before age 45 (RR 1.39, 95% CI 1.00-1.94) compared with menopause at 45-49 years (RR 1.58, 95% CI 1.24-2.01). Use of menopausal hormone therapy was not associated with risk of subsequent vulval cancer overall (Table 2).

In analyses starting at the first resurvey around four years after recruitment, when women were asked for the first time about marital status and attendance for cervical screening, there was no significant difference in risk of vulval cancer for women not currently married or living with a partner (RR 1.19, 95% CI 0.95-1.50) compared with those who were; or for those who reported having ever vs never attended for cervical screening (RR 0.96, 95% CI 0.57-1.62).

Two thirds of vulval cancers ($n = 609$, 68%) were specified as squamous cell carcinomas. Glandular tumours were less common, with 96 registered (11%), including Paget's disease and various types of adenocarcinoma. Basal cell tumours were the next most common, with 92 cases (10%). Melanocytic ($n = 55$, 6%) and other (unspecified and sarcomatous) tumours made up the remaining number ($n = 46$, 5%) (Table 3).

When we examined associations by histological subtype (Table 4), obese women (BMI of 30+) had a substantially and significantly elevated risk of squamous cell carcinoma (RR 1.84, 95% CI 1.53-2.21), but little or no associated increased risk for basal cell, glandular, or melanocytic tumours (test for heterogeneity $p = 0.01$). We also observed a reduction in melanocytic tumours in women who had ever smoked (RR 0.49, 95% CI 0.27-0.91) compared with never smokers.

The sensitivity analyses showed that our results are not likely to be due to reverse association (Web Figure 1). They also showed that any bias caused by changes in the exposures over time is likely to be small (Web Figures 2 and 3)

Discussion:

The strongest increase in risk of vulval cancer in our study was seen in women with a registration of CIN 3 prior to recruitment, who had more than a doubling in risk compared with women who had not had CIN 3. Adiposity is also significantly associated with an increased risk of vulval cancer in women over 50 years of age, principally in obese women, who have a 70% increase in vulval cancer incidence compared with those with a normal BMI; furthermore, the effect of BMI appears to be strongest for tumours with squamous cell morphology. Women who reported undergoing a natural or surgical menopause (oophorectomy) prior to age 50 have a 52% increase in risk compared with those reporting a later menopause at 50 years or older.

Risk of vulval cancer was not significantly associated with smoking; alcohol use; marital status; parity; hysterectomy; ever having attended for at cervical cancer screening; diabetes; prior tubal ligation; age at menarche; or use of exogenous hormones in the form of the oral contraceptive pill, or menopausal hormone therapy.

HrHPV-related anogenital cancers are known to be related to previous genital tract dysplasia, typically screen-detected disease of the cervix (Crawford *et al*, 2011). A Finnish retrospective cohort study (Kalliala *et al*, 2005) has previously looked at risk of vulval cancer following a diagnosis of any grade of CIN. They found a standardized incidence ratio of 4.1 (95% CI 1.5-8.9) for vulval cancer after treatment of CIN 1, 2 or 3. This was based on 6 cases of vulval cancer amongst 7564 women who had been treated between 1974-2001 (with follow-up to 2003).

The relative risks reported here for vulval cancer after CIN 3, though substantial, are lower than those seen for anal cancer in our previously published study (Coffey *et al*, 2015). We found a RR of 4.03 for incident anal cancer in women with a history of CIN 3 registration prior to recruitment, compared with the RR of 2.68 seen here for vulval cancer. Despite a strong association, vulval cancer remains an uncommon occurrence in women over 50 with prior cervical neoplasia. In our cohort, 20 cases of vulval cancer arose in the 12,533 women with a history of CIN 3. In other words, around 1 in 627 women with a history of CIN 3 have developed vulval cancer, and 2% of the vulval cancers in our study have occurred in women with prior CIN 3 (18 squamous cell carcinomas, and 2 melanomas).

A relationship between vulval cancer and obesity has been suspected since the first case series on vulval cancer were published (Green *et al*, 1958; Franklin & Rutledge, 1972). Although one uncontrolled study from Johns Hopkins Hospital (Japaze *et al*, 1977), reported an increased prevalence of obesity amongst women with vulval cancer, other small case-control studies have found either a non-significant (Newcomb *et al*, 1984; Parazzini *et al*, 1993), or no increase in risk of vulval cancer associated with increased weight or BMI (Brinton *et al*, 1990). Some (Franklin & Rutledge, 1972; Brinton *et al*, 1990; Parazzini *et al*, 1993) have also suggested a relationship between vulval cancer and diabetes, which we did not confirm with prospective evidence in our cohort.

Early age at menopause has also been linked with risk of vulval cancer (Green *et al*, 1958; Franklin & Rutledge, 1972). Franklin & Rutledge (1972) reported that 19% of cases had undergone menopause (natural or surgical) before the age of 41, and 54% by the age of 45. Other small studies that examined the association with age at menopause and related factors (Parazzini *et al*, 1993; Newcomb *et al*, 1984) reported no significant effects of menopausal status, age at menopause, or HT use on risk of vulval cancer. An American case-control study (Brinton *et al*, 1990), which included 209 vulval cancer cases and 348 age, race and residence matched controls, found an increased risk amongst women with early ages at natural or surgical menopause: RR 1.89 (95% CI 0.9-3.8) for surgical menopause < 40 years, and RR 1.75 (95% CI 0.8-4.1) for natural menopause < 45 years, but this association did not reach statistical significance.

A Danish case-control study (Madsen *et al*, 2008), which included 116 vulval cancer cases found that around half of the vulval tumour samples they examined (compared with 89% of vaginal tumours in the same study) were positive for HrHPV. When they examined associations between vulval cancer and various exposures stratified by HrHPV positivity, they found significant associations with smoking and cervical neoplasia for only the HrHPV-positive cases.

We found no association between smoking and overall risk of vulval cancer, but when we stratified by tumour histological subtype, we saw a reduced risk of melanocytic vulval cancers amongst women who reported ever having smoked. This is based on a small number of cases in a subgroup analysis, and therefore must be interpreted with caution. However, other groups have reported similar findings for cutaneous malignant melanoma, with a decrease in incidence and

mortality seen in smokers in a recent meta-analysis (Li *et al*, 2015).

A major strength of this study is that it is the first large prospective study to examine the risk of vulval cancer in older women, and our cohort has accrued a relatively large number of incident cases of this relatively uncommon cancer. In addition, CIN 3 status is obtained by routine reporting to cancer registries rather than potentially subjective self-reporting.

While the number of incident cases of vulval cancers in this cohort is large, the relatively small numbers of cases within exposure subgroups limits our ability to analyse association overall and by histological subtype. Another weakness lies in our inability to look at vulval dermatoses as an exposure, as we did not ask participants about vulval skin conditions. The vulval cancers which predominate at older ages are likely to be related to chronic vulval conditions, such as lichen sclerosis. It has been reported that 5% of women with symptomatic vulval lichen sclerosis have been found to develop squamous cell carcinomas, though 22% of women presenting with vulval cancers have been found to have 'clinically silent' lichen sclerosis adjacent to their tumours. An interval of approximately 20 years between mean age at diagnosis of vulval sclerosis (54 years) and development of squamous cell carcinoma (74 years) has been reported (Carlson *et al*, 1998), which is close to the age at which we see a sharp rise in incidence of vulval tumours in the UK (Figure 1)

We were also unable to distinguish between different types of squamous cell carcinomas. Keratinizing squamous cell carcinomas are reported to be the most common histological subtype of vulval cancer in older women, and are less commonly HPV related (de Sanjose *et al*, 2013). Of the 609 squamous cell carcinomas identified in our cohort, 131 (22 %) were specified as keratinizing, while 447 (73%) were 'squamous cell not otherwise specified'. We only had 8 registrations of tumours with warty (verrucous) morphology and no basaloid squamous cell tumours, the two morphologies most commonly associated with HrHPV infection. We were not able to tell whether tumours with typically HrHPV related morphologies are truly uncommon in our cohort or whether there is simply a lack of histopathological information captured during tumour registration. At best, tumour histology is a proxy marker of likely HPV-association, but it would be helpful to have more robust evidence of histological subtype with the squamous cell

group.

Conclusion:

In a large cohort of over a million women with prospectively collected information on exposures, and just under 14 years of follow-up, we found that history of CIN 3 registration prior to recruitment, overweight and obesity, and younger age at menopause were associated with an increased risk of incident vulval cancer after the age of 50. We also observed a reduction in risk of melanocytic vulval cancers in women who had ever smoked; but we interpret these findings with caution due to the potential role of chance.

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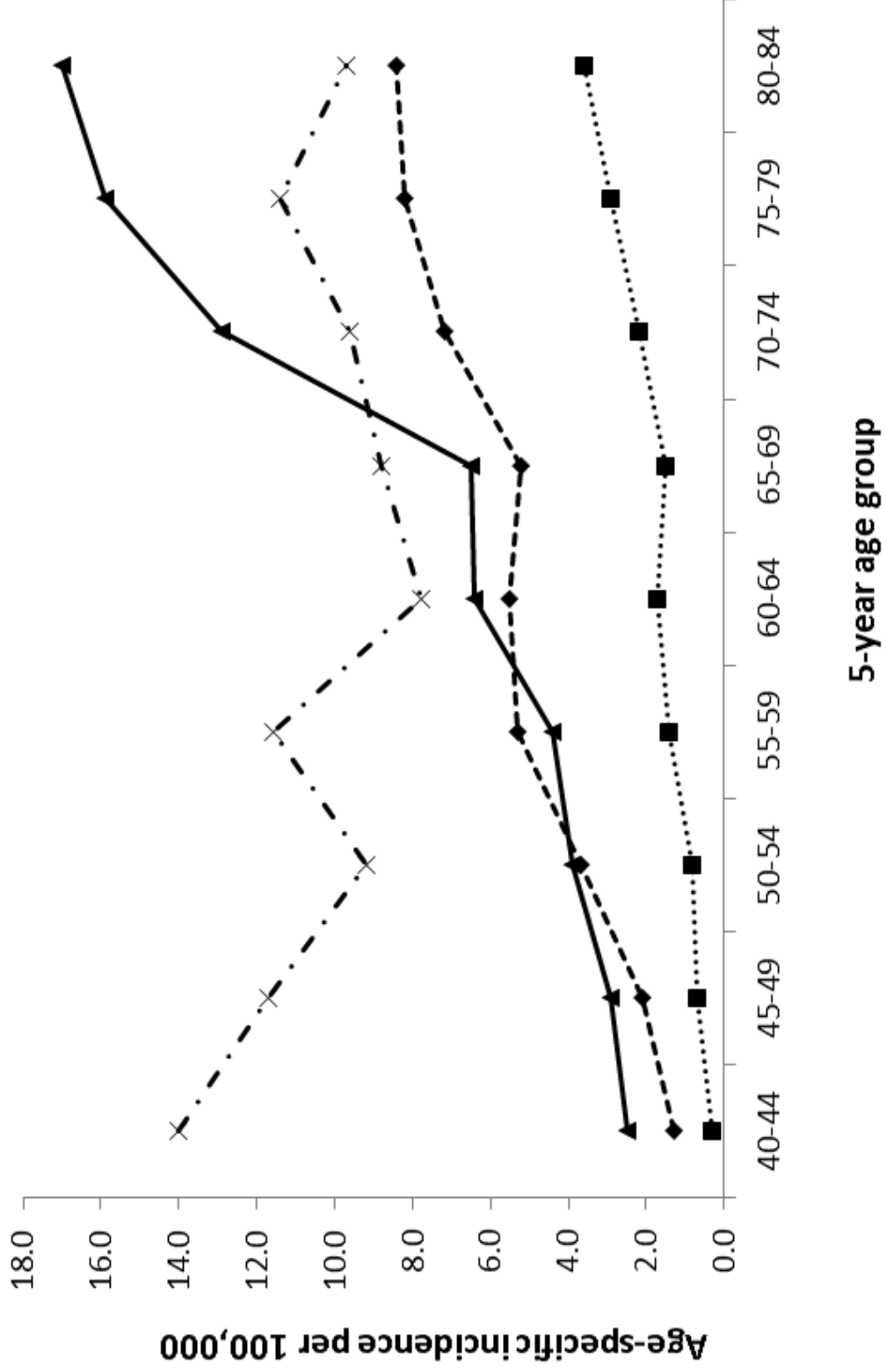
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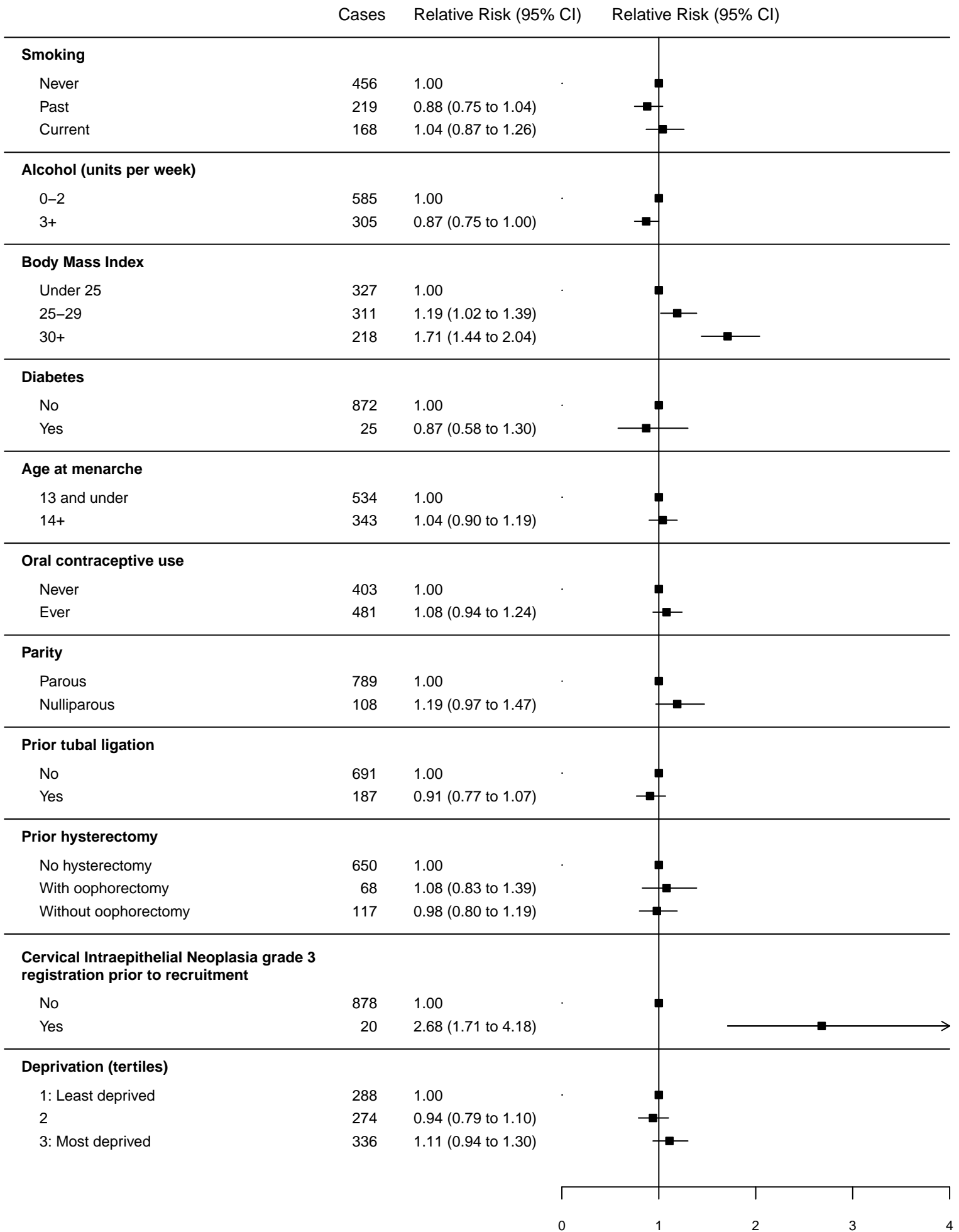
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Figure 1. Age-specific rates of vulval cancer (ICD-10 C51), compared with cervical (C53), anal (C21), and vaginal (C52) cancer, England 2012. Rates are per 100,000 women by 5-year age groups, starting at age 40 (ONS, 2014).

Figure 2. Associations between various reproductive and lifestyle exposures, including body mass index, diabetes, and past cervical intraepithelial neoplasia grade 3, and risk of vulval cancer (all histological types) in women aged 50+ years.

**Relative risks adjusted for smoking, alcohol use, body mass index, diabetes, age at menarche, oral contraceptive use, parity, prior tubal ligation, prior hysterectomy, cervical intraepithelial neoplasia grade 3 prior to recruitment, and deprivation.*





Characteristic at baseline		
Number of women (%)	1 300 042	(100.0)
Mean age at recruitment (SD)	56.6	(4.8)
Parous % (n)	89.0	(1,157,188)
Oral contraceptive user (ever) % (n)	58.6	(761,700)
Current smoker % (n)	19.2	(249,014)
Body mass index ≥ 30 kg/m ² % (n)	17.0	(220,976)
Most deprived tertile % (n)	33.0	(428,383)
Ever hormone therapy user % (n)	49.6	(644,804)
Hysterectomy % (n)	24.4	(316,927)
Registration of CIN 3 prior to recruitment % (n)	1.0	(12,533)
Follow-up		
Women-years (1000s)	17 956	
Mean length of follow-up per woman (SD)	13.8	(3.4)
Number of women with incident vulval cancer	898	

Table 1: Participant characteristics at baseline, and details of follow-up in the cohort.

Exposure	Cases/population at risk	Relative Risk*	95 % confidence interval	p-value
Age at menopause in women with natural menopause or oophorectomy who have never used hormone therapy				
50+	158/237,144	1.00		<0.001
<50	167/175,489	1.52	(1.22, 1.89)	
Use of menopausal hormone therapy at baseline, all postmenopausal women				
Never	401/493,167	1.00		0.54
Past	142/192,727	0.94	(0.77-1.14)	
Current	252/424,544	0.86	(0.73-1.02)	
*Relative risks adjusted, where possible, for smoking, alcohol use, body mass index, age at menarche, oral contraceptive use, parity, tubal ligation, Cervical Intraepithelial Neoplasia grade 3, diabetes, hysterectomy/oophorectomy and deprivation				

Table 2: Associations between risk of vulval cancer, age at menopause, and use of menopausal hormone therapy in postmenopausal women.

Table 3. Incident vulval cancer registrations in the cohort by histological subtype and International Classification of Diseases for Oncology, 3rd Edition (ICDO-3) morphology coding

ICDO-3 Morphology code	Histological subtype	Number (% of all vulval cancers)
Squamous tumours		
M8070/3	Squamous cell carcinoma, not otherwise specified	447 (50.0)
M8071/3	Squamous cell carcinoma, keratinizing, not otherwise specified	131 (14.6)
M8070/5, M8076/3	Squamous cell carcinoma, microinvasive	16 (1.8)
M8051/3	Verrucous carcinoma, not otherwise specified	8 (0.9)
M8072/3, 8074/3, 8075/3	Squamous cell carcinoma: large cell, non-keratinizing/spindle cell/adenoid	7 (0.8)
Total squamous cell tumours		609 (67.8)
Glandular tumours		
M8542/3	Paget's disease	73 (8.1)
M8480/3, M8400/3, M8140/3	Adenocarcinoma: mucinous/sweat gland/ not otherwise specified	13 (1.4)
M8200/3, M8390/3, M8560/3	Adenoid cystic/skin appendage/adenosquamous carcinoma	10 (1.1)
Total glandular tumours		96 (10.7)
Basal cell tumours		
M8090/3	Basal cell carcinoma, not otherwise specified	80 (8.9)
M8091/3	Multifocal superficial basal cell carcinoma	6 (0.7)
M8094/3, M8097/3	Basosquamous carcinoma, basal cell carcinoma (nodular)	6 (0.7)
Total basal cell carcinomas		92 (10.2)
Melanocytic tumours		
M8720/3	Malignant melanoma, not otherwise specified	21 (2.3)
M8721/3	Nodular melanoma	16 (1.8)
M8743/3	Superficial spreading melanoma	14 (1.6)
M8744/3	Acral lentiginous melanoma, malignant	4 (0.4)
M8746/3	Mucosal lentiginous melanoma	
Total melanocytic tumours		55 (6.1)
Other tumours: Unspecified and sarcomatous		
M8000/3, 8010/3	Neoplasm/epithelial tumour, malignant	37 (4.0)
M8032/3, M8033/3, M8800/3, M8832/3, M8851/3, M8890/3, M8891/3	Spindle cell carcinoma, not otherwise specified/ Pseudosarcomatous carcinoma/ Sarcoma, not otherwise specified/ Dermatofibrosarcoma, not otherwise specified/ Liposarcoma, well-differentiated / Leiomyosarcoma / Epithelioid leiomyosarcoma	9 (0.9)
Total 'other' tumours		46 (5.1)
Total incident vulval cancers		898 (100.0)

Exposure	Squamous cell carcinoma			Glandular tumours			Basal cell carcinoma			Melanocytic tumours			p-value**
	Cases/population at risk	RR*	95% CI	Cases/population at risk	RR*	95% CI	Cases/population at risk	RR*	95% CI	Cases/population at risk	RR*	95% CI	
Body mass index													
<30	406/1,010,993	1.00		78/1,010,993	1.00		76/1,010,993	1.00		43/1,0110,993	1.00		0.01
30+	168/220,976	1.84	(1.53,2.21)	15/220,976	0.87	(0.49,1.51)	16/220,976	1.03	(0.60,1.79)	11/220,976	1.20	(0.61,2.36)	
Smoking													
Never	294/627,145	1.00		47/627,145	1.00		52/627,145	1.00		36/627,145	1.00		0.06
Ever	276/596,249	1.04	(0.88,1.23)	46/596,249	1.13	(0.74,1.71)	34/596,249	0.75	(0.48,1.17)	15/596,249	0.49	(0.27,0.91)	
Age at menopause													
50+	112/237,144	1.00		13/237,144	1.00		15/237,144	1.00		9/237,144	1.00		0.94
<50	122/175,489	1.59	(1.22,2.06)	15/175,489	1.62	(0.76,3.45)	15/175,489	1.43	(0.69,2.97)	7/175,489	1.17	(0.42,3.23)	
Menopausal hormone therapy use													
Never	288/493,167	1.00		35/493,167	1.00		34/493,167	1.00		20/493,167	1.00		0.28
Past	87/192,727	0.84	(0.66,1.07)	20/192,727	1.51	(0.87,2.65)	20/192,727	1.69	(0.96,2.97)	6/192,727	0.79	(0.32,2.00)	
Current	159/424,544	0.82	(0.66,1.00)	33/424,544	1.26	(0.76,2.09)	25/424,54	1.15	(0.66,2.00)	24/424,544	1.53	(0.81,2.89)	
*Relative Risks (RRs) adjusted where appropriate for smoking, alcohol use, body mass index, age at menarche, parity, tubal ligation, hysterectomy/oophorectomy and deprivation													
** p for heterogeneity													

Table 4: Associations between body mass index, smoking, age at menopause, menopausal hormone therapy use and risk of vulval cancer by tumour histology subtype.