The positive predictive value of postmenopausal bleeding for uterine malignancy

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Abstract

Postmenopausal bleeding (PMB) is vaginal bleeding occurring after the menopause. The differing definitions of PMB used and need for a standard definition, including what this might be, are highlighted in the thesis. Benign and malignant causes of PMB have been identified, yet an accurate estimate of the risk of uterine malignancy in those with PMB remains undetermined. This thesis aims to establish the positive predictive value (PPV) of PMB for uterine malignancy by combining available evidence. Determining this will potentially improve management of PMB, ensuring detection of malignancies while not over investigating women.

A systematic review conducted identified existing studies providing a PPV in community, primary and secondary care populations. One study was identified in the community providing a PPV for uterine and endometrial cancer of 0.51% (95% CI 0.27-0.75) and 0.47% (95% CI 0.24-0.70) respectively for women aged 45-54. One primary care study was identified providing a PPV for endometrial cancer of 1.68% (95% CI 1.43-1.93) in women aged ≥35. Pooling findings from 26 secondary care studies via random effects meta-analysis produced an estimated PPV of 8.4% (95% CI 6.9-9.9) for endometrial cancer and 19.6% (95% CI 13.8-25.5) for uterine cancer.

The PPV derived for a community population was tested by analysing of a cohort of women with PMB from the community. No women identified had a subsequent cancer diagnosis, suggesting consistency with the low PPV established during the review.

The PPV applicable to a community population suggests women with PMB are unlikely to have cancer, indicating a public health initiative promoting awareness of PMB to be unwarranted. The primary care PPV suggests it may not be appropriate to refer all women with PMB for investigation. However, the increased PPVs in secondary care indicate it is appropriate to investigate all those presenting to secondary care with PMB for malignancy.

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List of Common Abbreviations

BMI	Body Mass Index
CASP	Critical Appraisal Skills Programme
CI	Confidence Interval
CIN	Cervical Intraepithelial Neoplasia
CT	Computer Tomography
D&C	Dilatation and Curettage
EMIS	Egton Medical Information Systems
HRT	Hormone Replacement Therapy
ICD	International Classification of Disease
MDT	Multi-disciplinary Team
MRI	Magnetic Resonance Imaging
NICE	National Institute of Health and Clinical Excellence
PMB	Postmenopausal Bleeding
PPV	Positive Predictive Value
QUIPS	Quality in Prognostic Studies
SIGN	Scottish Intercollegiate Guidelines Network
SOGC	Society of Obstetricians and Gynaecologists of Canada
TVUS	Transvaginal Ultrasound Scan
WHO	World Health Organisation

Aim and Objectives

Postmenopausal bleeding (PMB) is vaginal bleeding occurring after the menopause and is a relatively common complaint with diverse aetiology. The most frequent causes are benign conditions, yet there is potential of underlying malignancy including uterine cancer, which encompasses both cervical and endometrial cancer (SIGN 2002). PMB has been established as a common presenting symptom for these uterine cancers (Plataniotis & Castiglione 2010).

This thesis aims to establish an estimate of the positive predictive value (PPV) of PMB for uterine malignancy in community, primary and secondary care populations. This will provide an overview of the risk of malignancy in each of these populations independently and aid decision making in primary care about whom to investigate.

Specific objectives to achieve this aim will be to:

1. **Identify existing studies providing a PPV of PMB for uterine malignancy** – Such studies will be identified by a systematic review of current literature for community, primary and secondary care populations. The studies will either directly report PPVs or provide sufficient data to calculate a PPV.

2. **Derive a PPV of PMB for uterine malignancy if existing studies providing PPVs are not available** – During the systematic review studies reporting the rate of PMB and those providing the proportion of women with uterine cancer that presented with PMB will be

sought. This data can be used with National Statistics cancer incidence rates to derive a PPV.

3. **Combine available evidence to provide an accurate estimate of the risk of uterine malignancy in women with PMB** – Once PPV estimates have been obtained for each study they can be combined to produce a single reliable estimate for the PPV of PMB for uterine malignancy. This will be achieved by meta-analysis.

4. **Test the PPV obtained for a community population from the systematic review against a group of women with PMB from the community based PRIMROSE study** - This will ascertain whether the PPV of PMB for uterine malignancy in this population is consistent with the PPV derived for a community care consulting population in the systematic review.

Chapter 1. Background

1.1 Overview

This Chapter introduces the important features of PMB, uterine cancers and applicable epidemiological principles. The Chapter concludes by considering the importance of establishing a PPV of PMB for uterine malignancy.

1.2 Menopause

Postmenopausal bleeding is vaginal bleeding after the menopause. The World Health Organisation (WHO) defines the natural menopause as the "permanent cessation of menstruation resulting from loss of ovarian follicular activity and is recognised to have occurred after 12 consecutive months of amenorrhoea with no obvious pathological or physiological cause". Therefore, according to the WHO definition, the time at which the menopause occurs can only be known in retrospect, one year after the final menstrual period (WHO 1996).

In their report on the menopause the WHO acknowledge that the menopause commonly occurs between 45 and 55 years and the median age for occurrence to be 51 years. The report also recognises there is no test which can identify the occurrence of the menopause due to fluctuating hormonal levels during this period.

The loss of ovarian follicular activity during the menopause and fluctuating hormone levels leads to menopausal symptoms. These include (WHO 1996):

- Vasomotor symptoms such as thermoregulatory disturbances
- Urogenital atrophy which may cause dyspareunia
- Irregular vaginal bleeding during the menopausal transition

Menopausal symptoms have been shown to improve with the use of exogenous hormones in the form of hormone replacement therapy (HRT) (Greendale et al. 1998).

1.3 Postmenopausal Bleeding

1.3.1 Definition

Menopause has been defined in terms of the permanent cessation of menstruation due to loss of ovarian follicular activity. However, this definition of menopause does not determine at which point subsequent vaginal bleeding can be regarded as PMB. Symptomatically, PMB is any vaginal bleeding after the final menstrual period, yet definitions state a minimum time that must have elapsed after the final menstruation in order for vaginal bleeding to be deemed PMB. Clinical guidelines have emphasised the variability in PMB definition, some definitions state six months must have passed since the final menstrual period to the onset of vaginal bleeding whereas others will state 12 months (SIGN 2002).

1.3.2 Aetiology

There are many known causes of PMB, the most recognised of which are shown in Table 1.1.

Table 1.1 Causes of PMB	
Cause	**Comment**
Vaginal and endometrial atrophy	Benign condition causing bleeding due to lack of oestrogen after the menopause, resulting in age related thinning of vaginal and endometrial tissue
Uterine polyps	Benign localized uterine lesions due to proliferation of endometrium Occurs commonly, most frequently after 35 years
Endometrial hyperplasia	Usually benign proliferation of the cells lining the endometrium and can be classified as simple or complex dependent on histology Further classified dependent on atypia
Hormone replacement therapy	Women taking continuous combined HRT or cyclic regimens may experience some vaginal bleeding
Malignancy	Several different cancers of the genital tract can cause vaginal bleeding after the menopause

(HWHW 2011, Peterson & Novak 1956, DeWaay et al. 2002, Montgomery et al. 2004, SIGN 2002)

The most common of the causes appear to be the benign conditions such as vaginal and endometrial atrophy (SIGN 2002). Possible malignancies that can cause PMB include endometrial, cervical, vulval, vaginal and ovarian cancers. The uterine (endometrial and cervical) cancers will be the focus of this thesis as they have been established to be the most common of the malignancies to cause PMB (SIGN 2002).

1.3.3 Investigations for underlying endometrial cancer

After a detailed history and clinical examination to exclude carcinomas of the vulva, vagina and cervix, the common investigations a woman with PMB may undergo in order to determine underlying pathology include: transvaginal ultrasound scan (TVUS), hysteroscopy and endometrial

biopsy (SIGN 2002). Figure 1.1 illustrates the possible investigative pathways a patient with PMB may follow according to current guidelines.

In practice some units may not use first line investigations as illustrated but instead first opt to perform a hysteroscopy or use a combination of TVUS and endometrial sampling. This highlights the large degree of variation in the current management of women with PMB.

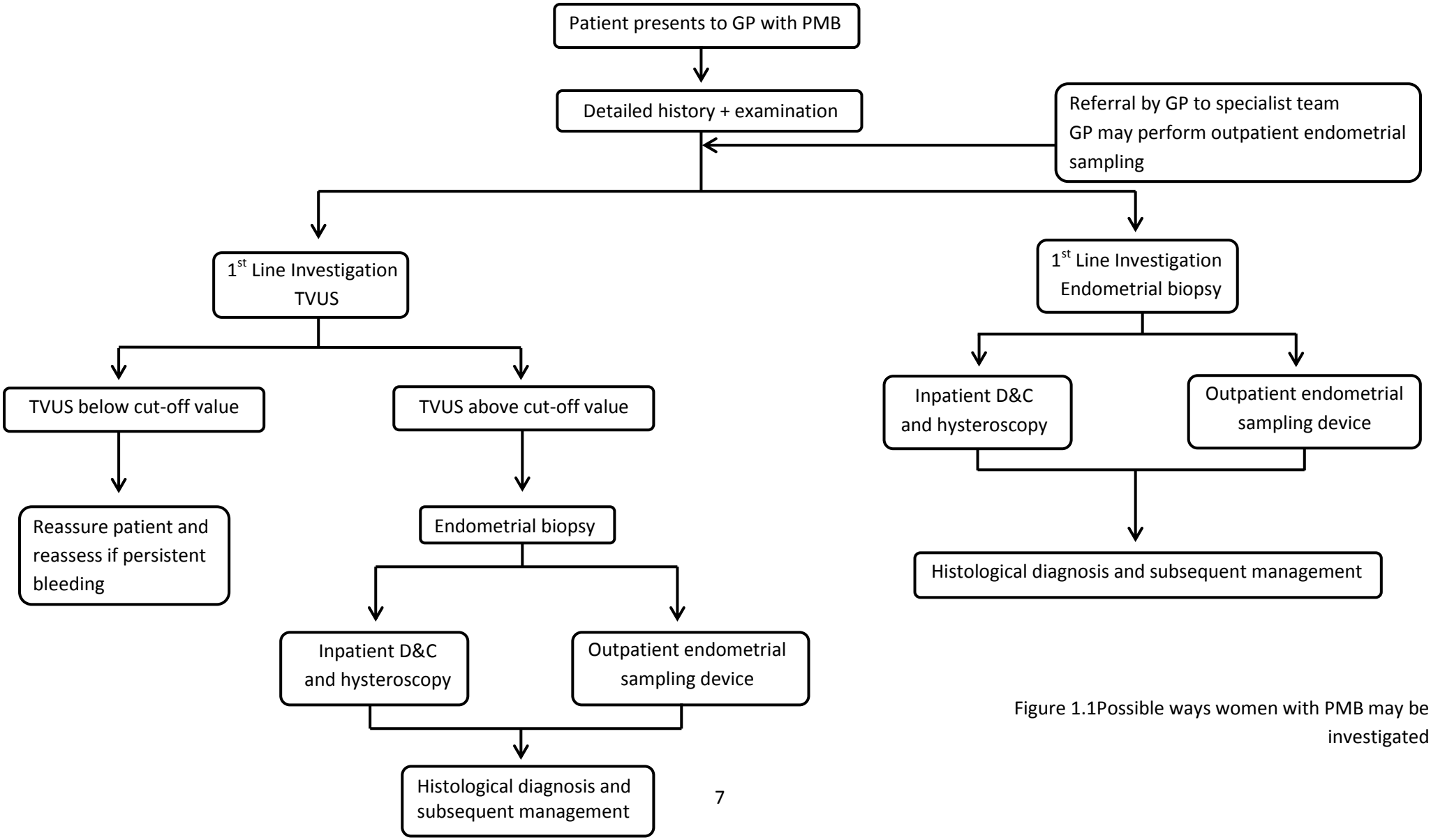


Figure 1.1Possible ways women with PMB may be investigated

Each of the individual investigations for PMB will now be discussed in greater detail.

1.3.3.1 Transvaginal ultrasound scan

When a TVUS is performed the thickness of the endometrium is measured. Conventionally the double thickness measurement of both endometrial surfaces in the mid-sagittal view at the thickest point is used and is performed by inserting a transvaginal transducer into the vagina (SIGN 2002).

TVUS is commonly a first-line investigation for PMB as thickening of the endometrium can suggest pathology is present (SIGN 2002). As highlighted by Wolman et al. (1998) a cut-off value can be applied to the endometrial thickness, below which no further investigation is required and the patient can be reassured. At values above the set cut-off a more detailed evaluation of the endometrium is required (usually hysteroscopy) in order to verify whether pathology is present, as the thicker the endometrium appears, the more likely an underlying malignancy is.

Cut-off values for endometrial thickness have become a topic of debate as no precise figure has been established. A systematic review conducted by Gupta et al. (2002) identified the most commonly used cut-off values for endometrial thickness when investigating PMB to be 4mm and 5mm. The review concluded TVUS cannot be used alone effectively to diagnose malignancy dependent on the measured endometrial thickness. However, a negative result of <5mm would be effective at ruling out the possibility of malignancy. In practice this is normally with the safety net that further investigation takes place if the bleeding persists.

Gupta et al. (2002) additionally suggested a cut-off of 3mm would be more sensitive in identifying possible pathologies, recognising that the commonly used cut-off of 5mm may not identify all malignancies. However, no endometrial thickness measurement will completely exclude the possibility of underlying malignancy in women with PMB. There is a recognised balance that needs to be made between the false negative rate of TVUS and the number of women who undergo the more invasive, risky and costly procedure of hysteroscopy.

TVUS additionally has the advantage of detecting ovarian cancer which is a rare cause of PMB. However, it is not known how many ovarian cancers are detected by TVUS; TVUS demonstrates an ability to aid early detection of ovarian cancer and decrease mortality yet problems arise with interpretation of the TVUS images (Nagell et al. 2007).

1.3.3.2 Hysteroscopy

Hysteroscopy allows direct visualisation of the endometrial cavity by introducing a fibre-optic telescope into the uterine cavity. With an experienced practitioner there may be no requirement for analgesia and hysteroscopy can therefore be performed successfully in an outpatient setting (Farquhar et al. 2003). However, if an outpatient procedure is unsuitable, hysteroscopy can be performed as an inpatient, while under general anaesthetic. Direct biopsy can be undertaken during hysteroscopy although this requires the introduction of a wider device which may increase discomfort. As indicated in guidelines blind endometrial sampling can be performed once hysteroscopy has been completed, whether as an inpatient or outpatient (SIGN 2002).

Hysteroscopy has been suggested to be a successful technique for identifying intrauterine abnormalities. The results of a systematic review by van Dongen et al. (2007) found hysteroscopy

to be an accurate investigative technique in women with PMB and that a negative result was beneficial in ruling out the possibility of an intrauterine abnormality, specifically malignancy.

The review also found hysteroscopy to have a low failure and complication rate. Over 95% of procedures were performed successfully in postmenopausal women and complications occurred in 1% of identified procedures. The majority of complications were due to vasovagal collapse. There is the possibility of uterine perforation with hysteroscopy, however this is a very rare complication with one identified from a total of 1399 procedures in the review. Similar complications are also possible with the other investigative techniques for PMB but are also extremely rare.

1.3.3.3 Endometrial sampling

Histology allows for a definitive diagnosis of PMB and can be achieved by either dilatation and curettage (D&C) or by using an endometrial sampler (SIGN 2002). The surgical procedure of D&C has traditionally been utilised to obtain endometrial samples and requires the use of general anaesthesia. However, newer procedures with endometrial sampling devices are now routinely used as they are less invasive and can be performed in an outpatient setting (Clark et al. 2002). These outpatient endometrial sampling devices are commonly used by secondary and tertiary care centres however they have also been introduced in primary care settings (Seamark 1998).

Biopsies with the endometrial sampling devices are considered simpler to perform than with D&C. A thin plastic tube is interested into the uterine cavity via the cervix, a plunger attached to the end of the device is then withdrawn creating a negative pressure causing aspiration of the tissue into the device (SIGN 2002). The most commonly used and seemingly superior device for this is

the Pipelle, with a high detection rate of endometrial malignancy in women with PMB (Dijkhuizen et al. 2000).

In a systematic review by Clark et al. (2002) the endometrial sampling devices were found to have a failure rate of 7% and inadequate samples were reported in approximately 15% of cases. This suggests the technique may not be consistent in providing samples adequate for histological evaluation. However, when satisfactory samples are obtained endometrial sampling devices can provide a high overall accuracy in diagnosing endometrial cancer. This was observed in the systematic review with results indicating endometrial sampling devices can diagnose endometrial cancer when test results are positive. However, a negative result was shown to not successfully exclude endometrial cancer. Therefore, an endometrial sampling device cannot, when used independently, undoubtedly exclude cancer diagnosis.

As none of the techniques above have been found most effective for diagnosing or excluding malignancy a combination are often used to investigate the cause of PMB.

1.3.4 Management of postmenopausal bleeding

The management of PMB ultimately depends upon the results of investigations performed as the differing causes of PMB will be managed accordingly. However, if the cause of the PMB remains undetermined and the PMB persists for more than six months it is recommended the patient is reinvestigated (SIGN 2002).

The most commonly worrisome cause of PMB, uterine malignancy, specifically endometrial and cervical carcinoma will now be considered in greater detail along with their specific management.

1.4 Endometrial Cancer

1.4.1 Definition

Endometrial carcinoma is a malignancy of the uterine lining or endometrium (HWHW 2011).

1.4.2 Epidemiology

Worldwide an estimated 142 000 women are diagnosed with, and 42 000 women die from endometrial cancer annually, making it the most common gynaecological malignancy in the developed world (Amant et al. 2005). Table 1.2 shows the number of new cases of endometrial cancer registered in England in 2010 along with the age-standardised incidence rates per 100,000 population. The incidence rates of cervical cancer for the same time period in England is also shown to allow for comparison. The figures in the table represent those for the relevant International Classification of Disease (ICD) codes, an international standard for defining diseases and symptoms used to ascertain global health trends and statistics (WHO 2012). Table 1.2 therefore includes figures for ICD-10 code C54, malignant neoplasm of corpus uteri and ICD-10 code C53, malignant neoplasm of cervix uteri.

Table 1.2 demonstrates a steep increase in the incidence of endometrial cancer from the age of 50, indicating the majority of cases of endometrial cancer occur in women likely to be postmenopausal. However there is an apparent decline in incidence after 80 years, signifying the greatest incidence of endometrial cancer is in those aged 50 to 80 years.

Endometrial cancer is more common than cervical cancer. However, cervical cancer affects primarily younger women, with the greatest incidence in those aged between 25 and 45 years. Nevertheless, there is a considerable number of women over 50 and therefore likely to be postmenopausal, affected by cervical cancer.

The overall higher incidence rates of uterine malignancy in women over 50 years illustrated in Table 1.2 suggests it is likely to be postmenopausal women predominantly affected by the uterine malignancies.

Table 1.2 Incidence of Endometrial and Cervical Cancer with Age-specific Incidence Rates per 100,000 Population in England for 2010(Office for National Statistics 2012)				
Age-Range	**Endometrial Cancer Cases**	**Endometrial Cancer Age-standardised Rates**	**Cervical Cancer Cases**	**Cervical Cancer Age-standardised Rates**
0-4	0	0	0	0
5-9	0	0	0	0
10-14	0	0	0	0
15-19	0	0	0	0
20-24	3	0.2	45	2.6
25-29	11	0.6	306	17.4
30-34	28	1.7	290	17.7
35-39	41	2.3	290	16.2
40-44	120	6.1	260	13.2
45-49	229	11.9	192	9.9
50-54	503	30.1	165	9.9
55-59	819	54.2	139	9.2
60-64	1198	74.6	159	9.9
65-69	997	79.1	94	7.5
70-74	984	90.8	103	9.5
75-80	755	82.1	81	8.8
80-84	520	70.3	88	11.9
85+	382	47.5	93	11.6
Total	**6590**	**24.9**	**2305**	**8.7**

Endometrial cancer accounts for 1-2% of deaths from cancer in Western Europe making it the seventh most common cause of death from cancer in women (Plataniotis & Castiglione 2010). The number of registered deaths for endometrial and cervical cancer in England and Wales during 2010 can be seen in Table 1.3.

Table 1.3 Number of Registered Deaths from Endometrial and Cervical Cancer in England and Wales during 2010 (Office for National Statistics 2011)		
Age-Range	**Endometrial Cancer**	**Cervical Cancer**
<1	0	0
1-4	0	0
15-24	1	6
25-34	6	56
35-44	18	106
45-54	76	135
55-64	287	123
65-74	479	149
75-84	509	145
≥85	309	96
Total	**1685**	**816**

The figures suggest the number of deaths from endometrial carcinoma increase with advancing age, with a minority of deaths in women aged below 50 years. The mortality rates for cervical cancer are generally lower than those for endometrial cancer. However, as with endometrial cancer mortality rates, those for cervical cancer generally increase with advancing age.

There is global variation in the incidence and mortality rates of endometrial cancer, with the majority of cases being in the developed world. Figure 1.2 illustrates the age-standardised incidence and mortality rates for endometrial cancer according to world region for the year 2008. Northern America and Europe seem to have the highest incidence rates for endometrial cancer with Africa and Asia having lower rates.

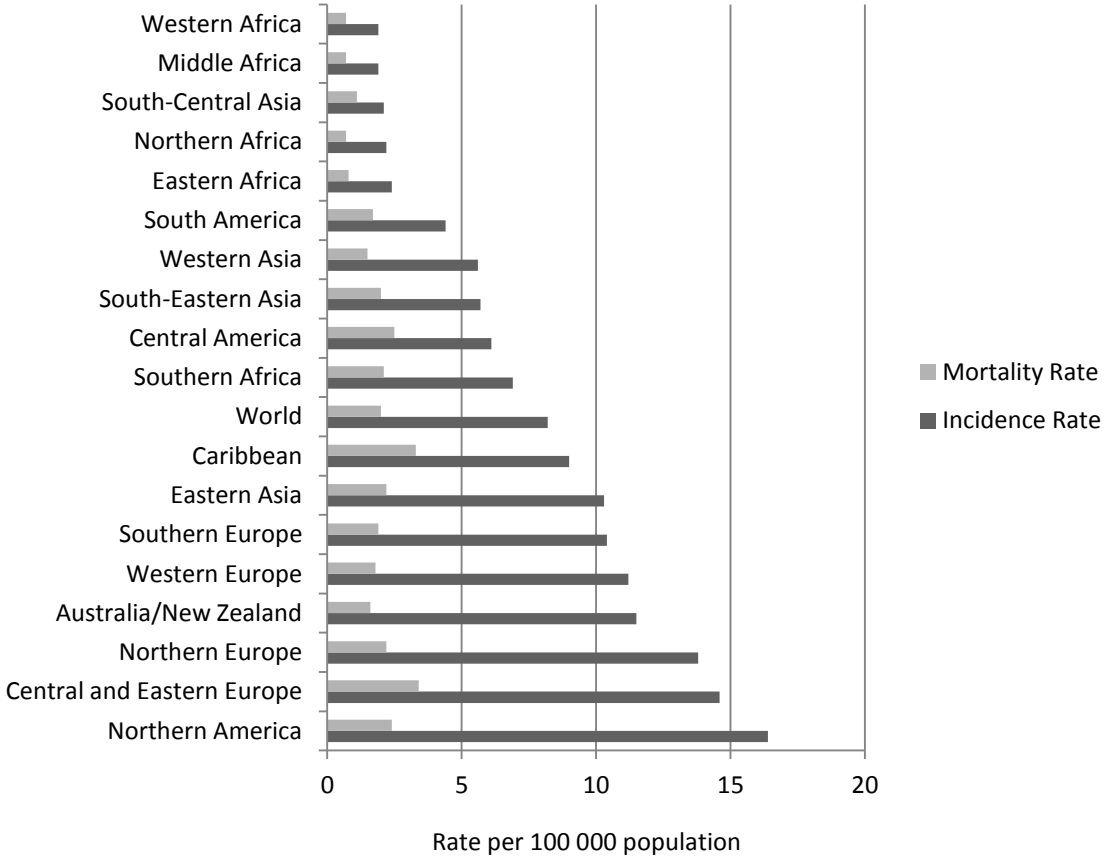


Figure 1.2 Age-standardised incidence and mortality rates for endometrial cancer according to world region for the year 2008 (Cancer Research UK 2012)

1.4.3 Pathophysiology

As highlighted by Saso et al. (2011) based on histopathology and molecular profile endometrial cancer can be classified into two types. Type 1 cancers are endometriod adenocarcinomas and oestrogen dependent. These have a better prognosis than the Type 2 cancers which are not oestrogen dependent and include the histological subtypes papillary serous, clear cell and mucinous adenocarcinomas. Type 2 cancers have poorer prognosis due to their high risk of reoccurrence and metastasis. However, Type 1 cancers are the commoner of the two accounting for 80-90% of endometrial cancers.

A potentially pre-malignant condition is endometrial hyperplasia. The normal fluctuations of oestrogen and progesterone in the menstrual cycle result in structural changes in the endometrium; however unopposed oestrogen initiates hyperplasia of endometrial cells (Amant et al. 2005). This hyperplasia may be histologically atypical and is associated with endometrial cancer. Atypical hyperplasia is of significance as a greater proportion of those with the condition will develop or have coexisting endometrial adenocarcinoma. Kurman et al. (1985) identified 2% of those with hyperplasia without atypia subsequently developed endometrial cancer compared to 23% with atypical hyperplasia.

1.4.4 Risk factors

There are several known risk factors for developing endometrial cancer. These may be either exogenous or endogenous factors. Commonly acknowledged risk factors are shown in Table 1.4. The majority of these factors are related to unopposed oestrogen exposure. Endometrial cells proliferate to a greater degree when increased oestrogen levels are unopposed by progesterone. Pike et al. (2004) illustrated that being overweight, an early menarche and late menopause can all increase unopposed oestrogen levels, increasing endometrial cell proliferation and hence the risk of cancer.

Table 1.4 Risk factors for Development of Endometrial Cancer (Saso et al. 2012)	
Exogenous	**Endogenous**
Unopposed oestrogen only HRT	Advancing age
Tamoxifen therapy	Obesity
Prior radiotherapy	Early menarche
	Late menopause
	Diabetes mellitus
	Hypertension
	Polycystic ovarian syndrome
	Family history
	Lynch syndrome (hereditary nonpolyposis colorectal cancer)
	Immunodeficiency
	History of breast cancer
	Oestrogen secreting tumour

Two exogenous risk factors for endometrial cancer are tamoxifen and HRT use, as these two medications are known effect the endometrium. Tamoxifen is a commonly used drug in breast cancer treatment known to reduce the risk of relapse. However, tamoxifen has a mild oestrogenic effect on the endometrium, resulting in a two to three fold increase the risk of developing endometrial cancer (Mourits et al. 2001).

HRT as previously mentioned is used successfully to treat menopausal symptoms. However, a multicentre randomised control trial discovered that treating postmenopausal women with oestrogen only HRT increased the development of endometrial hyperplasia but combining the oestrogen with a progestin protected the endometrium from such hyperplastic changes (Judd et

al. 1996). Therefore, newer HRT regimens are commonly given in either a continuous or cyclical form and contain both oestrogen and progesterone.

1.4.5 Clinical presentation of endometrial cancer

PMB is the classical presenting symptom of endometrial cancer however additional signs and symptoms are recognised and detailed in Table 1.5.

Table 1.5 Signs and Symptoms of Endometrial Cancer
Postmenopausal bleeding
Postcoital bleeding
Vaginal discharge
Abdominal or pelvic mass
Pyometra
Symptoms of advanced disease - pelvic pain, weight loss, haematuria, shortness of breath
Intermenstraul bleeding in pre and perimenopausal women

(SIGN 2002, Saso et al. 2011, NHS Choices 2011)

1.4.6 Management of endometrial cancer

Patients with suspected endometrial cancer will undergo the same examinations and investigations as those with PMB. Once endometrial cancer has been confirmed histologically the patient will be referred to health professionals specialised in gynaecological oncology and will be managed by a multi-disciplinary team (MDT). The MDT will organise imaging investigations such

as computer tomography (CT) and magnetic resonance imaging (MRI). These are performed to provisionally stage the cancer and subsequently decide upon the most appropriate treatment for the patient; MRI has been identified as the most beneficial technique for this purpose (Kinkel et al. 1999).

Treatment may consist of surgery to remove the tumour, typically a total abdominal hysterectomy with bilateral salpingo-oophoectomy (NICE 2005a). This procedure can either be performed laparoscopically or via open surgery, with no significant difference being demonstrated in the long-term outcomes of either procedure (Lin et al. 2008). Patients may also receive chemotherapy or radiotherapy if they are considered to be high risk of metastatic spread or reoccurrence. Those with early disease considered low risk will not routinely be given chemotherapy or radiotherapy as no proven benefit from this has been demonstrated (Brown et al. 2007).

Patients will routinely be followed-up after treatment. If the patient develops suspicious symptoms indicating disease reoccurrence or metastasis such as vaginal bleeding, unexplained weight loss and respiratory symptoms, thorough investigation of the patient is recommended (Plataniotis & Castiglione 2010).

1.5 Cervical Cancer

1.5.1 Definition

Cervical cancer is a malignancy of the cells of the cervix, the inferior part uterus joining to the vagina (Dunleavey 2004).

1.5.2 Epidemiology

In the UK cervical cancer accounts for approximately 2% of all female cancers and is the 11th most common cancer in women (Cancer Research UK 2010). As illustrated in Tables 1.2 and 1.3 cervical cancer occurs most frequently in women younger than 35 years, yet there is increasing mortality with advancing age.

Worldwide the incidence and mortality of cervical cancer varies considerably. In contrast to endometrial cancer, the greatest incidence rates of cervical cancer occur in less developed countries. Figure 1.3 shows age-standardised incidence and mortality rates for cervical cancer according to world region for the year 2008.

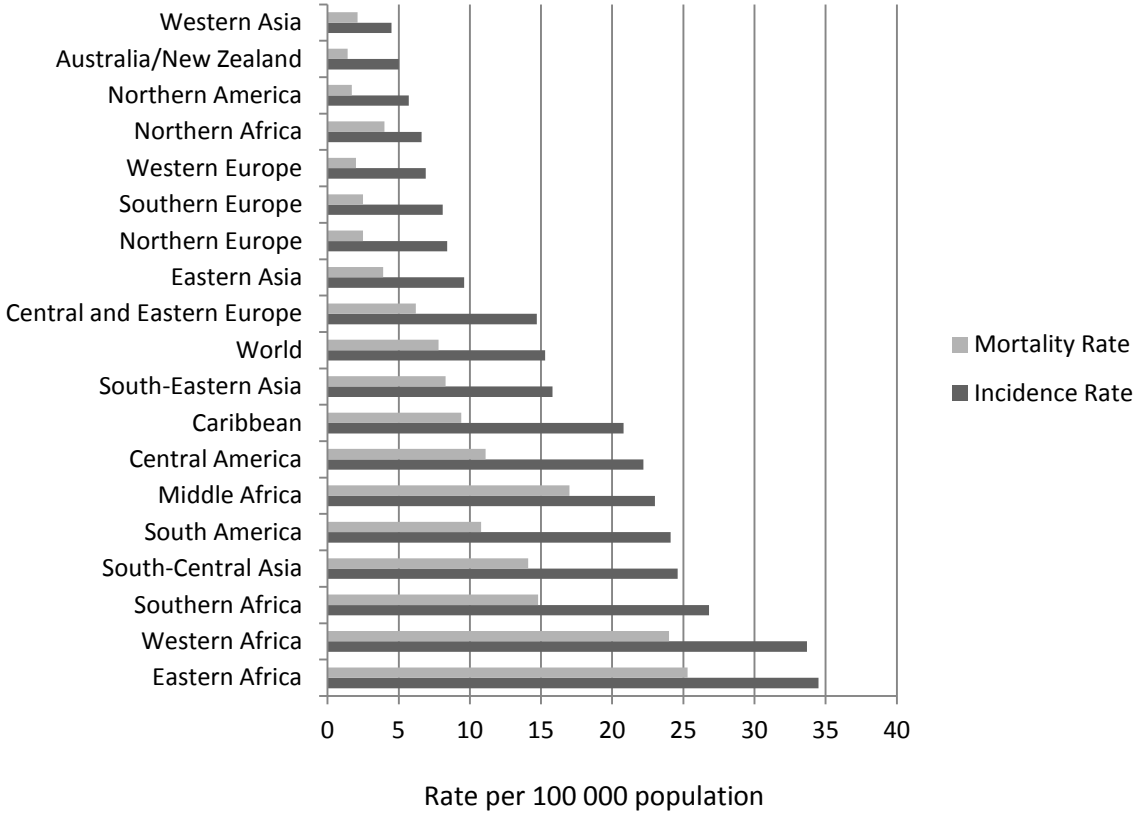


Figure 1.3 Age-standardised incidence and mortality rates for cervical cancer according to world region for 2008 (Cancer Research UK 2010)

The greatest incidence and mortality rates occur in African regions, whereas Europe, particularly Western Europe, has some of the lowest rates. There are many reasons attributed to this such as geographical variation of risk factors. In addition, the introduction of national cervical screening programmes has been demonstrated to considerably reduced incidence and mortality rates of cervical cancer (Anttila et al. 1999). Such screening programmes are more common in developed countries.

1.5.3 Pathophysiology

The cervix contains two types of epithelium. The ectocervix is the section of the cervix extending into the vagina and is composed of stratified squamous epithelium while the endocervix, extending towards the uterus is formed of simple columnar epithelium. These different histological cell types meet at the transformation zone, an area where abnormalities frequently arise (Dunleavey 2004).

The two epithelial types found in the cervix give rise to two histological forms of cervical cancer, squamous cell carcinoma and adenocarcinoma. Squamous cell carcinoma is the more common of the two however, the incidence of adenocarcinoma is rising (Vizcanio et al. 1998). A potentially premalignant condition of squamous cell cancer is cervical intraepithelial neoplasia (CIN). The CIN histopathological grading system ranges from CIN I to CIN III, dependent upon the degree of cellular dysplasia. CIN I represents mild dysplasia, CIN II moderate dysplasia and CIN III, severe dysplasia. The risk of cervical cancer development had been demonstrated to increase as the CIN grade advances (Melnikow et al. 2009).

Human papilloma virus (HPV) is a virus spread by sexual contact. Baseman & Koutsky (2005) acknowledge the virus to be a contributory factor to the cellular changes in both CIN and cervical cancer. However not all individuals with HPV will develop clinical manifestations and cervical cancer, a reason for this being there are numerous types of HPV. Some types are low-risk and associated with cutaneous infections such as genital warts, while others are high-risk and oncogenic, associated with genital tract infections and the development of cervical cancer. HPV 16 and 18 have been identified to be the most commonly detected types in cervical cancer

(Franceschi 2005). The mechanism by which the virus acts to result in cellular dysplasia and malignancy is not fully understood.

1.5.4 Risk factors

Several risk factors for the development of cervical cancer have been identified and are shown in Table 1.6.

Table 1.6 Risk Factors for Development of Cervical Cancer (Franceschi 2005)
Human Papilloma Virus (HPV)
Cigarette smoking
Oral contraceptive use

As HPV is transmitted sexually, risk factors for contracting HPV itself have been identified by Deacon et al. (2000). These include an increased number of sexual partners, initiation of a new sexual relationship and a history of previous miscarriage. Women with such risk factors were found to have at least twice the odds of HPV infection.

Cigarette smoking is an established risk factor for cervical cancer. Smokers have been shown to have a 50% increase in their risk for developing cervical cancer when compared to those that do not smoke (International Collaboration of Epidemiological Studies of Cervical Cancer 2007).

The suggested association between the use of oral contraceptives and cervical cancer has been supported by Appleby et al. (2007) who established an increased risk of cervical cancer development in those using oral contraceptives for five or more years compared to those who never used oral contraceptives. This risk decreases on cessation of oral contraceptive use and after 10 years returns to that of a none user. Oral contraceptives have however, been demonstrated to reduce the risk of endometrial cancer, particularly in long-term users (Weiderpass 1999).

1.5.5 Clinical presentation

The signs and symptoms of cervical cancer are common and non-specific (SIGN 2008). Early cervical cancer can be asymptomatic however the signs and symptoms which may develop are shown in Table 1.7. The symptoms of cervical cancer are similar to those for endometrial cancer, described in Table 1.5. The cardinal symptom of cervical cancer is postcoital bleeding which in postmenopausal women is a subcategory of PMB.

Table 1.7. Signs and Symptoms of Cervical Cancer (SIGN 2008)
Postcoital bleeding
Postmenopausal bleeding
Blood stained vaginal discharge
Pelvic pain
Abnormal appearance of cervix on examination
Intermenstrual bleeding

1.5.6 Management of cervical cancer

Women with cervical cancer who present to their GP with PMB will commonly have a gynaecological examination which may discover an abnormal cervix. It is recommended women with suspected cervical cancer are referred for colposcopy and direct biopsy (SIGN 2008). Colposcopy allows detailed visualisation of the cervix. A meta-analysis by Mitchell et al. (1998) found colposcopy to be an effective technique for successfully identifying those with cervical cancer and excluding those without. A biopsy of the cervix can also be taken during the procedure, providing histological diagnosis.

Once cervical cancer has been diagnosed radiological investigations such as chest X-rays, CT and MRI scans are suggested in order to assess spread and lymphatic involvement (SIGN 2008). MRI scans are considered superior to CT and include pelvic and abdominal imaging however both techniques have a low sensitivity for identifying nodal involvement (Haie-Meder et al. 2010).

The treatment of cervical cancer is managed and planned by an MDT. Guidelines indicate the mainstay of treatment to be surgery. Patients with low stage tumours can have either conisation with free margins or simple hysterectomy, dependent upon age; whereas higher grade tumours require radical hysterectomy, bilateral oophorectomy and pelvic lymphadenectomy (Haie-Meder et al. 2010). Such guidelines also highlight that if the patient is young and wishes to preserve fertility, providing the tumour has good prognostic factors, more conservative surgery can be performed.

Chemoradiotherapy is often employed for advanced disease due to an increased risk of positive margins and nodes (SIGN 2008). However, for wide-spread metastatic disease palliative chemotherapy is standard. Patients are routinely followed up after treatment however no standard follow-up strategy has been adopted due to lack of consistent evidence (Haie-Meder et al. 2010, SIGN 2008).

1.6 Current Guidelines

Several guidelines exist to aid clinicians when a patient presents with either PMB or suspected uterine cancer. A summary of the current guidelines available is shown in Table 1.8.

There is a large degree of variation in the recommendations guidelines provide, particularly concerning investigations. The contradictions primarily concern which investigations should be first line and the cut-off values of endometrial thickness that should be applied to TVUS results. For example, the SIGN guideline recommends the use of TVUS as a first line investigation for PMB and a cut-off value of 3mm for endometrial thickness (SIGN 2002). Whereas the SOCG guideline suggests using endometrial biopsy as a first line investigation and a cut-off value for endometrial thickness between 4mm and 8mm (Brand et al. 2000). The variations observed in guidelines may reflect differences in the health care systems from which they are produced or differences in opinions of the expert panels they are formed by.

Three of the guidelines are produced in the UK (NICE 2005a, SIGN 2002, SIGN 2008) and are therefore the most likely to be used by UK clinicians. All of these guidelines recommend referral

of women with suspected cancer to secondary care. Referral may be advised in order for health professionals with specialist knowledge of gynaecological oncology to assess women with PMB. It may additionally be advised if required investigations are not available in primary care. However, investigations such as TVUS and endometrial sampling can be performed in primary care and as guidelines aid clinicians, and are not mandatory, it may be not all women with PMB are referred. This is supported by findings that approximately 60% of those presenting to primary care with PMB are subsequently referred (McBride et al. 2010).

There are criticisms of guidelines concerning early detection of cancer such as those in Table 1.8. One such criticism is that they lack a "sound epidemiological base" (Rubin et al. 2011). This highlights the need for improved epidemiological understanding of symptoms suggestive of cancer.

Table 1.8 Current Guidelines for Postmenopausal Bleeding and Uterine Malignancy	
Guideline	**Recommendations**
Referral for Suspected Cancer 2005 (NICE 2005a)	Anyone with suspected symptoms of gynaecological cancer should be referred to specialist team Thorough history and pelvic examination should be performed including speculum examination of cervix if patient presents with PMB PMB in women not using HRT requires urgent referral (two week wait) PMB in women using HRT requires urgent referral if persistent or unexplained PMB after stopping HRT for 6 weeks PMB in women on tamoxifen requires urgent referral Investigations in primary care should not delay referral
SIGN 61 Investigation of Post-Menopausal Bleeding 2002 (SIGN 2002)	The risk of endometrial cancer in non-HRT users complaining of PMB and in HRT users experiencing abnormal bleeding is sufficient to recommend referring all patients for investigation Women presenting with PMB need pelvic examination at some stage during clinical assessment, not necessarily by GP if referred to gynaecologist TVUS is appropriate first-line investigation to identify women with PMB at higher risk of endometrial cancer rather than D&C Women on tamoxifen should only be investigated if they have vaginal bleeding Re-investigation of recurrent PMB should be considered after 6 months Endometrial thickness of 3mm cut-off should be used for TVUS in women with PMB who; have never used HRT, not used HRT for over a year or using continuous combined HRT If endometrial thickness 3mm or less no further investigation needed if agreed between patient and clinician If patient has endometrial thickness over the cut-off they need investigation for tissue sampling including endometrial sampling or biopsy usually combined with hysteroscopy
SIGN 99 Management of Cervical Cancer 2008 (SIGN 2008)	Postmenopausal women presenting with abnormal vaginal bleeding should be referred for investigation and tested for Chlamydia if appropriate Women with symptoms suggestive of cervical cancer should be referred to gynaecologist if cancer is suspected on examination

Table 1.8 cont Current Guidelines for Postmenopausal Bleeding and Uterine Malignancy	
Guideline	**Recommendations**
US Department of Health Postmenopausal Uterine Bleeding 2006 (US Department of Health 2006)	Women with spontaneous PMB should have either endometrial biopsy or TVUS as primary evaluation Women with endometrial thickness >5mm should have further evaluation Women with persistent spontaneous PMB should have office based hysteroscopy despite any normal biopsy results and regardless of endometrial thickness D&C should be performed when endometrial biopsy cannot be for technical reasons or if inconclusive and ultrasound not reassuring Women having D&C should have hysteroscopy simultaneously If spotting/light bleeding in first 6 months on HRT women should not be routinely investigated In women with PMB and taking tamoxifen endometrial sampling should be used as first-line investigation not TVUS
SOCG Diagnosis of Endometrial Cancer in Women with Abnormal Vaginal Bleeding 2000 (Brand et al. 2000)	First-line investigation is endometrial biopsy If biopsy impossibility/insufficient sample then triaged according to risk with high risk patients having D&C and low risk undergoing TVUS Cut-off of endometrial thickness ranges from 4-8mm Persistent bleeding should always be investigated further If continuous HRT and bleeding over six months of therapy should have endometrial biopsy If sequential HRT and unscheduled bleeding should have endometrial biopsy If PMB while on tamoxifen should have endometrial biopsy
Uterus Commission of Gynaecological Oncology Working Group Interdisciplinary S2k 2009 (Emons G, Kimmig 2009)	Women with PMB should have a gynaecological examination, TVUS, hysteroscopy and fractionated curettage Endometrial thickness considered suspicious if >5mm in postmenopausal women with bleeding Need histological sample to confirm diagnosis

1.7 Epidemiological Principles

The epidemiological principles of importance when attempting to derive a PPV of PMB for uterine malignancy will be discussed in the following subsections.

1.7.1 Incidence and prevalence

The terms prevalence and incidence are frequently used to describe how common a condition is in a certain population. Prevalence relates to the number of individuals in a population with a condition at a given time and the prevalence rate is calculated as the total number of individuals with the condition in the population divided by all of those in the population.

Incidence refers to the number of new cases of a condition in a population. The incidence rate can be calculated by dividing the number of new cases of a condition in a population over a given period of time by all of those in the population at risk. Commonly incidence rates are calculated for a specified time period, accounting for the total time individuals are at risk and can be reported as a person time incidence.

1.7.2 Predictive values

A positive predictive value (PPV) signifies how likely a patient with a positive test result is to have the condition being tested. Therefore, the aim of the PPV calculated in this thesis will be to

establish how likely a patient with PMB is to have a uterine malignancy. The PPV can be calculated with the use of a 2x2 contingency table as demonstrated below:

	Disease Positive	**Disease Negative**
Test Positive	a	b
Test Negative	c	d

The PPV is all those that test positive and have the disease (a) divided by all those that test positive (a + b).

Negative predictive value (NPV), sensitivity and specificity can also be calculated in a similar manner. The NPV represents how likely a person that tests negative is to be free of the disease. It is therefore those who test negative and are disease negative (d) divided by all those who test negative (c + d).

Sensitivity and specificity, unlike the predictive values quantify the performance characteristics of a test. Sensitivity signifies the proportion of those with a disease that test positive. Consequently, it is calculated by dividing those that test positive and have the disease (a) by those that have the disease (a + c). Specificity however, identifies those with a negative result who do not have the disease. Hence, specificity can be calculated by dividing those who do not have the disease and test negative (d) by all those who do not have the disease (b + d).

A predictive value will vary depending upon the prevalence of the disease. The PPV will increase if the prevalence of a disease increases, as there would be a greater number of individuals that are disease positive (a); conversely if prevalence of the disease is low. This is of importance as it signifies PPVs are dependent upon the prevalence of a disease in a population from which it is derived and therefore, to which it can be applied.

The clinical significance of symptoms has been shown to vary according to population. This is reflected in the PPV of a symptom which has been demonstrated to increase from a community, to primary care and secondary care population (Fijten et al. 1994). Consequently, PPVs will only be beneficial when applied to a population from which they are derived. This indicates in this thesis independent PPVs will need to be established for a community, primary and secondary care population and that clinical rules derived in one setting may not be applicable to another with a different prevalence of the illness.

A definition used for each of these populations in this thesis is as follows:

Community Population – the PPV identified for a community population will be provided by women living in any local or national social unit that have not necessarily sought medical advice regarding their PMB symptom.

Primary Care Population – the PPV established for primary care will be calculated from findings in women presenting to a principle point of health care such as general practice in the UK and equivalent health care settings in other countries.

Secondary Care Population – the PPV identified for secondary care will be provided by women presenting to medical specialists for their PMB symptom. This will include those attending outpatients and being admitted to hospital.

1.8 Postmenopausal Bleeding, Cancer and the Positive Predictive Value

The topics of PMB, uterine malignancy and relevant epidemiological principles have now been addressed. The importance of applying a PPV to PMB and uterine malignancy will be explored in the following subsections.

1.8.1 Risk communication and joint decision making

An accurate estimate of the PPV of PMB for uterine malignancy will improve knowledge concerning the risk of malignancy in women with PMB. This will aid risk communication in consultations between clinicians and women with PMB and allow for improved joint decision making regarding subsequent management. The active involvement of a patient in joint decision making is of importance as it allows for greater patient satisfaction, enhances patient adherence and in some circumstances can improve health outcomes (Elwyn et al. 1999).

Such information will benefit clinicians in addition to patients, allowing clinicians to make more informed decisions regarding patient management. For example, it may aid in the decision as to

which investigation to request or in the interpretation of investigation results. Consequently, this will potentially result in patients not being over or under investigated for PMB.

1.8.2 Ethical implications and resource allocations

The active involvement of patients in decision making is also important ethically as it adheres to the principle of autonomy. Autonomy is one of the four pillars of medical ethics as laid out by Beauchamp and Childress (1979), the others being non-maleficence, beneficence and justice. In addition to improving patient autonomy this research will additionally address the ethical issue of justice. As highlighted, the results of the research have the capability of assisting clinical decisions; ensuring patients with PMB are not over or under investigated. This will consequently aid allocation of health care resources.

There are also challenges concerning equity and fairness. As previously highlighted current NICE guidelines regarding referral for suspected cancer suggest urgent referral for all women with PMB. The same guidelines state that individuals with rectal bleeding must have had the symptom for at least six weeks and have additional symptoms if under 60 years (NICE 2005a). If the risk of uterine malignancy is less in women with PMB than bowel cancer is in those with rectal bleeding, this could be seen as unfair. Therefore by improving understanding regarding the PPV of PMB such issues can begin to be addressed.

1.9 Summary

This Chapter has detailed the important features of PMB, uterine malignancy and relevant epidemiological principles. The established association between PMB and uterine malignancy has been outlined. It is likely this association is apparent in available medical literature, with studies providing a PPV of PMB for uterine malignancy or data allowing its calculation. Therefore, the next Chapter will attempt to identify such studies and combine their results to provide an improved, reliable estimate for the PPV of PMB for uterine malignancy in a community, primary and secondary care population. These results can subsequently be used to aid decision making in primary care about who to investigate.

Chapter 2. Systematic Literature Review and Meta-analysis

2.1 Overview

This Chapter describes a study in which the primary objective is to identify, critically appraise and synthesise current available medical literature in order to obtain an estimate of the PPV of PMB for uterine malignancy. A PPV will be established for community, primary and secondary care populations independently in order to account for variations within the incidence of malignancy in each of these populations. It is then intended for the PPVs obtained to be quantitatively pooled into a single reliable estimate for each population by means of a meta-analysis.

However, as uterine cancer is exceptionally rare in community population it is not expected for studies to be identified which directly measure the PPV of PMB for uterine malignancy in this setting. Therefore, studies providing a rate of PMB in a community population and those stating the proportion of women with uterine cancer that presented with PMB will additionally be obtained. This information, along with National Statistics data regarding the incidence of uterine cancer, will allow for a PPV of PMB for uterine malignancy to be derived.

The methods of study identification and selection to achieve this will be outlined in this Chapter. The relevant information extracted from included studies and how this information was synthesised in order to obtain the required PPVs will also be described. The PPVs derived for a community, primary and secondary population, along with their pooled estimates, will then be reported and discussed.

2.2 Methods

The following sections will describe the methods employed to identify relevant medical literature. The methodology follows that recommended by the Centre for Reviews and Dissemination of the National Institute for Health Research at York University (CRD 2009).

2.2.1 Review team

A review team was established consisting of myself as the lead reviewer (RL), a research fellow at the department (MS), a statistician at the department (MB) and a systematic reviewer at the department (GM). The review team conducted and managed the review.

2.2.2 Protocol

The methods for the review were specified in advance in a review protocol. The protocol detailed the review question, how studies would be identified and then selected for inclusion, critically appraised and have data extracted. The protocol was developed by the review team and was approved by the Research Institute.

The study was piloted using the protocol and amendments made to the methods prior to commencing the review. This included amendments to the search strategy used to identify studies. An original search strategy was formed after discussion with the review team based on the primary objective of the study and was tested on relevant key papers known to the review team. The strategy was then modified on the basis of the testing and further discussion with the team to achieve a strategy which fulfilled the primary objective of the study and identified all the

key research papers. The table used to extract data was also piloted on key papers and modified accordingly to obtain all relevant information from studies.

2.2.3 Eligibility criteria

In order to fulfil the aim of the review, studies were required to meet any of the following criteria:

1. **Contain information regarding women in a community, primary or secondary care population with PMB and subsequent uterine cancer diagnosis –** this provided a PPV of PMB for uterine cancer for the relevant population

2. **Contain data regarding the rate of PMB in a community population** – this was required to derive the PPV of PMB for uterine malignancy if no studies were available measuring the PPV directly

3. **Contain information regarding the proportion of those with uterine malignancy that presented with PMB** – this was used in addition to data regarding the rate of PMB and incidence of uterine cancer from National Statistics to derive a PPV where required

These therefore formed the inclusion criteria for the review. The criteria used to exclude studies from the review are detailed in Table 2.1.

Table 2.1 Exclusion Criteria for Studies	
Studies to be excluded	**Justification**
Studies not in English language	No resources available to translate papers in other languages
Solely animal studies	Concerned with only human subjects
Studies concerning screening	Screening will be concerned with asymptomatic individuals who by definition do not have PMB
Studies in populations on methods or comparing methods of investigations for PMB where there is no statement that all the presenting population was included or the population was unselected or consecutively presenting	Such populations are selected and not representative of women in the community, those who present to primary care or attend gynaecological out-patient departments
Studies dealing with only treatments of gynaecological malignancy and postmenopausal symptoms	This is not an objective of the review so will not aid the research question being addressed
Studies that illicit the effect of a drug on vaginal bleeding or risk of uterine malignancy	Findings regarding this do not aid identifying a PPV of PMB for gynaecological malignancy
Studies concerned with diseases or malignancies other than primary adenocarcinoma and squamous cell carcinoma of the uterus	Primary adenocarcinoma and squamous cell carcinoma of the uterus are the only malignancies the research question addresses, as these represent over 95% of malignancies
Studies with less than 15 cases or participants	Unlikely to produce reliable conclusions
Studies that do not contain sufficient information to calculate the prevalence or incidence of PMB	Data must be available in the selected studies or studies must have sufficient data to enable calculation of prevalence or incidence in the study population or the proportion of women with uterine malignancy who present with PMB as this is required to calculate a PPV
Studies where participants with PMB are not from a measured population, presenting to primary or secondary care or in a population diagnosed with uterine cancer	If the population of patients is highly selected the derived PPV will not be generalisable to the community, populations presenting to general practice and secondary care and those with uterine malignancy

The eligibility criteria formed identified studies which contained participants with PMB and a relevant uterine malignancy in the desired populations, consequently providing a PPV of PMB for uterine malignancy or allowing a PPV to be derived. In addition the criteria ensured studies to be included in the review were likely to contain reliable results. For example, studies with small populations and those liable to selection bias, concerning investigations and not describing adequate selection of participants, were excluded.

2.2.4 Information sources

Six major databases were searched on the National Health Service (NHS) Interface from their time of inception to October 2011. The databases selected were those which would provide a broad search of the literature, covering a diverse range of journals. The databases searched were as follows:

- **MEDLINE** – An American based bibliographic database containing citations from over 5600 worldwide journals broadly comprising of biomedicine and health topics, dating from 1946 to present. MEDLINE utilises Medical Subject Headings (MeSH) descriptors, a vocabulary thesaurus allowing searching on the database to be performed at differing levels of specificity.

- **EMBASE** – A bibliographic database containing biomedical and pharmaceutical literature from over 7600 peer-reviewed journals, dating from 1947 to present. EMBASE also employs use of its own vocabulary thesaurus named EMTREE.

- **CINAHL** – A bibliographic database containing literature from over 770 journals concerning aspects of nursing and allied health disciplines, dating from 1981 to present. CINAHL subject headings specific to the database are used as a thesaurus.

- **AMED** – A bibliographic database produced by the Health Care Information Service of the British Library, dating from 1985 to present, containing journals in complementary medicine, palliative care and allied health professions. Terms are indexed with the AMED thesaurus based on MeSH descriptors.

- **BNI** – A bibliographic database dating from 1985 to present and containing over 250 journals concerning nursing and midwifery primarily published in the UK.

- **PsycINFO** –The oldest of the databases searched dating from 1806 to present containing international journals covering psychology and allied fields.

Additionally, experts in the field providing knowledge of PMB and risk of gynaecological malignancy were identified by discussion with the review team. These experts were contacted via email in order to identify any grey literature that would not have been available from the databases of published literature searched. However, no replies were received to these emails.

2.2.5 Search strategy

The search of literature aimed to identify observational studies specific for uterine malignancy and PMB. To achieve this, possible synonyms describing established search terms were researched. The search strategy was constructed with the aid of the review team.

Once suitable search terms were identified the search was made as broad as possible by utilising MeSH, EMTREE and CINAHL subject headings dependent on the database being searched. Subject headings were exploded where appropriate in order to gather a comprehensive selection of studies. The exploded heading terms were assessed to ensure they comprised of relevant phrases. Synonyms identified were truncated where possible to allow greater flexibility with the search. The terms and synonyms searched covered the subjects below and are shown in Table 2.2 as searched on MEDLINE:

- **Postmenopausal bleeding** - Terms for PMB were searched as free text and MeSH, EMTREE terms or CINAHL headings. Terms for postmenopausal and for bleeding were combined using the Boolean AND operator to obtain studies concerning postmenopausal bleeding.

- **Uterine malignancy** - In the study uterine malignancy encompassed endometrial and cervical cancer therefore, free text terms for the uterus, endometrium and cervix were searched along with MeSH, EMTREE, or CINAHL headings. These terms were then combined using the Boolean AND operator with those for malignancy. This identified studies containing information regarding endometrial and cervical malignancies. In MEDLINE there were MeSH headings specific for endometrial neoplasms and uterine cervical neoplasms. These MeSH headings were therefore combined with those for uterine malignancy with the Boolean OR operator.

- **Observational studies** - The aim of review was to identify studies reporting rates regarding PMB and uterine malignancy. This information would be expected to be found in observational studies therefore, free text, MeSH, EMTREE or CINAHL heading terms for such observational, epidemiological studies were included in the search.

Table 2.2 Synonyms and MeSH Terms for Database Search					
Postmenopausal	**Bleeding**	**Uterine**	**Malignancy**	**Uterine Malignancy**	**Epidemiology**
postmenopaus*	bleed*	endometri*	malignan*	exp ENDOMETRIAL	epidemiolog*
(post ADJ menopaus*)	hemorrhag*	cervi*	cancer*	NEOPLASMS/	inciden*
post-menopaus*	haemorrhag*	(uterus OR uterine)	neoplasm*	exp UTERINE CERVICAL	prevalen*
(after ADJ2 menopause)	exp HEMORRHAGE/	exp ENDOMETRIUM/	carcinoma*	NEOPLASMS/	frequen*
exp POSTMENOPAUSE/		exp UTERUS/	lesion*		cohort
			(tumour OR tumor*)		cross-sectional
			exp NEOPLASMS/		longitudinal
					prospective
					retrospective
					survey
					exp PREVALENCE/
					exp INCIDENCE/
					exp EPIDEMIOLOGY/
					exp EPIDEMIOLOGIC STUDIES/

* Term truncated

ADJ Two terms which appear next to one another

ADJ2 Two terms which appear within two terms of one another

"exp" term exploded

CAPITALS/ MeSH term used

Terms used in the search strategy were combined with the Boolean AND or OR operators.

During the pilot phase of the study it was established that if all the terms for postmenopausal bleeding and uterine malignancy and observational studies were combined together in one search, studies reporting rates of postmenopausal bleeding were not identified as they did not necessarily contain terms related to malignancy. These studies were required to derive an estimated PPV of PMB for uterine malignancy should no studies be identified that directly measured the PPV hence, were important to obtain. Therefore the final search contained two separate searches which were conducted as follows:

Search 1. Terms for "postmenopausal bleeding" AND "uterine malignancy"
Search 2. Terms for "postmenopausal bleeding" AND "observational studies"

At the end of each search a limit was applied to exclude studies not in the English language to fulfil the exclusion criterion.

The full search carried out on Medline can be seen in Appendix 1.

After all searches had been completed the results from each database were exported into the reference management system RefWorks Version2.0. Once in RefWorks all duplicates were removed. There was one near duplicate identified which was published by the same author, in the same year, with both studies containing the same original data. Only one of these studies was included in the review. The decision as to which to exclude was made by two reviewers (RL and MS) and was based upon the aim of each study. One focused upon development of a risk assessment tool (Burbos et al. 2010b) and the other aimed to obtain the age-related differential

diagnosis of PMB (Burbos et al. 2010a). The latter had an aim more conducive to that of this review and was therefore included.

2.2.6 Study selection

Figure 2.1 shows a flow diagram of the study selection process, detailing the number of studies retrieved and excluded at each stage of the review.

During the initial stage of study selection all titles and abstracts were screened for eligibility by myself, RL. A second reviewer, MS screened 200 (6.5% of the total) of the titles and abstracts to assess agreement on eligibility. Inter-rater agreement was tested via Cohen's kappa statistic (Cohen 1960), which attempts to take into account that some degree of agreement may have occurred by chance. Kappa statistic lies on a scale from 0 (agreement due to chance) to 1 (perfect agreement).

The estimated kappa statistic for title and abstract selection was 0.63 (95% CI 0.50-0.77), indicative of substantial inter-rater agreement (Landis & Koch 1977). The discrepancies that occurred were discussed and consensus agreed on all. A third reviewer, MB was available if consensus could not be achieved in order to resolve the issue.

The studies which met eligibility criteria were then obtained in full for a more detailed evaluation. RL read all full papers and assessed their eligibility for inclusion in the review. MS read 95 (55%) of the full papers. This included all the papers RL had identified as relevant for inclusion in the review and a random sample of the studies RL deemed to be inadequate for inclusion. The

associated kappa statistic was 0.84 (95% CI 0.72-0.95), demonstrating almost perfect agreement (Landis & Koch 1977), unlikely to be due to chance. Any disagreements were discussed and consensus reached in all cases. A total of 31 papers were deemed relevant for inclusion in the review.

It was not possible to obtain one full paper as the British Library did not have an available copy. The author of the study was contacted in an attempt to obtain the full paper however there was no reply. This paper therefore, had to be excluded as the abstract did not contain sufficient detail to ascertain whether eligibility criteria were met.

The studies identified by the search varied in aim. Many analysed and compared investigative techniques for PMB, while others examined the feasibility of services such as one stop PMB clinics to aid cancer detection. Several studies investigated the association between PMB and malignancy development specifically. There were also a number of studies that established the effect of various drugs on the endometrium; however these were not included in the final review as they did not address the required aim.

In order to identify additional relevant papers not obtained from the database searches all 31 papers deemed relevant for inclusion in the review were reference checked. Additionally, citation searching of these papers was performed with use of 'Web of Science'. This was completed by RL. No further studies were identified from the citation search. Two additional studies were obtained from the reference search, resulting in a total of 33 studies being included in this review.

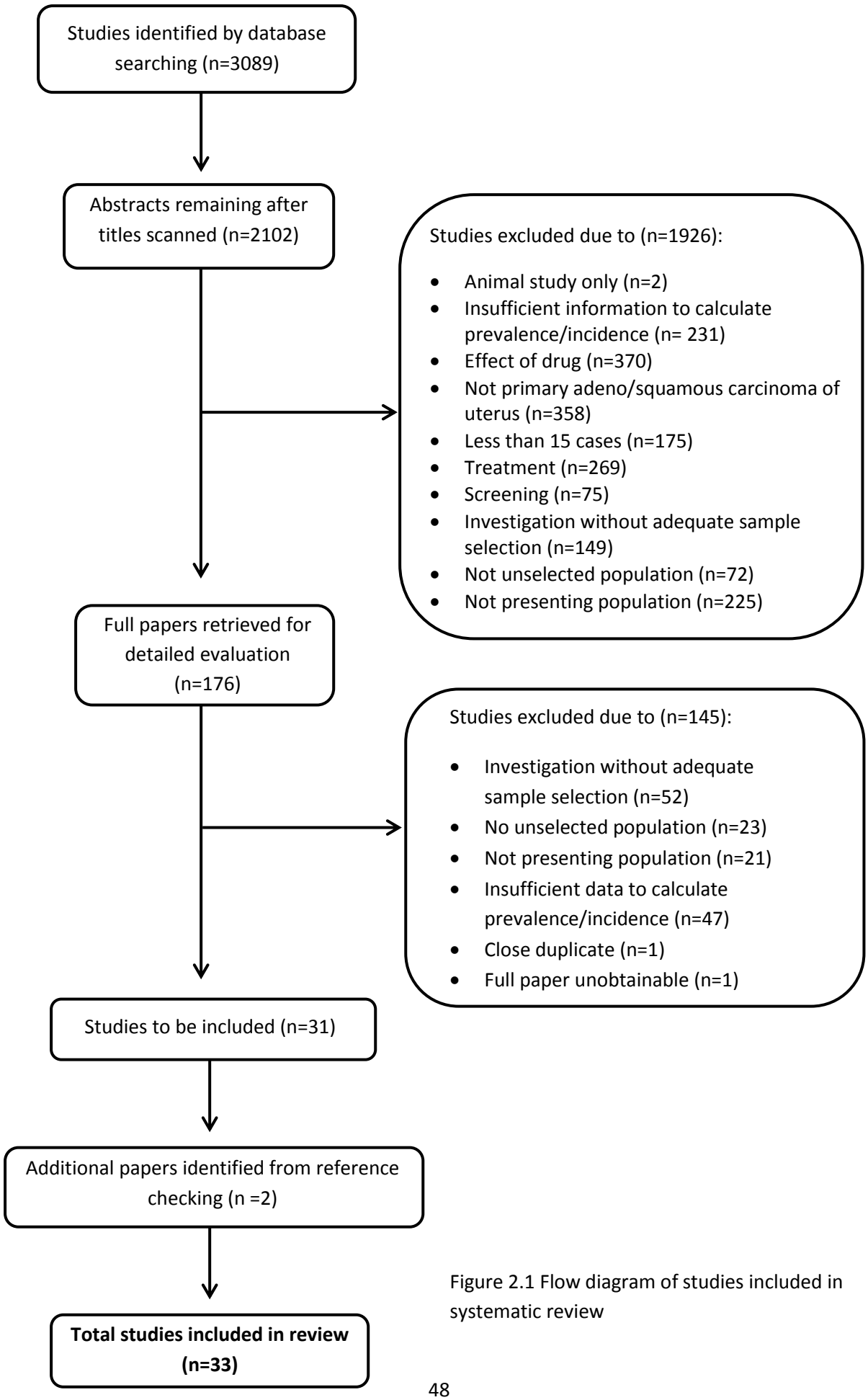


Figure 2.1 Flow diagram of studies included in systematic review

2.3 Quality Assessment

The quality of identified studies was assessed as the PPVs obtained were dependent upon the validity of included studies. The following subsections will describe the development and outcome of the quality assessment.

2.3.1 Development of a quality assessment tool

During the pilot phase of the study the review team identified the main theoretical reasons as to why studies identified by the systematic review may be of poor quality and their results unreliable. Experts within the department were approached to recommend quality assessment tools and searches were undertaken to find additional tools. Using those identified, two tools appeared to most closely match the reasons for poor quality identified by the review team. This included the Critical Appraisal Skills Programme (CASP) (CASP 2004) for cohort studies and the Quality in Prognostic Studies (QUIPS) tool (QUIPS 2009). The relevant sections were then extracted and combined to produce a quality assessment tool for this study. It was piloted and approved by the review team.

An additional question not contained within the CASP or QUIPS tool was required and regarded a definition of PMB. This was deemed necessary as Chapter 1 highlighted that there is more than one possible definition of PMB. Hence, it was important to establish which if any definition of PMB studies had used.

Table 2.3 shows the final quality assessment tool. The table additionally identifies from where each question originated and guidance comments when answering each question.

Two questions in the tool concerned follow-up, the response required to meet these criteria were clarified by the review team. Participants were deemed to have been followed up if they underwent histological assessment. However, this form of follow-up alone was not deemed to be of sufficient length due to the possibility of a false negative result. Therefore, more formal follow-up methods, assessing for subsequent malignancy development at least 6 months after initial PMB presentation, had to be used to meet this criterion.

Table2.3 Quality Assessment Tool					
Assessment Criteria		**Criteria Outcome**		**Basis**	**Comment**
General Screening	1. Is the study addressed in an appropriate method with a clearly focused issue?	Yes □	Can't tell □ No □	CASP	Was the study design used an appropriate way to collect the data and is there a focused aim?
Selection	2. Are study participants with PMB recruited in an acceptable way?	Yes □	Can't tell □ No □	CASP/QUIPS	Were participants consecutively presenting patients?
	3. Are the characteristics of study participants described?	Yes □	Can't tell □ No □	QUIPS	Are demographics, symptoms and menopausal status of participants adequately described?
	4. Are the inclusion/exclusion criteria of participants described?	Yes □	Can't tell □ No □	QUIPS	Are participants excluded if on HRT, had hysterectomy or chemo/radiotherapy?
Symptom Definition	5. Is there a definition of PMB?	Yes □	Can't tell □ No □	Additional question	Do the authors define what they have considered to be PMB?
Attrition	6. Are attempts to collect information on drop-outs described?	Yes □ Not relevant □	Can't tell □ No □	QUIPS	If there are drop-outs in the study do the authors detail how many and reasons why?
Outcome	7. Is the outcome of interest (in this study) accurately measured to minimise bias?	Yes □	Can't tell □ No □	CASP	Is there a reliable system for identifying women with malignancy or PMB?
	8. Is the method and setting of measurement the same for all study participants?	Yes □	Can't tell □ No □	QUIPS	Are all participants dealt with in the same way?

Table2.3cont. Cont. Quality Assessment Tool				
Assessment Criteria	**Criteria Outcome**		**Basis**	**Comment**
Follow-up	9. Are study participants followed up?	Yes □ Can't tell □ No □ Not relevant □	Adapted from CASP	Are participants followed up to determine if consequent malignancy developed?
	10. Are study participants followed up for long enough?	Yes □ Can't tell □ No □ Not relevant □	CASP	Was the follow-up of participants at least six months?
Results	11. Are the results precise?	Yes □ Can't tell □ No □	CASP	If confidence intervals are used how wide are they?
	12. Are the results believable?	Yes □ Can't tell □ No □	CASP	Are the study design and methods sufficiently flawed to make the results unreliable?
Generalisability	13. Can the results be applied to the local population?	Yes □ Can't tell □ No □	CASP	Are participants similar enough to the general woman presenting with PMB?
	14. Do the results of this study fit with other available evidence?	Yes □ Can't tell □ No □	CASP	Are the results of this study comparable to similar studies?

2.3.2 Use of the quality assessment tool

The quality of each paper was assessed independently by RL and MS. The reviewers determined whether the response to each question would be; yes, can't tell, no or not relevant.

Reviewers agreed on the outcome of each question in 95% of cases. Discrepancies were discussed and consensus reached on all questions. The final outcome of the quality assessment as agreed by reviewers can be seen in Table 2.4. All studies met at least nine of the 14 quality assessment criteria (over 60%) and were therefore deemed to have a sufficient level of quality to be included within the review. It was decided the "best quality" studies were those which met at least 11 of the 14 criteria, as this ensured over 75% of all criteria were met.

Table2.4 Outcomes of Quality Assessment Criteria Questions																
Study Details			Quality Assessment Criteria Question													
Study ID	Author & Year		1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total no. criteria met
1	Astrup	2004	+	+	+	+	+	-	+	+	-	-	+	+	+	+	11 (79%)
2	Parker	2007	+	+	+	+	+	-	+	+	+	+	+	+	+	+	13 (93%)
3	Sadoon	2007	+	+	+	+	+	NR	+	+	+	-	+	+	+	+	12 (86%)
4	Keirse	1973	+	+	+	+	+	NR	+	+	+	-	+	-	-	+	10 (71%)
5	Atiomo	1998	+	+	+	+	-	NR	+	+	+	-	+	+	+	+	11 (79%)
6	Dawood	2010	+	+	+	+	+	-	+	+	+	-	+	+	-	+	11 (79%)
7	Bani-Irshaid	2011	+	?	+	+	+	NR	+	+	+	-	+	-	-	+	9 (64%)
8	Sousa	2001	+	+	+	+	+	-	+	+	-	-	+	+	+	+	11 (79%)
9	Opmeer	2007	+	+	+	+	-	-	+	-	+	-	+	+	+	+	10 (71%)
10	Sheikh	2000	+	+	+	-	-	NR	+	+	+	-	+	+	?	+	9 (64%)
11	Wong	2001	+	+	+	+	+	-	+	+	+	-	+	+	+	+	12 (86%)
12	Neto	1995	+	?	+	+	+	?	+	+	+	-	+	+	-	+	10 (71%)
13	Linasmita	1983	+	+	+	+	+	+	+	+	+	-	+	+	-	+	12 (86%)
14	Sarin	1985	+	+	+	+	+	-	+	+	+	-	+	+	-	+	11 (79%)
15	Liaquat	2000	+	?	+	+	+	NR	+	?	+	-	+	+	-	+	9 (64%)
16	Procope	1971	+	+	+	-	+	NR	+	+	+	-	+	+	-	+	10 (71%)
17	Niklasson	2007	+	+	+	+	+	NR	+	+	+	+	+	+	+	+	13 (93%)
18	Lee	1995	+	+	+	+	+	NR	+	+	+	-	+	+	-	+	11 (79%)
19	Buyuk	1999	+	+	+	+	+	NR	+	+	+	-	+	+	+	+	12 (86%)
20	Burbos	2010	+	+	+	+	+	NR	+	+	+	-	+	+	+	+	12 (86%)
21	Pacheco	1968	+	+	+	+	+	NR	+	+	?	?	+	+	-	+	10 (71%)
22	Wang	2007	+	+	+	-	-	-	+	+	+	-	+	+	+	+	10 (71%)
23	Gorostiaga	2001	+	+	+	+	+	NR	+	+	+	-	+	+	+	+	12 (86%)

Table 2.4 cont. Outcomes of Quality Assessment Criteria Questions																
Study Details			Quality Assessment Criteria Question													
Study ID	Author & Year		1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total no. criteria met
24	Ewies	2010	+	+	+	+	+	-	+	-	+	+	+	+	+	+	12 (86%)
25	Elliott	2003	+	+	+	+	-	NR	+	+	+	-	+	+	+	+	11 (79%)
26	Mohamed	2003	+	+	+	+	+	NR	+	+	+	-	+	+	-	+	11 (79%)
27	McFadyen	1952	+	+	+	+	-	NR	+	+	-	-	+	+	-	+	9 (64%)
28	Woodruff	1958	+	+	+	-	+	NR	+	+	+	+	+	+	-	+	11 (79%)
29	Krissi	1996	+	+	+	+	-	NR	+	+	NR	NR	+	+	+	+	10 (71%)
30	Sharon	1977	+	+	+	+	-	NR	+	+	NR	NR	+	+	-	+	9(64%)
31	Redman	2000	+	+	+	+	-	-	+	+	NR	NR	-	+	+	+	9 (64%)
32	Seebacher	2009	+	+	+	+	+	NR	+	+	NR	NR	+	+	-	+	10 (71%)
33	Piura	1997	+	+	+	+	-	NR	+	+	NR	NR	+	+	+	+	10 (71%)

Key	
+	Yes
-	No
?	Can't tell
NR	Not Relevant

2.4 Data Extraction

Relevant data was collected from all papers to be included in the systematic review and was performed by RL. MS independently checked for accuracy and completeness of information collected. Any disagreements were again resolved by consensus.

The following section contains the tables used to extract data from included studies. The data extracted was done so for descriptive purposes, to allow primary objectives to be met and also to assess potential sources of heterogeneity. Table 2.5 shows data extracted concerning the basic characteristics of studies. Table 2.6 contains information regarding outcomes of interest, including symptom definition and number of women with PMB who developed malignancy, specifically those with endometrial and cervical cancer. Table 2.7 shows studies reporting the number of women with malignancy that were known to present with PMB.

Table 2.5 Basic Characteristics of Studies Included in the Review							
Study ID	**Author & Year**	**Country**	**Setting**	**Study Design**	**Sample Size**	**Selection**	**Follow-up**
1	Astrup 2004	Denmark	Community	Prospective cohort study	271	• 2000 Danish women aged 45-54 sent postal questionnaire • Excluded if not natural menopause/HRT	None
2	Parker 2007	UK	Primary Care	Retrospective cohort study	3867132	• All patients with first coded consultation for PMB registered with eligible practice • Excluded if prior relevant cancer diagnosis	2 years
3	Sadoon 2007	UK	Secondary Care	Retrospective case note review	142	• All patients referred to Rapid Access Clinic • Excluded if on HRT or tamoxifen	Histological assessment only
4	Keirse 1973	Belgium	Secondary Care	Retrospective case note review	160	• All patients over 45 years seen at clinic for PMB	Histological assessment only
5	Atiomo 1998	UK	Secondary Care	Retrospective case note review	212	• All women attending clinic for PMB • Excluded if had hysterectomy or deemed not to have PMB	Histological assessment only
6	Dawood 2010	Pakistan	Secondary Care	Prospective cohort study	167	• Consecutive presenting patients • Excluded if HRT use, hysterectomy, radio/chemotherapy or trauma	Histological assessment only
7	Bani-Irshaid 2011	Jordan	Secondary Care	Retrospective cohort study	482	• All women presenting with PMB • Excluded if on HRT	Histological assessment only
8	Sousa 2001	Portugal	Secondary Care	Prospective cohort study	88	• Consecutive patients with PMB referred from outpatients, emergency departments and General Practices	None

Table 2.5 cont. Basic Characteristics of Studies Included in the Review							
Study ID	**Author & Year**	**Country**	**Setting**	**Study Design**	**Sample Size**	**Selection**	**Follow-up**
9	Opmeer 2007	Netherlands	Secondary Care	Prospective cohort study	540	• Consecutive presenting patients • Excluded if hysterectomy, using HRT and if not first bleeding episode	6 months
10	Sheikh 2000	India	Secondary Care	Prospective cohort study	207	• Consecutive presenting patients • Excluded if on HRT/tamoxifen or an unknown drug	Histological assessment only
11	Wong 2001	Hong Kong	Secondary Care	Retrospective cohort study	208	• All patients presenting with PMB • Excluded if HRT, rectal bleeding or haematuria	Histological assessment only
12	Neto 1995	Brazil	Secondary Care	Prospective cohort study	748	• Patients with PMB from all 3300 gynaecology patients seen	Histological assessment only
13	Linasmita 1983	Thailand	Secondary Care	Prospective cohort study	196	• All patients seen in outpatients over 15 month period	Histological assessment only
14	Sarin 1985	India	Secondary Care	Prospective cohort study	2000	• All women >40 years with established menopause and were symptomatic	Histological assessment only
15	Liaquat 2000	Pakistan	Secondary Care	Prospective cohort study	328	• Patients seen in gynaecological unit over 10 years period	Histological assessment only
16	Procope 1971	Finland	Secondary Care	Retrospective case note review	1085	• All patients presenting with PMB	Histological assessment only

Table 2.5 cont. Basic Characteristics of Studies Included in the Review							
Study ID	**Author & Year**	**Country**	**Setting**	**Study Design**	**Sample Size**	**Selection**	**Follow-up**
17	Niklasson 2007	Sweden	Secondary Care	Prospective cohort study	72	• Consecutive presenting patients	4-9 years after bleeding registry checked
18	Lee 1995	Singapore	Secondary Care	Retrospective case note review	163	• Consecutive presenting patients aged >40 years with first episode of PMB	Histological assessment only
19	Buyuk 1999	Turkey	Secondary Care	Prospective cohort study	54	• Consecutive presenting patients	Histological assessment only
20	Burbos 2010	UK	Secondary Care	Prospective cohort study	3047	• All postmenopausal women presenting with PMB • Excluded if asymptomatic	Histological assessment only
21	Pacheco 1968	USA	Secondary Care	Retrospective case note review	401	• All women >45 years presenting with PMB	"Partial follow-up" for 1.5-6.5 years
22	Wang 2007	Taiwan	Secondary Care	Prospective cohort study	2033	• Consecutively presenting women referred for various indications	Histological assessment only
23	Gorostiaga 2001	Spain	Secondary Care	Prospective cohort study	100	• Consecutive patients >45 years referred to clinic • Excluded if on HRT	Histological assessment only
24	Ewies 2010	UK	Secondary Care	Retrospective case note review and cross-sectional study	326	• Consecutive women referred to clinic with PMB • Excluded if had hysterectomy	6 months

Table 2.5 cont. Basic Characteristics of Studies Included in the Review							
Study ID	**Author & Year**	**Country**	**Setting**	**Study Design**	**Sample Size**	**Selection**	**Follow-up**
25	Elliott 2003	UK	Secondary Care	Retrospective observational and comparative study	503	• All patients presenting to hysteroscopy clinics	Histological assessment only
26	Mohamed 2003	UK	Secondary Care	Prospective cohort study	80	• Women referred to clinic with PMB since it began	Histological assessment only
27	McFadyen 1952	Canada	Secondary Care	Retrospective cohort study	100	• Consecutive presenting patients	Histological assessment only
28	Woodruff 1958	USA	Secondary Care	Retrospective cohort study	574	• All cases of genital bleeding • Excluded if not natural menopause	1-8 years
29	Krissi 1996	Israel	Secondary Care	Retrospective case note review	181	• Consecutive patients with histologically confirmed malignancy	Not relevant as already known to have cancer
30	Sharon 1977	Israel	Secondary Care	Retrospective case note review	638	• Jewish patients with diagnosed malignancy	Not relevant as already known to have cancer
31	Redman 2000	UK	Secondary Care	Retrospective case note review	96	• Last 10 patients from cancer teams in the region with diagnosis of uterine malignancy	Not relevant as already known to have cancer
32	Seebacher 2009	Austria	Secondary Care	Retrospective case note review	543	• Consecutive patients undergoing surgery for endometrial cancer	Not relevant as already known to have cancer
33	Piura 1997	Israel	Secondary Care	Retrospective case note review	231	• Patients managed at unit for endometrial cancer	Not relevant as already known to have cancer

Table 2.6 Women with PMB and Subsequent Cancer Diagnosis						
Study ID	**Author & Year**	**Age-Range (Years)**	**Symptom Definition**	**No. with PMB**	**No. with PMB and endometrial cancer**	**No. with PMB and cervical cancer**
2	Parker 2007	Median 58	Coded as first consultation for PMB on EMIS computer system	10122	170	-
3	Sadoon 2007	50-85	Episode of bleeding 12 months or more after last period	142	7	-
4	Keirse 1973	45-83	Bleeding that began two years after cessation of the menses	160	21	12
5	Atiomo 1998	43-91	None given	212	14	1
6	Dawood 2010	40 - 81	Spontaneously occurring bleeding after one year of the menopause	156	13	5
7	Bani-Irshaid 2011	41-85	Uterine bleeding occurring one year after menopause	468	42	3
8	Sousa 2001	43-82	Bleeding after spontaneous cessation of the menses for more than one year	69	9	-
9	Opmeer 2007	37-91	None given	540	56	-
10	Sheikh 2000	42-84	None given	207	14	-
11	Wong 2001	38-94	Vaginal bleeding after 12 months of amenorrhoea in women >45 years	199	17	12
12	Neto 1995	>45	Genital bleeding occurring at least one full year after last menstruation	748	72	144

Table 2.6 cont. Women with PMB and Subsequent Cancer Diagnosis						
Study ID	**Author & Year**	**Age-Range (Years)**	**Symptom Definition**	**No. with PMB**	**No. with PMB and endometrial cancer**	**No. with PMB and cervical cancer**
13	Linasmita 1983	45-91	Bleeding occurring more than one year after cessation of menstruation	195	14	53
14	Sarin 1985	>40	Genital bleeding one or more years after the last normal menstrual period	750	64	156
15	Liaquat 2000	45-85	Bleeding starting one year or more after cessation of menstruation	328	35	130
16	Procope 1971	45-87	Blood stained discharge at least one year from cessation of menstruation	1085	154	141
17	Niklasson 2007	46-89	Bleeding after six or more months of amenorrhoea	72	6	-
18	Lee 1995	43-84	Genital bleeding after six months of amenorrhoea	163	18	21
19	Buyuk 1999	42-84	Bleeding occurring after 12 months of amenorrhoea	54	8	-
20	Burbos 2010	<50->70	Bleeding after 12 months of spontaneous amenorrhoea	3047	149	2
21	Pacheco 1968	45-80+	Genital bleeding after two years from cessation of the menses	401	65	4
22	Wang 2007	Not given	None given	199	5	-
23	Gorostiaga 2001	46-89	Bleeding occurring after one year of complete amenorrhoea	100	6	-
24	Ewies 2010	Median 57	An episode of bleeding 12 months or more after cessation of menstruation	326	18	-

Table 2.6 cont. Women with PMB and Subsequent Cancer Diagnosis						
Study ID	**Author & Year**	**Age-Range (Years)**	**Symptom Definition**	**No. with PMB**	**No. with PMB and endometrial cancer**	**No. with PMB and cervical cancer**
25	Elliott 2003	Median 59.4	None given	299	14	1
26	Mohamed 2003	45-84	Abnormal bleeding if using HRT, women >45 with regular or irregular heavy periods	80	1	-
27	McFadyen 1952	Not given	None given	100	14	2
28	Woodruff 1958	Not given	Bleeding occurring one or more years after last presumably normal period	574	53	34

Table 2.7 Women with Uterine Malignancy that Presented with PMB							
Study ID	**Author & Year**	**Age-Range (Years)**	**Symptom Definition**	**No. with endometrial cancer**	**No. with endometrial cancer who presented with PMB**	**No. with cervical cancer**	**No. with cervical cancer who presented with PMB**
29	Krissi 1996	32-86	None given	181	126	-	-
30	Sharon 1977	30-60+	None given	378	262	252	91
31	Redman 2000	37-85	None given	96	81	-	-
32	Seebacher 2009	Not given	Bleeding in the past 12 moths	605	456	-	-
33	Piura 1997	20-99.9	None given	195	164	-	-

2.5 Data Synthesis

The following subsections will describe how PPVs of PMB for uterine malignancy were established and methods used to quantitatively pool estimates of the PPVs in order to produce a single reliable estimate. In addition the means of assessing studies for publication bias will be addressed.

2.5.1 Positive predictive values

Once relevant data had been extracted from studies PPVs of PMB for uterine or endometrial malignancy with corresponding 95% confidence intervals (CI) were calculated independently for all studies. PPVs were derived by calculating the number of women who developed malignancy and presented with PMB, expressed as a proportion of all women that had PMB. A PPV for uterine malignancy was calculated if the incidence or prevalence for both endometrial and cervical cancer were available. However, if no details of cervical cancer were presented a PPV for endometrial cancer alone was calculated. The calculations used for the PPVs are shown below:

$$\textbf{Endometrial Cancer PPV} = \frac{\text{Those with PMB and endometrial cancer}}{n}$$

$$\textbf{Uterine Cancer PPV} = \frac{\text{Those with PMB and endometrial cancer plus cervical cancer}}{n}$$

Where n = all those with PMB

A 95% CI was calculated for each PPV by first establishing a standard error (SE):

$$\textbf{SE (PPV)} = \sqrt{\frac{PPV\,(1 - PPV)}{n}}$$

Subsequently, SE was then used to calculate the upper and lower limits of the 95% CI :

Lower Limit 95% CI = PPV – (1.96 x SE(PPV))

Upper Limit 95% CI = PPV + (1.96 x SE(PPV))

2.5.2 Meta-analysis

A meta-analysis was performed in order to obtain pooled estimates of the PPVs where appropriate. There are two methods for combining results in such a way, the fixed effects and random effects models. A decision as to which model to use is based upon presence of and amount of heterogeneity between the studies, i.e. the degree with which study specific PPV estimates differ from each other. If there is little evidence of heterogeneity the fixed effects model is used, whereas the random effects model is applied if a large degree of heterogeneity is demonstrated. The greater the degree of heterogeneity, the greater the discrepancy will be between fixed and random effects models.

In a fixed effect model, only within study variability is considered and the model uses inverse variance method as means of obtaining a pooled estimate, i.e. reciprocals of within study

variances (SE squared) are used as study weights. Thus the method gives more weight to studies that have small variances.

Random effects model on the other hand, accounts for variance both within and between individual studies. The method used is a variation of inverse variance approach (DerSimonian & Laird 1986), with weight being given as reciprocals of the sum of within and between study variances. The confidence intervals for the pooled estimates obtained via random effects model will be wider compared to using fixed effects model.

Forest plots of results from the meta-analysis were produced, which illustrate individual study estimates together with pooled estimates, as well as the weights used in the analysis, thus aiding in visualisation of the results.

The Cochran Q statistic (Cochran 1954) was used to assess the presence of heterogeneity. The I^2 statistic (Higgins et al. 2003), which represents the proportion of total variation in study estimates explained by heterogeneity, was also calculated.

When evidence of heterogeneity between studies was found, and hence random effects model had to be used, potential available sources of heterogeneity were examined. For simplification, some of these factors of interest were dichotomised:

- **Date of publication** – Studies stratified according to whether they were published prior to or proceeding the year 2000 as this provides an indication as to former and more recent publications

- **Country conducted in** – Studies were stratified according to whether they were conducted in Europe/USA/ Canada or in Asia/ South America as it may be plausible to assume that these two groups consist of countries with comparable health system

- **Symptom definition** – Studies stratified in relation to whether the WHO definition of 12 months of amenorrhoea was utilised

- **Availability of national programme for cervical screening**– Studies stratified according to whether a national cervical screening programme was available in the country and the year the study was conducted in

- **Critical appraisal outcome**– Stratified dependent on whether studies met (answer to criterion was "yes") at least 75% of quality appraisal criteria

Subsequently, these factors were used in a meta-regression, aimed at investigating which, if any of these factors had impact on the heterogeneity of results.

2.5.3 Publication bias

Studies allowing calculation of pooled estimates were additionally evaluated by Begg's test to attempt to identify possible publication bias. Publication bias occurs when studies reporting significant results are more likely to be published than those that do not, which may in turn lead

to biased pooled estimates. Begg's funnel plot, which graphs effect estimates versus standard errors was produced for purposes of visualising publication bias. A symmetrical funnel plot indicates no publication bias.

Stata version 12.1 (Stata Corp 2012) was used to perform all analysis. Statistical significance was taken as a P value of less than 0.05.

2.6 Results

There were a total of 33 identified eligible studies dating from 1952 to 2011. Eight studies were based in the UK with the remainder based in Europe, Asia, the Americas and Canada. Studies were either prospective or retrospective cohort studies or case note reviews. One study identified was based in a community setting, one in primary care and the remaining 31 from a secondary care setting. The sample size of studies ranged from 54 (Buyuk et al. 1999) to 3867132 (Parker et al. 2007).

The PPVs of PMB for endometrial and uterine malignancy will now be described separately for community, primary and secondary care populations.

2.6.1. Positive predictive values in a community population

A single study was identified in a community setting. The authors did not directly report a PPV of interest however did present the incidence of PMB (Astrup & Olivarius 2004). Using menstrual diaries the study identified 271 postmenopausal women and 592 women that were

premenopausal, all aged between 45 and 54 years. The premenopausal women were excluded from analysis and of the postmenopausal women, 29 experienced PMB.

This provided an incidence of PMB of 10.7/100 postmenopausal women per year. Using information presented in the study regarding the total number of participants and the number of women that experienced PMB an estimated incidence of PMB in all women aged 45 to 54 years was established to be 3.4/100 women per year. However, as 592 premenopausal women were excluded from the analyses it is not known how many of these developed PMB. Therefore in order to calculate incidence rate among all women aged 45 to 54 years, we make a strong assumption that there were no cases of PMB among premenopausal women. This approach may have underestimated the true incidence rate of PMB in this population, and this is addressed in the discussion, subsection 2.7.1.1.

As a PPV was not directly reported in this study an estimated PPV for a community population was derived using the following components:

1. The incidence of PMB detailed in the study by Astrup & Olivarius (2004) identified in the systematic review (as calculated above)
2. Data from studies regarding the proportion of women with malignancy that presented with PMB, also identified during the systematic review
3. National Statistics data of cancer incidence

As discussed above, the incidence of 3.4/100 women per year was used to derive a PPV as this was the only available proxy for the incidence of PMB in all women aged 45 to 54 years in the

community. As the National Statistics cancer data will provide cancer rates within entire population of women within specific age ranges (rather than just among those that are postmenopausal), this incidence of 3.4/100 had to be used as a denominator.

Regarding (2) above, Table 2.8 shows studies identified from the review reporting the proportion of women with malignancy that presented with PMB. The figures in Table 2.8 were calculated from relevant data extracted shown in Table 2.7.

Table 2.8 Proportion of Women with Malignancy Presenting with PMB

Study ID	Author	Year	Proportion of those with endometrial cancer presenting with PMB (95% CI)	Proportion of those with uterine malignancy presenting with PMB (95% CI)
29	Krissi	1996	69.6% (62.9-76.3)	-
30	Sharon	1977	69.3% (64.7-74.0)	56.0% (52.2-59.9)
31	Redman	2000	84.3% (77.0-91.6)	-
32	Seebacher	2009	75.4% (71.9-78.8)	-
33	Piura	2007	84.1% (79.0-89.2)	-

A mean value of the five studies identified was used to obtain a PPV for endometrial cancer. Using data from the table above the mean proportion of women with endometrial cancer presenting with PMB was 76.6% (95% CI 71.7-81.2). One study provided information regarding clinical presentation of those with cervical cancer in addition to endometrial and reported 56.0% of those with uterine malignancy presented with PMB (Sharon et al. 1977). Therefore, only this study is available to calculate the PPV of PMB for uterine malignancy in a community population.

Data regarding the incidence of endometrial and cervical cancer, representing ICD-10 codes C53 and C54 was taken from the National Statistics Cancer Register which has previously been reported in Table 1.2.

The National Statistics data is given in 5 year age bands. Therefore, the rates of cancer in those aged between 45 and 49 years and 50 to 54 years were identified. The rates for both cancers were combined and a mean among the two 5-year age bands calculated to obtain the incidence of uterine malignancy in those aged 45 to 54 years. This was found to be 31/100 000 women in 2010. The mean rate of endometrial cancer alone in those aged 45-54 was established to be 21/100 000 women in 2010.

The PPV for endometrial cancer was then derived as shown below:

$$\textbf{PPV endometrial cancer} = \frac{\text{Those with endometrial cancer on National Registry x Proportion of women with endometrial cancer presenting with PMB}}{\text{Incidence of PMB in community population}}$$

$$\textbf{PPV endometrial cancer} = \frac{21 \times (76.6/100)}{3.4 \times 1000} = 0.0047$$

Therefore, the derived PPV of PMB for endometrial cancer in a community population of women aged 45 to 54 years was 0.47% (95% CI 0.24-0.70).

Similarly, the PPV for uterine cancer was derived as:

$$\textbf{PPV uterine cancer} = \frac{\text{Those with uterine cancer on National Registry x Proportion of women with uterine cancer presenting with PMB}}{\text{Incidence of PMB in community population}}$$

$$\textbf{PPV uterine cancer} = \frac{31 \times (56/100)}{3.4 \times 1000} = 0.0051$$

Therefore, the derived PPV of PMB for uterine cancer in a community population of women aged 45 to 54 years was 0.51% (95% CI 0.27-0.75).

A meta-analysis was not possible as only one study was identified providing a PPV.

2.6.2 Positive predictive values in a primary care population

The single study identified in primary care provided a PPV of PMB for endometrial cancer. Table 2.9 shows the PPVs with 95% CI. This was the only study that provided sufficient data to calculate the PPV for endometrial cancer in age bands.

Table 2.9 PPV of PMB for Endometrial Cancer in Primary Care (Parker et al. 2007)

Age Group (Years)	No. with PMB	No. with endometrial cancer	PPV for endometrial cancer (95% CI)
35-44	77	0	0%
45-54	2896	10	0.35% (0.13-0.55)
55-64	4278	49	1.15% (0.83-1.46)
65-74	1718	54	3.14% (2.32-3.97)
75-84	856	46	5.37% (3.86-6.88)
≥85	297	11	3.70% (1.56-5.85)
Total	**10122**	**170**	**1.68% (1.43-1.93)**

Parker et al. (2007) identified the greatest number of women with PMB was in those aged 55-64 years and an age-related increase in the PPV until the age of 85. The overall PPV of PMB for endometrial cancer in women aged 35 years was 1.68% (1.43-1.93). As this was the only primary care based study identified meta-analysis was not possible.

2.6.3 Positive predictive values in a secondary care population

Table 2.10 shows 26 secondary care based studies allowed a PPV of PMB for endometrial cancer to be calculated of which 16 also provided data regarding cervical cancer, allowing a PPV for uterine malignancy to be calculated. A total of 10 647 women with PMB were identified in all secondary care based studies reporting the proportion of women with PMB and a subsequent malignancy. Of those with PMB, 889 were identified as having endometrial cancer, 721 as having cervical cancer and consequently 1610 with a uterine malignancy.

There was a sufficient number of studies for quantitative pooling of estimated PPVs to be performed via meta-analysis. Both individual and pooled PPV estimates along with corresponding 95% confidence intervals are shown in Table 2.10. Furthermore both fixed effect and random effect pooled estimates are presented along with results of the I^2 test for heterogeneity.

Table 2.10 PPVs of PMB for Endometrial and Uterine Cancer in Secondary Care							
Study ID	**Study**		**No. with PMB**	**No. with endometrial cancer**	**No. with cervical cancer**	**PPV for endometrial cancer (95% CI)**	**PPV for uterine malignancy (95%CI)**
3	Sadoon	2007	142	7	-	4.9% (1.4-8.5)	-
4	Keirse	1973	160	21	12	13.1% (7.9-18.4)	20.6% (14.4-26.9)
5	Atiomo	1998	212	14	1	6.6% (3.3-9.9)	7.1% (3.6-10.5)
6	Dawood	2010	156	13	5	8.3% (4.0-12.7)	11.5% (6.5-16.6)
7	Bani- Irshaid	2011	468	42	3	9.0% (6.4-11.6)	9.6% (7.0-12.3)
8	Sousa	2001	69	9	-	13.0% (5.1-21.0)	-
9	Opmeer	2007	540	56	-	10.4% (5.3-15.4)	-
10	Sheikh	2000	207	14	-	6.8% (3.3-10.2)	-
11	Wong	2001	199	17	12	8.5% (4.7-12.4)	14.6% (9.7-19.5)
12	Neto	1995	748	72	144	9.6% (7.5-11.7)	28.9% (25.6-32.1)
13	Linasmita	1983	195	14	53	7.2% (3.6-10.8)	34.4% (27.7-41.0)
14	Sarin	1985	750	64	156	8.5% (6.5-10.5)	29.3% (26.1-32.6)
15	Liaquat	2000	328	35	130	10.7% (7.3-14.0)	50.3% (44.9-55.7)
16	Procope	1971	1085	154	141	14.2% (12.1-16.3)	27.2% (24.5-29.8)
17	Niklasson	2007	72	6	-	8.3% (1.9-14.7)	-
18	Lee	1995	163	18	21	11.0% (6.2-15.9)	23.9% (23.3-24.6)
19	Buyuk	1999	54	8	-	14.8% (5.3-24.3)	-
20	Burbos	2010	3047	149	2	4.9% (4.1-5.7)	5.0% (4.2-5.7)
21	Pacheco	1968	401	65	4	16.2% (12.6-19.8)	17.2% (13.5-20.9)
22	Wang	2007	199	5	-	2.5% (0.3-4.7)	-
23	Gorostiaga	2001	100	6	-	6.0% (1.4-10.6)	-
24	Ewies	2010	326	18	-	5.5% (3.1-8.0)	-
25	Elliott	2003	299	14	1	4.7% (2.3-7.1)	5.0% (2.6-7.5)
26	Mohamed	2003	80	1	-	1.3% (-1.2-3.7)	-
27	McFadyen	1952	100	14	2	14.0% (7.2-20.8)	16.0% (8.8-23.2)
28	Woodruff	1958	574	53	34	9.2% (6.9-11.6)	15.2% (12.2-18.1)
	Fixed-effects estimate [95% CI]					6.8% [6.3-7.3]	16.3% [15.8-16.7]
	Random-effects estimate [95% CI]					8.4% [6.9-9.9]	19.6% [13.8-25.5]
	I^2, P value					86.3%, 0.000	99.2%, 0.000

The PPVs for endometrial cancer in the secondary care based studies ranged from 1.3% (95% CI -1.2-3.7) to 16.2% (95% CI 12.6-19.8), implying considerable variability in the PPVs. The I^2 test for heterogeneity confirmed there was significant heterogeneity in results. Due to this the random effects method was applied. Therefore, the pooled estimate for the PPV of PMB for endometrial cancer in a secondary care population is 8.4% (95% CI 6.9-9.9). A forest plot depicting these observations and constructed using the random effects method can be seen in Figure 2.2.

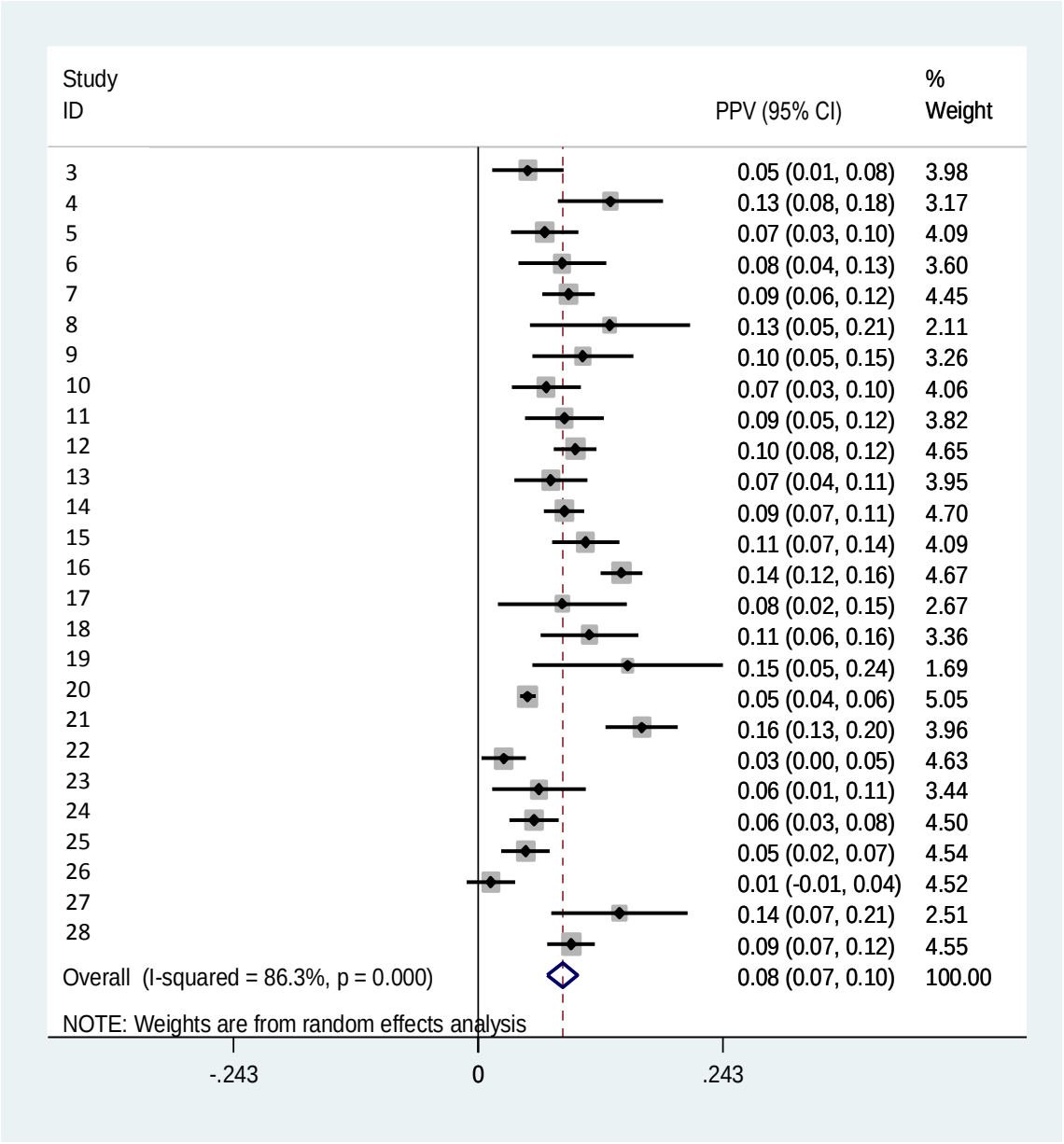


Figure 2.2 Forest plot of PPVs for endometrial cancer and corresponding 95% CI for secondary care population

The PPVs for uterine cancer in a secondary care based population ranged from 5.0% (95% CI 2.5-7.5) to 50.3% (95% CI 44.9-55.7) suggesting considerable variability in results. This was confirmed with the I^2 statistic which indicated significant heterogeneity. Consequently, the random effects method was utilised, resulting in the pooled estimate for the PPV of PMB in uterine malignancy to be 19.6% (95% CI 13.8-25.5). A corresponding forest plot is presented in Figure 2.3.

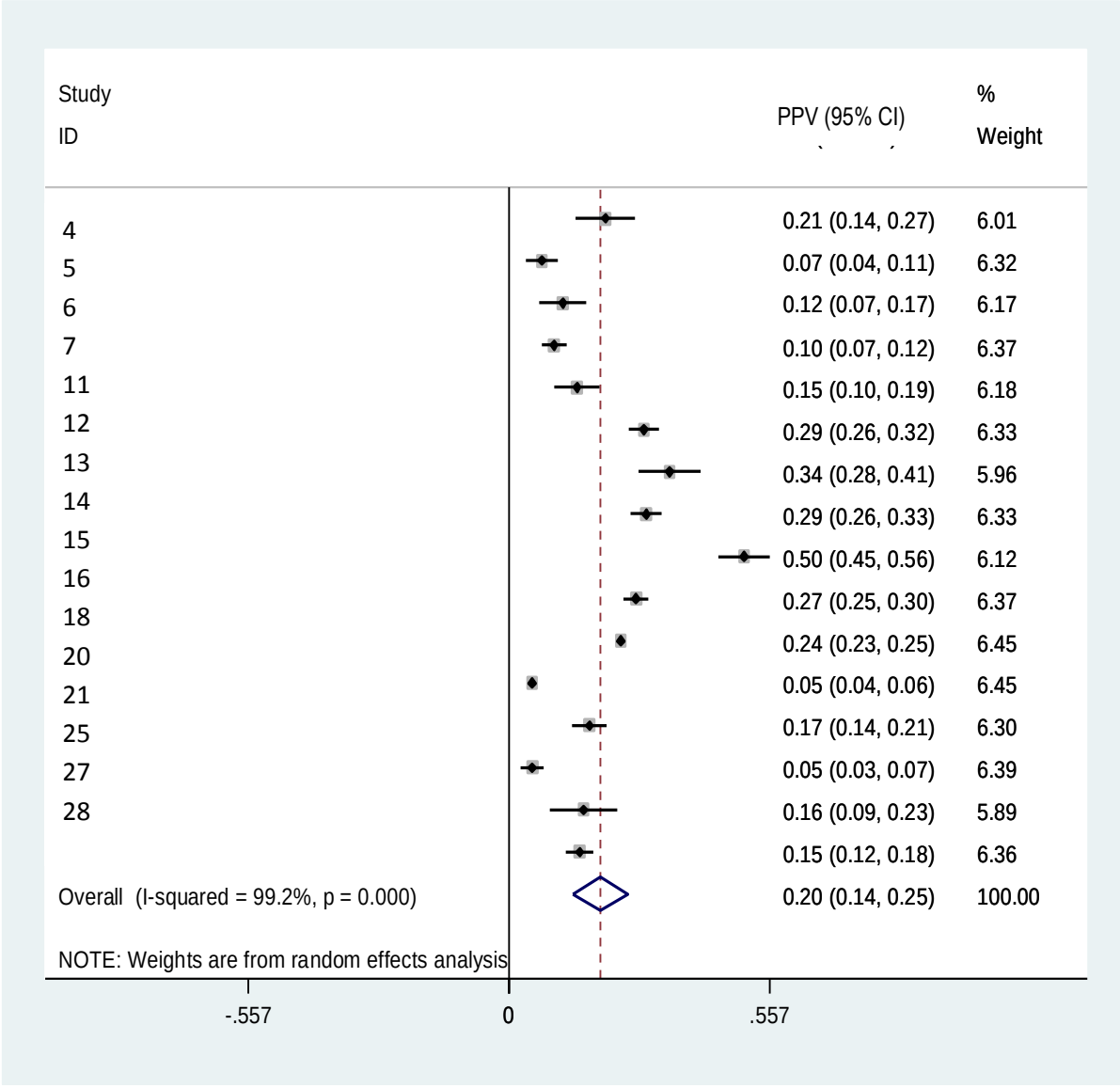


Figure 2.3 Forest plot of PPVs for uterine malignancy and corresponding 95% CI for secondary care population

2.6.4 Summary of the positive predictive values in each population

Table 2.11 summaries the PPVs of PMB for uterine and endometrial cancer obtained for a community, primary and secondary care population.

Table 2.11 Summary of the PPV of PMB for Uterine and Endometrial Cancer in Each Population

Population	Endometrial Cancer PPV (95% CI)	Uterine Cancer PPV (95% CI)	Age-Range PPV applicable to (Years)
Community	0.47% (0.24-0.70)	0.51% (0.27-0.75)	45-54
Primary Care	1.68% (1.43-1.93)	-	≥35
Secondary Care	8.40% (6.9-9.9)	19.60% (13.8-25.5)	37-94

2.6.5 Possible explanations for observed heterogeneity

The following subsections will attempt to establish an explanation for the observed heterogeneity in the secondary care results for both endometrial and uterine cancer. This was achieved by performing a univariable meta-regression, regressing PPV values on various study characteristics of interest as outlined in section 2.5.2.

Two factors were found to be statistically significant for the variation within the results for endometrial cancer. The first was date of publication; studies dating prior to 2000 were found to have a significantly greater value (P=0.002) for PPVs than those published after 2000. The random effects pooled estimate for the PPV of PMB for endometrial cancer for studies dating prior to 2000 was 8.4% (95%CI 6.9-9.9) whereas the estimate after 2000 was 6.3% (95%CI 4.9-7.7). The

forest plot of PPVs of PMB for endometrial cancer according to year of publication can be seen in Figure 2.4.

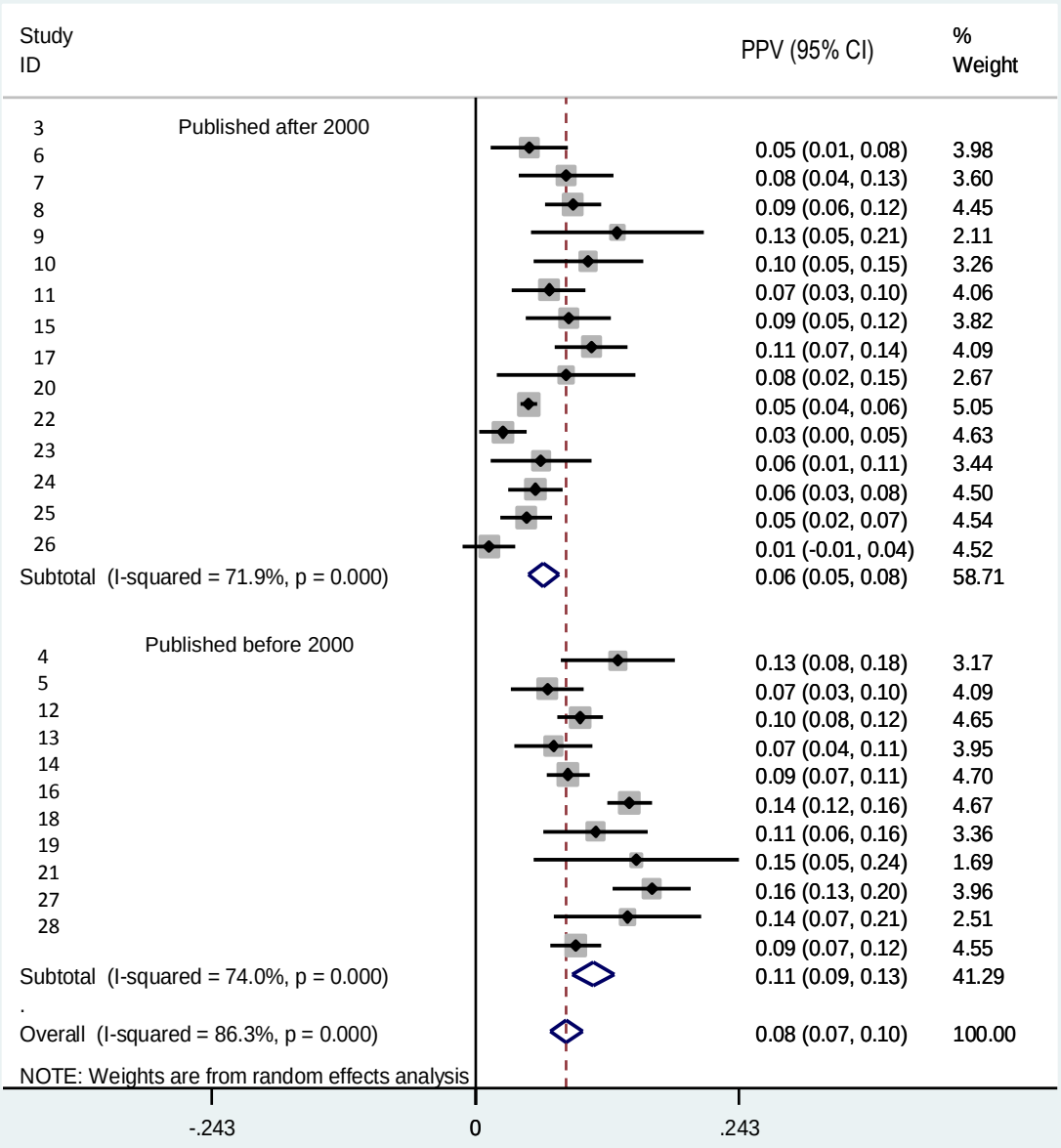


Figure 2.4 Forest plot of PPVs for endometrial cancer in secondary care studies according to year of publication

The second feature found to be statistically significant (P=0.029) was the outcome of the quality appraisal. Studies which met at least 75% of criteria had a significantly lower pooled estimate of 6.8% (95% CI 5.4-8.1) than those that did not meet the criteria whose pooled estimate was 10.4% (95% CI 7.5-13.3). The forest plot of PPVs according to quality appraisal outcome can be seen in Figure 2.5.

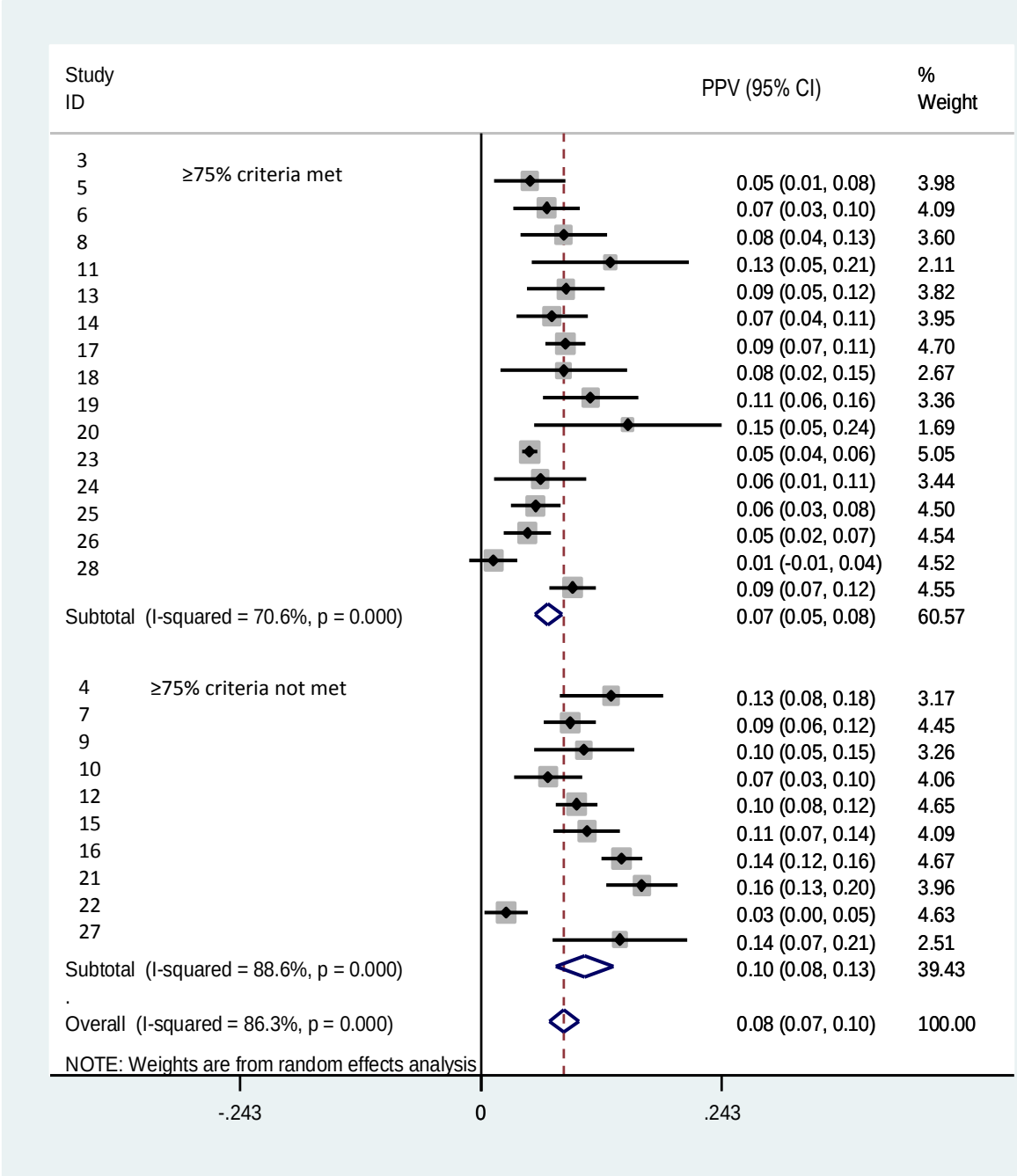


Figure 2.5 Forest plot of PPVs for endometrial cancer in secondary care studies according to critical appraisal outcome

Significant heterogeneity was demonstrated in the PPVs of PMB for uterine cancer in secondary care based studies. However, no single study feature appeared to be significantly related to heterogeneity between the results after a meta-regression was performed.

2.6.6 Assessment of publication bias

The secondary care studies used to calculate pooled estimates for the PPVs were additionally evaluated for publication bias with the use of Begg's test. Figures 2.6 and 2.7 show the resultant funnel plots for studies reporting data allowing calculation of PPVs for endometrial and uterine cancer respectively.

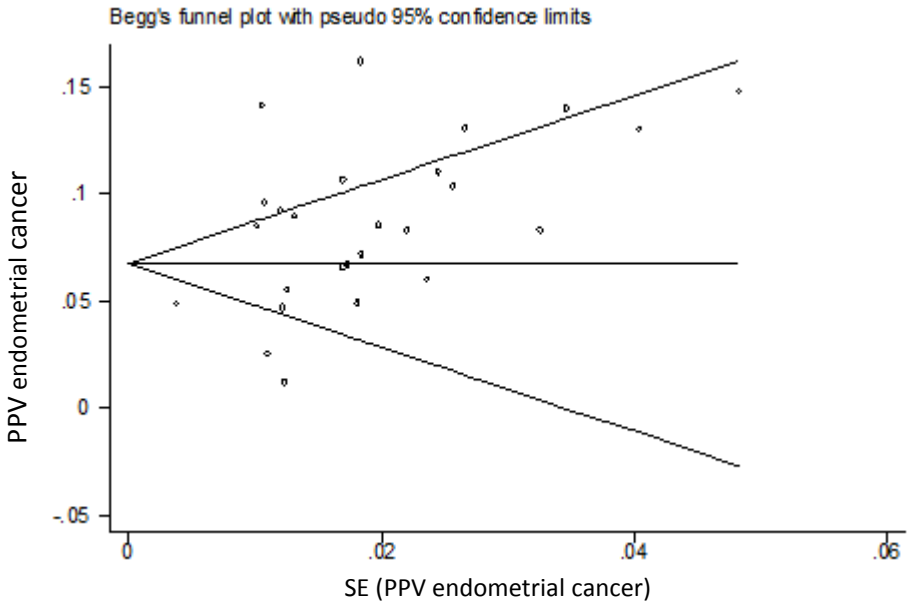


Figure 2.6 Begg's funnel plot for studies allowing calculation of PPV of PMB for endometrial cancer

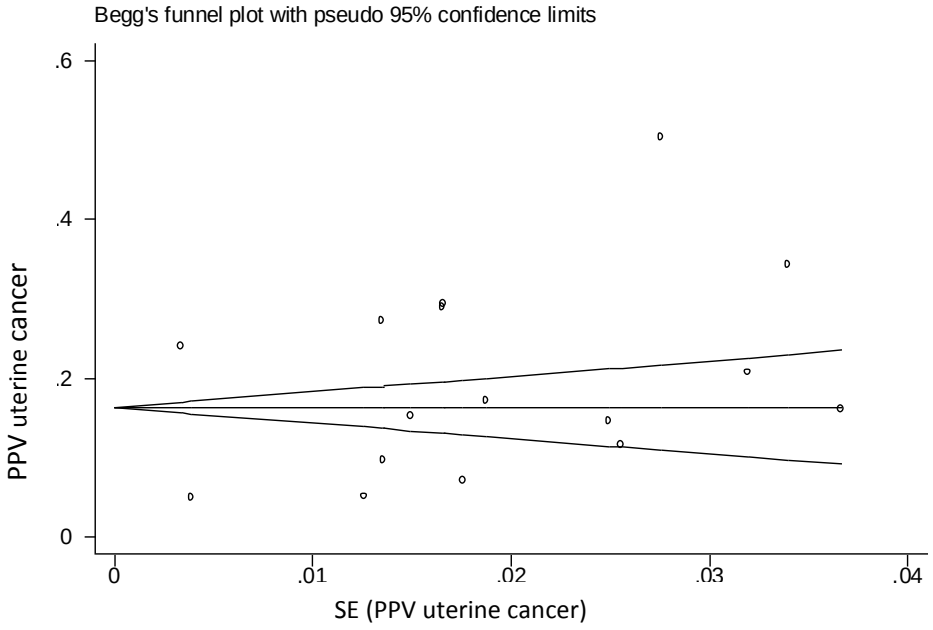


Figure 2.7 Begg's funnel plot for studies allowing calculation of PPV of PMB for uterine cancer

Symmetry of funnel plots were tested formally via Begg's test. There was no evidence of publication bias in either cases (endometrial P=0.243, uterine cancer P=0.471).

2.7 Discussion

The following section will discuss the results obtained from available literature and the strength and limitations of the methods employed.

2.7.1 Results

The following subsections will discuss the PPVs obtained for a community, primary and secondary care population.

2.7.1.1 Community positive predictive value

A PPV of PMB for both uterine and endometrial cancer in a community population was established. However, as no studies were identified directly reporting a PPV it was necessary to derive a PPV from additional information gathered during the review process. This did therefore create several difficulties.

The initial problem related to whether to use the incidence rate reported by Astrup & Olivarius (2004) concerning the incidence of PMB in postmenopausal women (10.7/100 postmenopausal women per year) or the incidence rate calculated from findings presented in the study relating to all women aged 45 to 54 years (3.4/100 women per/year). A decision was made to use the latter. This was necessary in order for a suitable denominator to be used when deriving a PPV with the National Statistics data, which also referred to all women aged 45 to 54 years, not only those that were postmenopausal.

However, using this figure may have underestimated the true incidence of PMB as premenopausal women were excluded from analysis by Astrup & Olivarius (2004). These premenopausal women may have experienced a PMB episode that was unaccounted for.

It seems contradictory to state premenopausal women experience PMB, as by definition such women have not yet experienced the menopause. However, in the study menstrual diaries were used to establish whether women had experienced the menopause and necessitated no vaginal bleeding in the 12 months following the final menstrual period. Due to the nature of menstrual diaries there may be some recall bias in women recollecting the date of their final menstrual period. Therefore bleeding in the study that was used to classify women as premenopausal may in fact be a postmenopausal bleed if the date of the final menstrual period is stated to be later than the actual bleed was. Underestimating the incidence of PMB may have in turn resulted in overestimating the PPV of PMB for both uterine and endometrial malignancy in the community population.

An issue also arose concerning which of the studies reporting the proportion of those with cancer that presented with PMB was most appropriate to use. The decision was made to use the mean of all five studies as this would provide a more reliable estimate than using one study alone.

There was only one study which detailed the proportion of those with both endometrial and cervical cancer that presented with PMB (Sharon et al. 1977) and could consequently be used to calculate a PPV of PMB for uterine malignancy. This study was conducted from 1961 to 1965. The results may therefore not be representative of a modern population as in the last 40 years there have been changes in screening techniques for cervical cancer in addition to histological subtype (Vizcanio et al. 1998). Therefore the results of the study may not be applicable to a current population. Nevertheless, the National Statics data used to derive the PPV was for the year 2010,

the most recent data available, therefore providing a PPV most applicable to the current population.

There is however concern regarding the National Statistics data. When determining the incidence of uterine cancer the combined means for both cervical and endometrial cancer were used. This assumes that women do not experience concurrent cancers and women are therefore registered with only one cancer. If this is not so, the PPV of PMB for uterine cancer could be overestimated.

Despite the concerns regarding the accuracy of the derived PPVs, they do indicate a very small proportion of women with PMB in a community population will develop malignancy, the possible implications for which will be discussed in Chapter 4.

2.7.1.2 Primary care positive predictive value

The primary care study identified by Parker et al. (2007) provided information regarding endometrial cancer alone therefore a PPV of PMB for uterine cancer could not be determined.

As only one study was identified providing a PPV for a primary care population the PPV provided has to be interpreted cautiously as there is a lack of comparable studies. However, the study comprised of a cohort based on the QRESEARCH database which at the time contained over nine million EMIS (Egton Medical Information Systems) computerised patient records from 518 participating general practices throughout the UK. It was therefore plausible to assume that it was a representative sample of a primary care population based in the UK, suggesting the PPV provided is applicable to a general primary care population in the UK.

The extent of the QRESEARCH database allowed for analysis of 10 122 patients with an episode of PMB on their medical records. This was the largest sample of women with PMB of any study in the review. Therefore, a narrow confidence interval was generated reducing the possibility that the PPV estimate has arisen as a consequence of chance.

The study by Parker et al. (2007) was based on EMIS computerised patient records. Read Codes are used in EMIS to manage data and act as a hierarchical thesaurus of clinical terms, covering all aspects of clinical care including signs and symptoms, investigations, diagnoses and treatments (NHS Information Authority 2000). Read Codes are entered into the computer by the GP and are therefore dependent upon appropriate coding by the practitioner.

A systematic review investigated whether morbidity coding in computerised patient records in general practice was complete and accurate (Jordan et al. 2004). A large degree of variability was found between the morbidity codes allocated to consultations amongst the different practices studied, especially those for cancer. The results of the study by Parker et al. (2007) are dependent upon GPs recording of Read Codes and therefore liable to bias as it is possible some women should have, but did not have, the symptom or cancer Read Coded in their medical records. As a result the PPVs calculated could be inaccurate.

Despite this potential bias the study methods employed by Parker et al. (2007) were sufficient to produce reliable results and therefore a reliable PPV of PMB for endometrial cancer that can be applied to a UK primary care population. The PPV provided is relatively low, suggesting women in primary care with PMB do not have a substantial risk of an underlying malignancy. The significance of this finding for managing patients with PMB in primary care will be discussed in Chapter 4.

2.7.1.3 Secondary care positive predictive value

The meta-analysis conducted using the secondary care based studies provided pooled estimates of the PPVs for both uterine and endometrial cancer. The pooled estimates for the PPVs differed substantially, varying from 8.4% (95% CI 6.9-9.9) for endometrial cancer to 19.6% (95% CI 13.8-25.5) for uterine cancer, partially as a consequence of the latter including cervical cancer.

The variation between the rate of uterine and endometrial cancer will be reflected in the PPV. As illustrated from the data extracted in Table 2.6 the number of women with cervical cancer is substantially greater than those with endometrial in three studies (Neto et al. 1995, Sarin et al. 1985, Liaquat et al. 2000). Therefore, the increased rates of uterine malignancy when both endometrial and cervical cancers are combined in such cases could account for some of the variation between pooled estimates for endometrial and uterine cancer.

In addition to variation between pooled estimates of PPVs for uterine and endometrial cancer there was also variation between the PPVs derived from individual studies. Significant heterogeneity was demonstrated between results from studies used in the meta-analysis for both uterine and endometrial cancer. Meta-regression was employed to assess a number of study characteristics that could potentially account for the heterogeneity identified.

Two potential causes were discovered for the observed heterogeneity in the PPVs associated with endometrial cancer. The first of these was the date of publication, indicating more recent studies have identified women with PMB to be less likely to have an underlying malignancy. This decrease in the PPV over time may be due to a decrease in the incidence of endometrial cancer. However,

the opposite has been demonstrated in a recent study which found the incidence of endometrial cancer in postmenopausal women to be increasing (Bray et al. 2005).

Another explanation for the apparent decline may be associated with the selection of participants for studies. As methodological quality of observational studies is now more frequently discussed and assessed (Deeks et al. 2003), more recent studies may be less likely to knowingly recruit participants with an increased chance of a malignancy; therefore fewer women will be discovered to have endometrial cancer.

Selection of participants was addressed within the quality appraisal of studies. The quality appraisal highlighted the majority of studies recruited participants in an appropriate manner, either including all patients presenting during the study period or including only consecutively presenting patients. In three studies however, reviewers were unable to determine if selection of participants was adequate and hence whether there was a possibility of selection bias (Neto et al. 1995, Bani-Irshaid & Al-Sumadi (2011), Liaquat et al. 2000).

The meta-regression identified quality appraisal outcome as another possible cause of heterogeneity in the PPVs for endometrial cancer. During the quality appraisal the criteria which were poorly met included selection, as discussed, but also the definition of PMB, outcome measures, follow-up and generalisability of studies. It is likely to be a combination of these factors causing studies to not meet at least 75% of quality appraisal criteria, leading to the demonstrated heterogeneity in results.

As shown in Table 2.6 six of the studies providing a PPV in secondary care did not contain a definition for PMB. Amongst those with a definition, the length of time required since the menopause in order for women to be considered postmenopausal and hence, bleeding to be

defined as PMB, differed. The majority of studies adhered to the WHO definition of 12 months of amenorrhoea. However, two studies stated that two years of amenorrhoea must have passed since the final menstrual period for bleeding to be considered PMB (Kerise 1973, Pacheco & Kempers 1968) while two further studies state six months of amenorrhoea must have passed (Lee et al. 1995, Niklasson et al. 2007). However, this difference in PMB definition alone was not found to be a significant cause of the variation in PPVs during the meta-regression.

A large proportion of studies were deemed to have measured the outcome of interest sufficiently to minimise bias. However, of those that did not, a subject that arose was that some study participants did not receive investigations such as endometrial biopsies that all other participants did. In three studies the reason for this was a woman having a 'thin' endometrium on TVUS (Burbos et al. 2010, Ewies & Musonda 2010, Opmeer et al. 2007) however, in two others no reason was given (Liquat et al. 2000, Mohamed & Nair 2003). This could be a potential source of bias as the participants not subject to histological assessment could have an undiagnosed malignancy. Therefore, the incidence of malignancies in these studies may be underestimated leading to variation in PPVs.

The criteria concerning generalisability were some of the poorest met in the quality appraisal. Many studies were conducted in countries where health systems are not comparable and not applicable to the UK. In particular several of the studies are set in countries, where unlike the UK, a national cervical screening programme does not exist (Dawood 2010), or did not exist at the time the study was conducted (Procope 1971).

The uterine cancer results could have been affected by the availability of a national cervical screening programme. As highlighted in Chapter 1 national screening programmes have been shown to reduce the incidence of cervical cancer (Anttila et al. 1999). It was thought in countries

where a screening programme is available the incidence of cervical cancer and hence the incidence of uterine cancer would be reduced, explaining part of the heterogeneity in uterine cancer results. Therefore availability of a national cervical screening programme was investigated during the meta-regression. However, this alone was found not to be a significant cause of the heterogeneity in PPVs for uterine cancer.

None of the factors investigated in the meta-regression had the ability to individually explain observed heterogeneity in results. There could however, be variables which have not been accounted for that explain the heterogeneity.

The overall random effects estimates of PPVs for both endometrial and uterine cancer were high compared to those for the community and primary care. This indicates women in secondary care with PMB have a considerable risk of an underlying malignancy and should therefore be investigated as such. The higher PPVs for secondary care highlight how the PPVs established for each population vary. There is an apparent increase in PPV from the community to primary care and finally secondary care. Explanations and implications for this will be discussed in Chapter 4.

2.7.2 Assessment of the systematic review for bias

The following subsections will discuss the methods employed to undertake the review and any potential bias or limitations that may have arisen.

2.7.2.1 Protocol

A protocol for the systematic review was developed to reduce likelihood of bias being introduced into the review once it had commenced. The protocol was approved by the review team to ensure that it met the primary objective and that potential bias was minimised.

2.7.2.2 Search and study selection

The search strategy was constructed and implemented with the aid of the review team. This may have reduced bias from one individual and ensured all relevant search terms were identified and combined in a suitable manner.

A language limit was implemented during the search as no resources were available for translation. This could have resulted in relevant studies in languages other than English not being obtained. However, this is unlikely as when the language limit was applied less than 1% of the total number of studies identified during the search were excluded. The studies excluded may also have been duplicates of studies already translated into English.

Two additional papers were identified from the reference checking. It should be noted the two studies were published in 1952 (McFadyen 1952) and 1958 (Woodruff et al. 1958) therefore may not be available in the databases searched due to their early date of publication.

During the study selection process only RL read all full papers. This could have led to human error and bias. Nevertheless, over 50% of full papers were read by a second reviewer, MS in order to ensure the eligibility criteria were adhered to and decisions made were reproducible. The

agreement rate between the two was high, reducing the chance of bias. If the intra-rater reliability had not been as high MS would have read a greater proportion of all full papers.

2.7.2.3 Publication bias

Begg's test was performed and did not demonstrate significant publication bias. However, this test was only performed in secondary care studies providing PPVs. An attempt to locate any unpublished grey literature was made.

2.7.4 Quality appraisal

The CASP and QUIPS quality appraisal tools were both utilised to form the quality appraisal criteria. This could have led to bias as not one tool in its entirety was used. The tools were adapted for the specific purpose of addressing subjects considered relevant by the review team. The quality appraisal criteria used therefore contained appropriate questions of satisfactory detail in order to appraise the studies in the review. However, the adequacy of the appraisal tool has not been validated.

2.7.5 Data extraction

There is potential for human error during the extraction of data from studies. Therefore, a second reviewer independently checked for completeness and accuracy of all the data extracted, reducing the likelihood of this.

2.7.6 Data analysis

As only one relevant paper was identified for each community and primary care based settings, quantitative pooling of the results could not be performed. However, there was a sufficient sample of secondary care based studies containing adequate data to perform a meta-analysis and calculate pooled estimates of the PPVs. The resultant heterogeneity found between studies was also examined further, ensuring the analysis conducted was as detailed as possible.

2.8 Summary

The systematic review and meta-analysis has identified a PPV of PMB for uterine and endometrial cancer in a community, primary and secondary care population.

PPVs were directly reported in studies for a primary and secondary care population. A sufficient number of results were obtained from secondary care based studies to enable pooling by meta-analysis, providing a single, plausibly reliable estimate of the PPV of PMB for endometrial and uterine cancer. However, an estimated PPV was derived from additional information gathered during the review process for a community population as no study directly reported a PPV. It is important to test the derived PPV to determine whether the findings of the review are consistent with that within a population of women with PMB in the community. Chapter 3 will therefore aim to establish this.

The PPVs established from the review for each population vary, with an apparent increase in the PPV from a community to primary care to secondary care setting. The reasons for this and implications each of these PPVs holds for aiding decision making in primary care and more generally will be explored in Chapter 4.

Chapter 3. Testing the Derived PPV of PMB for Uterine Malignancy in a Community Population

3.1 Overview

The previous Chapter detailed a review of the current medical literature providing a PPV of PMB for uterine malignancy. A PPV was established for community, primary and secondary care populations independently.

However, as highlighted in Chapter 2 the PPV for a community population was not reported in the associated study (Astrup & Olivarius 2004) and was instead derived using relevant raw data presented in the study. This Chapter will therefore aim to establish a PPV of PMB for uterine malignancy in a community population and determine whether this PPV is consistent with that derived from the systematic review. If the PPV obtained is consistent it will provide additional evidence that the risk of malignancy in women with PMB in the community is small.

This will be achieved with use of data from the PRIMROSE study, a prospective cohort study conducted by Shapley et al. (2012) which followed a group of naturally menstruating perimenopausal women for two years. Changes in menstruation and other vaginal bleeding were identified. A relevant cohort of naturally menstruating women was produced, from which I am able to identify women that became menopausal and subsequently bled. These women will then be investigated by reviewing their medical records, to assess how many developed uterine cancer

in the subsequent two years, providing a PPV. It can then be determined whether the established PPV in the PRIMROSE cohort with PMB is consistent with that obtained from the systematic review.

3.2 PRIMROSE

A brief outline of PRIMROSE study is given below, full details may be found in Shapley et al. (2012).

The PRIMROSE study was a two year prospective cohort study conducted from 2007 to 2009. It was based in the UK and involved women aged 40 to 54 years registered with one of seven General Practices forming the North Staffordshire and Cheshire General Practice Research Network. Combined, these practices contained a total registered population of 67 100 patients, covering both rural and urban areas in addition to affluent and deprived communities. The study had ethical approval from South Staffordshire Local Research Ethics Committee reference 06/Q2602/38.

The primary objective of the study was to obtain an estimate of the probability that a woman with a menstrual disturbance in the perimenopausal years will have a natural resolution within a subsequent year. The study was conducted in two phases, an initial baseline cross-sectional postal survey in 2007 and a subsequent prospective cohort study following naturally menstruating women aged 40 to 54 years responding to the baseline postal survey, who consented to further contact, at 6, 12, 18 and 24 months.

If with either the baseline or follow-up questionnaires women did not respond within two weeks a reminder postcard was sent; if there was no response a further two weeks after this the participant was sent the questionnaire again. If the participant did not respond after both the postcard remainder and second copy of the questionnaire they were excluded from the study.

Respondents that changed their registered practice during the study period were traced using the NHS Strategic Tracing Service situated at the University Hospital North Staffordshire. Questionnaires were subsequently sent to the new address identified.

Questionnaire content

The questionnaires identified menstruating women from the question "Have you had a period in the last 6 months?". From additional responses to items regarding treatments and medical history women were deemed as naturally menstruating. Such women reported having a menstrual period in the last six months and had not, in the last six months, used hormones, treatment for heavy and/or irregular menstrual periods, an intrauterine contraceptive device or had a gynaecological operation, been pregnant or had ever had endometrial ablation.

The questionnaires contained a validated instrument to determine participant's perceptions of heaviness of menstruation. Questionnaires also established other vaginal bleeding symptoms, factors predictive and known to influence menopause onset, previous relevant treatments, consultation behaviours and perceived interference of symptoms with life. Relevant questions were ascertained from previous studies and clinical guidelines. Respondents to the baseline questionnaire were additionally asked to consent to partaking in the 6, 12, 18 and 24 month follow-up questionnaires and for their medical records to be viewed.

One section in the follow-up questionnaires was specific to those that had not experienced a menstrual period in the previous six months and measured whether PMB occurred. This asked if participant's had experienced "bleeding during sexual intercourse (making love)" or in a separate question "any other vaginal bleeding (excluding menstrual periods and during or after sexual intercourse (making love))".

Both the baseline and follow-up questionnaires were piloted for comprehension and completeness before the study began.

The baseline and follow-up questionnaire can be seen in Appendix 2 and Appendix 3.

Response rate to questionnaires

The number of questionnaires sent was established from a pilot study and resulting sample size calculation performed prior to the study. A total of 7121 baseline postal questionnaires were sent to all women in the target population with 4455 eligible questionnaire being returned, resulting in a response rate of 63%. Figure 3.1 illustrates the reasons as to why the remaining 2666 baseline questionnaires were deemed unsuitable or not returned.

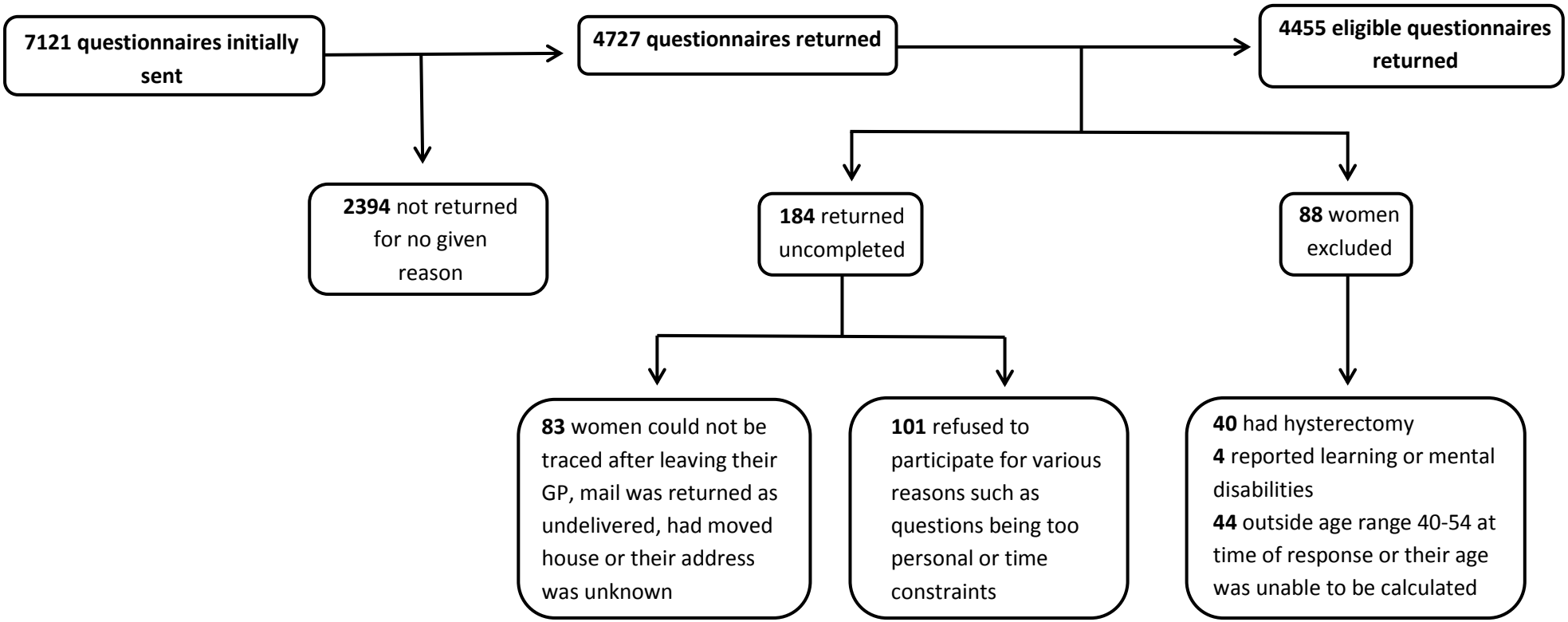
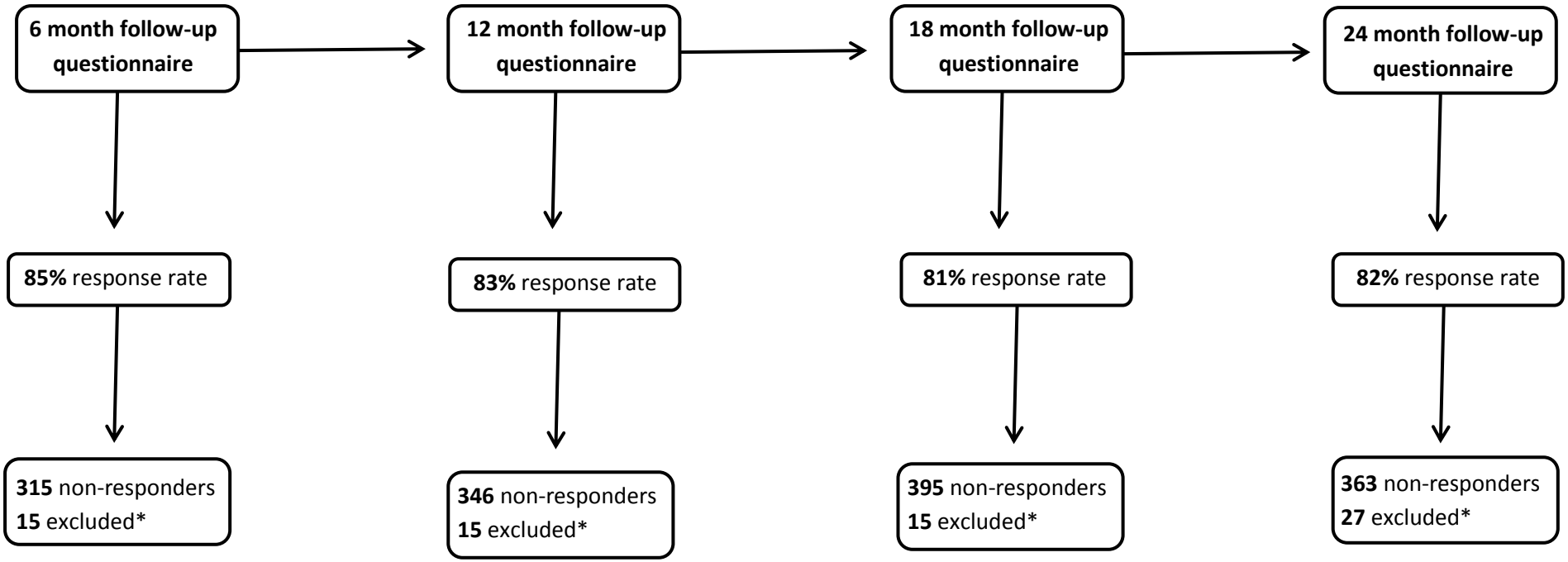


Figure 3.1 Number of baseline questionnaires sent and returned with reasons for deeming questionnaires unsuitable (Shapley et al. 2012)

The baseline questionnaire established 2949 (66%) women were menstruating of which 2167 (73%) were menstruating naturally. Those not naturally menstruating were excluded. Therefore, 2167 women were eligible to be sent the follow-up questionnaires however, 116 of these women did not consent to receiving the follow-up questionnaire. The 2051 eligible women that had consented were sent the follow-up questionnaires at 6, 12, 18 and 24 months. This formed a prospective cohort study of naturally menstruating women in the community. Figure 3.2 shows the response rates for the 6, 12, 18 and 24 month follow-up questionnaires, detailing how many women did not respond and were excluded at each stage.



*Excluded if participant withdrew, incorrect postal address or questionnaire returned too late

Figure 3.2 Response rate and numbers of participants that did not respond or were excluded during follow-up (Shapley et al. 2012)

3.3 Calculating the Positive Predictive Value in the PRIMROSE Cohort

To fulfil the aim of this chapter, women in the PRIMROSE cohort with PMB were identified and their electronic GP medical records reviewed. Medical records are documentation of a patient's medical history including past and present morbidities, investigations and accounts of consultations with clinicians. Medical records are an important source of information about the symptoms and morbidities experienced by a patient. The medical records of those in the PRIMROSE cohort with PMB were therefore reviewed to establish whether a uterine malignancy diagnosis was made within two years following reported PMB.

The community based study from the systematic review identified two of the 29 women with PMB in the community subsequently contacted a GP or gynaecologist for examination (Astrup & Olivarius 2004). This suggests not all of those with PMB in the community based PRIMROSE cohort may have visited their GP regarding the symptom. Using medical records this could therefore also be investigated in the PRIMROSE cohort.

Similarly, the primary care study identified in the systematic review reported 40% of women presenting with PMB had a relevant referral or investigation on their medical records (Parker et al. 2007). This implies GPs do not always refer women with PMB for investigation or to secondary care, as advised in current UK guidelines (NICE 2005a). The proportion of the PRIMROSE cohort consulting their GP for PMB that were then investigated or referred to secondary care was examined by reviewing the medical records to investigate this finding further. This additional

analysis of the medical records can be used in conjunction with the obtained PPVs to aid conclusions regarding improved management of patients with PMB in primary care.

Differences in the rate of uterine malignancy between the time elapsed from the menopause to the onset of PMB was able to be investigated. A study identified in the systematic review reported the greater the length of time from the menopause to the onset of vaginal bleeding, the more likely it is for bleeding to be due to an underlying malignancy (Lee et al. 1995). Therefore, women that are six months postmenopausal and have PMB may be less likely to suffer from a malignancy than those that are 12 months postmenopausal.

Basic demographic data provided from the PRIMROSE study enabled comparisons to be drawn between those with PMB and those without, such as examining whether any of the risk factors known to increase the risk of uterine malignancy vary among those with PMB and those without.

Therefore secondary objectives of this Chapter determined:

1. The proportion of women in the community aged 45 to 54 years with PMB that consulted their GP for the symptom
2. The proportion of women that present to the GP with PMB and are subsequently investigated or referred to secondary care
3. Whether time elapsed since the menopause to PMB onset influenced the likelihood of malignancy detection
4. Whether there are significant differences in demographics between those with PMB and those without

3.3.1 Methods

The following subsections will describe how a PRIMROSE cohort with PMB was selected and followed up to satisfy the outlined objectives.

3.3.1.1 Identifying a cohort of PRIMROSE participants with postmenopausal bleeding

The researcher involved in the PRIMROSE study did not produce a definition of PMB. Therefore, a scheme was designed using the PRIMROSE questionnaires to identify women suffering from variably defined PMB. The varying PMB definitions applied to the PRIMROSE cohort were created based upon those discovered during the systematic review and during background reading. The following subsection will outline how these definitions arose and how, using the PRIMROSE questionnaires, women fulfilling such definitions were identified.

Postmenopausal women were distinguished and then those with PMB identified. Women were identified as postmenopausal from reporting amenorrhoea on the 6, 12, 18 and 24 month follow-up questionnaires. The baseline questionnaires were not suitable for this purpose as those reporting amenorrhoea at this point were excluded from the study. Baseline questionnaires were used to ascertain whether women with PMB had consented for their medical records to be reviewed. If women did not consent to their medical records being viewed they were excluded from analysis.

In order to ensure that reported amenorrhoea may indeed be attributed to the menopause, women were required to be “natural”; excluding women whose menstrual periods may have stopped due to pregnancy or the use of medical interventions as listed below in the previous six months:

- Use of HRT
- Use of the contraceptive pill, mini-pill, injection or implants
- Use of hormone (Mirena) or copper intrauterine device
- Use of female hormones, hormone suppressors or blockers (e.g. zoladex injections)
- Having a gynaecological operation
- Ever having a hysterectomy or endometrial ablation

Women had to be natural throughout all of the follow-up questionnaires to ensure any subsequent bleeding was also due to "natural" causes, not for example as a result of HRT.

The systematic review did not identify a single definition of PMB used by all studies that could therefore be applied to the PRIMROSE cohort, but instead five inconsistent definitions. It was therefore determined women in the PRIMROSE cohort would be postmenopausal after their final menstrual period and therefore bleeding after this would be PMB.

However, as highlighted in Chapter 1 the final menstrual period can only be known in retrospect and the time that must have elapsed before this retrospective diagnosis can be made varies. The WHO state 12 months of amenorrhoea must have passed after the final menstrual period so it can be defined as so (WHO 1996).

This is a definition commonly utilised by clinicians in addition to several of the studies during the systematic review (Sadoon et al 2007, Dawood et al. 2010, Linasmita 1983). Adhering to this convention, women in the PRIMROSE cohort with at least 12 months amenorrhoea were deemed postmenopausal. This was women that answered no to the question "Have you had a period in

the last 6 months?" on two consecutive questionnaires. Bleeding during or after this amenorrhoea was defined as PMB as it would have occurred after the final menstrual period. Therefore women reporting a menstrual period on a subsequent questionnaire or answered yes to the questions below on the same or subsequent questionnaire on which they reported no menstrual period were considered to have PMB:

- "Over the last 6 months have you bled during or after sexual intercourse (making love) when you were not on a period?"
- "Over the last 6 months have you had any other vaginal bleeding (excluding periods and after sexual intercourse)?"

The systematic review also identified studies which defined PMB as bleeding six months after the final menstrual period (Niklasson et al. 2007, Lee et al. 1995). Therefore, those in the PRIMROSE cohort with at least 6 months amenorrhoea were also considered to be postmenopausal. This was women that answered no to the question "Have you had a period in the last 6 months?" on one questionnaire. Vaginal bleeding during or after these six months of amenorrhoea was considered PMB as it would have occurred after the final menstrual period. Therefore women reporting a menstrual period on a subsequent questionnaire or answered yes to the questions above on the same or subsequent questionnaire on which they reported no menstrual period were also deemed to have PMB.

Participants with PMB were subdivided into groups dependent upon when they reported their PMB. These groups can be seen in Table 3.1 and examples illustrated in Appendix 4. Subdividing participants in such a way determined whether the timing of the PMB episode altered the

likelihood of a cancer diagnosis, whether women with PMB presented to primary care and affected referrals by GPs.

Table 3.1 Groups Applied to PRIMROSE Cohort Dependent on PMB Definition	
Group	**Description**
A	Amenorrhoea on two consecutive questionnaires with any form of vaginal bleeding on third questionnaire - at least 12 months with no menstrual period and any form of vaginal bleeding in the following 6 months
B	Amenorrhoea on two consecutive questionnaires with vaginal bleeding other than a menstrual period on the first questionnaire - at least 12 months with no menstrual period and vaginal bleeding other than a menstrual period in the first six months
C	Amenorrhoea on two consecutive questionnaires with vaginal bleeding other than a menstrual period reported on the second questionnaire – at least 12 months with no menstrual period and vaginal bleeding other than a menstrual period within the last six months
D	Amenorrhoea on one questionnaire with any form of vaginal bleeding on the second questionnaire - at least 6 months with no menstrual period and any form of vaginal bleeding in the following 6 months
E	Amenorrhoea on one questionnaire with vaginal bleeding other than a menstrual period on the same questionnaire - at least 6 months with no menstrual period and vaginal bleeding other than a menstrual period within same 6 months

3.3.1.2 Reviewing medical records of PRIMROSE participants with postmenopausal bleeding

All participants in the PRIMROSE study were anonymised on the research database for ethical purposes. The unique anonymised PRIMROSE study identification numbers of those with PMB and had consented to their medical records being viewed were matched to the corresponding patient identification within one of the seven research practices they were registered with. This allowed for the corresponding GP and medical records to be identified.

I consequently made visits to these practices myself to review each of the participant's records, for two years from the date of the follow-up questionnaire on which PMB was reported. If there was more than one questionnaire in which PMB was reported, the date of the first reported bleed was that from which the records were reviewed.

All practices used the primary care information provider EMIS for storing patient records. As described in Chapter 2 Read Codes are used in EMIS to manage data, acting as a thesaurus of clinical terms and are entered by clinicians in primary care. Relevant Read Codes for uterine cancer were identified prior to visiting practices to ensure all records of uterine malignancy diagnosis were discovered. Read Codes were also identified for varying descriptions of bleeding after the menopause to determine whether the medical records detailed if those reporting PMB in the community presented to primary care with the symptom. Appropriate Read Codes were identified with the aid of a senior clinical research fellow and are shown in Table 3.2 with corresponding clinical terms.

Table 3.2 Read Codes Examined for in Medical Records

Read Code	Clinical Term
B43..	Malignant neoplasm of body of uterus
B40..	Malignant neoplasm of uterus, parts unspecified
B41..	Malignant neoplasm of cervix uteri
K5A1.	Postmenopausal bleeding
K56y1	Haemorrhage of vagina
K597	Postcoital bleeding
K59B	Postmenopausal postcoital bleeding
1583	History of postmenopausal bleeding
1582	History of abnormal uterine bleeding not otherwise specified

EMIS was used to obtain an overview of the medical records of each of the PRIMROSE cohort with PMB, detailing Read Codes with corresponding clinical terms for active and past problems. This allowed entries for Read Codes signifying a uterine cancer diagnosis in the two years following the reported PMB to be viewed in addition to Read Codes indicating the participant had presented to primary care regarding PMB.

The EMIS function allowing free text of recorded consultations to be viewed was additionally utilised. All consultations of those with PMB were reviewed for two years from the date of the reported bleed. This assessed whether the participant had presented with PMB or been diagnosed with a malignancy that had been entered as free text but not been Read Coded. Free text of consultations was additionally examined for records of relevant investigations or referrals to secondary care for PMB. Details of relevant referrals to secondary care, letters from secondary care to the GP and investigation findings were also sought by the use of the electronic document management system for healthcare, docman.

None of those reviewed had left their practice during the two year follow-up period. Therefore full medical records were available for the two years from the date of the reported bleed for all women with PMB.

If any of the PRIMROSE cohort with PMB were found to have a uterine cancer diagnosis, presented to primary care with PMB, had an investigation for PMB or relevant referral to secondary care, details were recorded on an Excel spread sheet to act as a record.

3.3.1.3 Analysis

The cohort of PRIMROSE participants reporting no menstrual period on one questionnaire or two consecutive questionnaires had their baseline demographic data analysed. This information included age-range, BMI, smoking status, ethnic origin, employment and marital status. In addition a variable indicating whether a woman had PMB or not was created. This allowed for a cross-tab analysis to be performed in order to compare demographic information for those with and without PMB, applying a chi-squared test to establish whether any such differences were significant. A P-value of less than 0.05 was considered statistically significant. SPSS version 20 (SPSS 2011) was used to analyse all data.

3.3.2 Results

Of the 2051 women that partook in the PRIMROSE study and were eligible for follow-up, 206 were identified as reporting no menstrual period on one questionnaire or two consecutive questionnaires, being natural throughout follow-up and consenting to their medical records being viewed. Eighty-six women reported having no menstrual period on one follow-up questionnaire and 120 women had no menstrual period on two consecutive questionnaires. Of the 206 women 75 were found to report PMB.

The demographics recorded on the baseline questionnaire of all women reporting no menstrual period on one questionnaire or two consecutive questionnaires can be seen in Table 3.3. The table shows demographic information for those with PMB and those without.

Table 3.3 Demographics of PRIMROSE Cohort with No Menstrual Period on One or Two Consecutive Questionnaires Including those with PMB and those Without			
Variable	**PMB (n= 75)**	**No PMB (n =131)**	**All (n= 206)**
Age-Range			
40-44	9 (12.0%)	10 (7.6 %)	19 (9.2%)
45-49	30 (40.0%)	48 (36.6%)	78 (37.9%)
50-54	36 (48.0%)	73 (55.7%)	109 (52.9%)
BMI			
Underweight/Normal	29 (38.7%)	52 (39.7%)	81 (39.3%)
Overweight	17 (22.7%)	34 (26.0%)	51 (24.8%)
Obese	12 (16.0%)	22 (16.8%)	34 (16.4%)
Unknown	17 (22.7%)	23 (17.6%)	40 (19.4%)
Smoking Status			
Never smoked	56 (74.7%)	77 (58.8%)	133 (64.6%)
Ex-smoker	13 (17.3%)	32 (24.4%)	45 (21.8%)
Currently smokes	5 (6.7%)	21 (16.0%)	26 (12.6%)
Unknown	1 (0.8%)	1 (0.8%)	2 (1.0%)
Ethnic Origin			
White UK/European	74 (98.7%)	128 (97.7%)	202 (98.1%)
Afro-Caribbean	0 (0.0%)	1 (0.8%)	1 (0.5%)
Other	0 (0.0%)	1 (0.8%)	1 (0.5%)
Unknown	1 (1.3%)	1 (0.8%)	2 (1.0%)
Employment			
Employed	56 (74.7%)	98 (74.8%)	154 (74.8%)
Unemployed	17 (22.7%)	31 (23.7%)	48 (23.3%)
Unknown	2 (2.7%)	2 (1.5%)	4 (1.9%)
Marital Status			
Married	61 (81.3%)	96 (73.3%)	157 (76.2%)
Cohabiting	6 (8.0%)	7 (5.3%)	13 (6.3%)
Single	3 (4.0%)	9 (6.9%)	12 (5.8%)
Divorced/separated	5 (6.7%)	17 (13.0%)	22 (10.7%)
Widowed	0 (0.0%)	1 (0.8%)	1 (0.5%)
Unknown	0 (0.0%)	1 (0.8%)	1 (0.5%)

Most of the 206 women were aged between 50 and 54 years. The majority of women had a BMI that placed them in the normal or underweight category. As the number of underweight women was very small, these were grouped with the normal BMI category. There were a minority of women considered obese in both those with PMB and those without. Most women had never smoked however, there were a higher proportion of women that were ex-smokers or currently smoking among those that did not have PMB. Almost all women in the cohort were of white UK or

European descent, with most in employment and married. None of the demographic variables were found to be significantly different between those that experienced PMB and those that did not.

3.3.2.1 Positive predictive value of postmenopausal bleeding for uterine malignancy in the PRIMROSE cohort

None of the 75 women with PMB and had their medical records reviewed were found to have a Read Code for uterine cancer or cancer diagnosis recorded as free text on their medical records during the two years following the reported bleed.

The lack of malignancy diagnosis resulted in the inability to establish a PPV of PMB for uterine malignancy in the PRIMROSE cohort. However, the fact uterine cancer was not detected suggests the PPV for such a community population would be a small value.

3.3.2.3 Proportion of those with postmenopausal bleeding consulting primary care

Of the 75 women with PMB 12 (16%) visited their registered practice and had a complaint of PMB recorded on their medical records. Eight (66.7%) of the women that visited their GP and had an episode of PMB detailed on their medical records were those reporting no menstrual period on one questionnaire (at least six months amenorrhoea). The remaining four women with an episode of PMB documented on their medical records were those having no menstrual period reported on two consecutive questionnaires (at least 12 months amenorrhoea).

3.3.2.4 Proportion of those consulting primary care investigated or referred to secondary care

Six (50%) of the women consulting primary care for PMB were subsequently referred to secondary care or for investigation, with the remaining six being monitored by their GP. One of the four women with no menstrual period on two consecutive questionnaires (at least 12 months amenorrhoea) and PMB was referred to secondary care. The remaining five referrals to secondary care or for investigation were for those reporting no menstrual period on one questionnaire only (at least six months amenorrhoea). Four of these were women that had no menstrual period on one questionnaire and experienced vaginal bleeding in the following 6 months. This group was the only one in which all women who visited their GP were referred to secondary care or investigated.

Figure 3.3 summaries the results of reviewing the medical records of the PRIMROSE cohort with PMB, including the proportion of those that visited primary care and were subsequently referred to secondary care for PMB. The information has been presented according to the groups participants were subdivided into depending upon the definitions of PMB fulfilled as described in Table 3.1. The key for Figure 3.3, shown on the following page, is as follows:

Key – Groups participants subdivided into and definitions

Group	Definition
A	Amenorrhoea on 2 consecutive questionnaires with any vaginal bleeding on 3rd questionnaire
B	Amenorrhoea on 2 consecutive questionnaires with vaginal bleeding other than a menstrual period on the 1st questionnaire
C	Amenorrhoea on 2 consecutive questionnaires with vaginal bleeding other than a menstrual period reported on the 2nd questionnaire
D	Amenorrhoea on 1 questionnaire with any vaginal bleeding on the 2nd questionnaire
E	Amenorrhoea on 1 questionnaire with vaginal bleeding other than a menstrual period on the same questionnaire

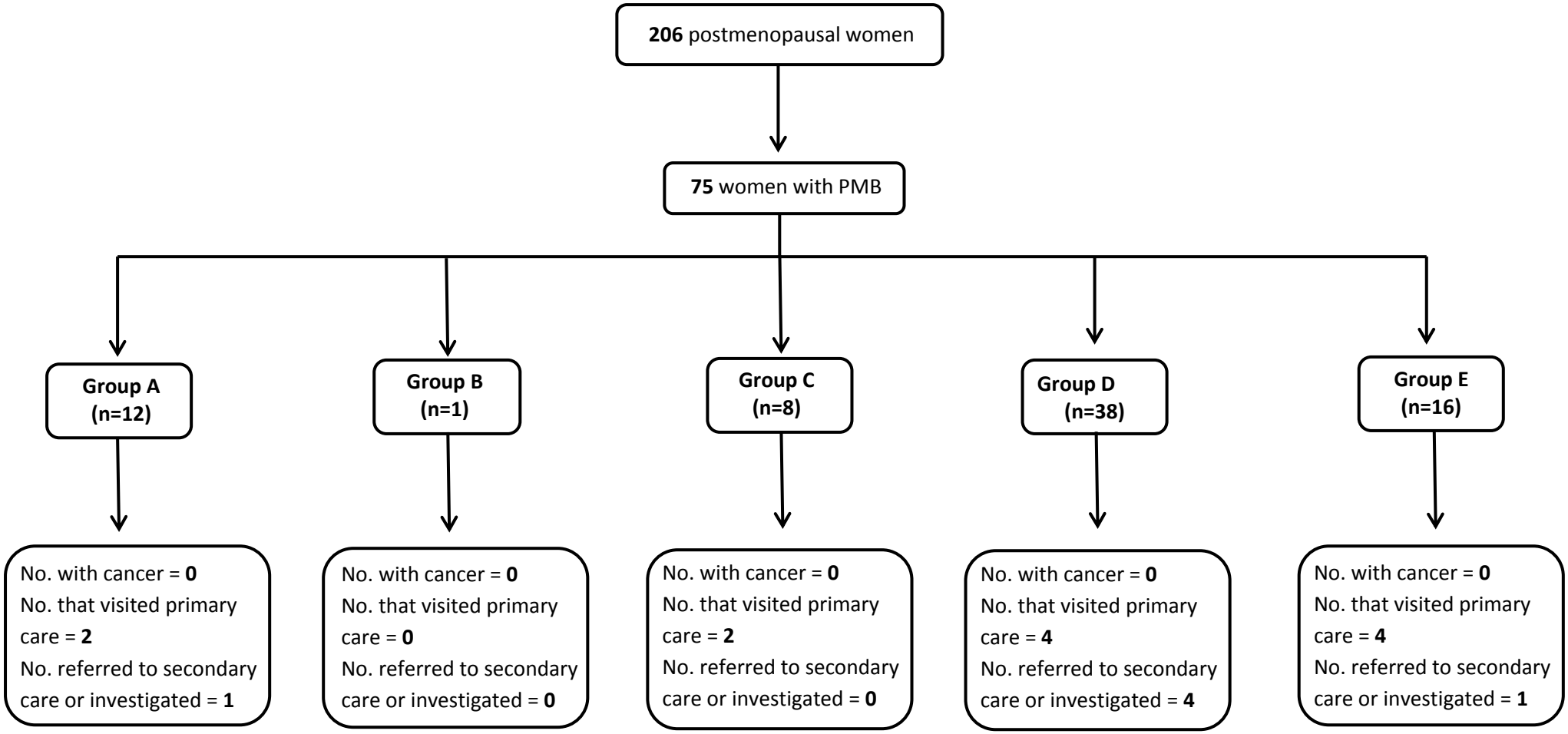


Figure 3.3 Summary of how many women with PMB visited their GP, were referred to secondary care or investigated and diagnosed with cancer according to PMB definitions

3.4 Discussion

The results and possible limitations of the methods employed in this Chapter to obtain a PPV of PMB for uterine malignancy in a community population will now be discussed.

3.4.1 Results

The aim of this chapter was to determine whether the PPV of PMB for uterine malignancy in the PRIMROSE cohort is consistent with the PPV derived in Chapter 2. However, as no women with PMB were found to have uterine cancer recorded on their medical records in the two years following a reported bleed, a PPV of PMB for uterine malignancy could not be obtained for the PRIMROSE cohort. However, the lack of malignancy demonstrated does indicate the probable PPV for such a community population would be very small and the risk of malignancy in those with PMB is not great. Whether this can be considered consistent with findings from the systematic review will be discussed in Chapter 4.

Reviewing the medical records additionally established a small proportion of the PRIMROSE cohort with PMB consulted their GP regarding the symptom. Subsequently half of those that visited primary care were investigated or referred to secondary care. This indicates not all women with PMB in the community visit their GP and that GPs do not always refer or investigate all those that present with PMB. This correlates with the findings of studies identified during the systematic review (Astrup & Olivarius 2004, Parker et al. 2007). Possible explanations for these findings and how they may aid decision making in primary care are outlined in Chapter 4.

The lack of uterine malignancies detected amongst those with PMB resulted in an inability to draw conclusions regarding any association between the period of time elapsed from the last menstruation to onset of PMB and the likelihood of uterine malignancy detection. Therefore, further research would be required to fulfil this objective.

The analysis of demographic data showed the majority of women reporting amenorrhoea and therefore defined as having experienced the menopause to be aged over 50 years, as would be expected. There was no significant variation detected in age or other demographic variables between those with PMB and those without. This indicates those with PMB were not more likely to have some of the known risk factors for uterine cancer development, such as increasing age and obesity, as those without PMB.

3.4.2 Strengths and limitations of methods

There are several strengths and limitations of the methods employed in this Chapter.

One particular limitation may be the two year follow-up period used to review the medical records of those with PMB. Extending the medical record review would potentially capture related malignancies occurring more than two years after the PMB symptom. However, the PRIMROSE study is a fairly recent study, conducted from 2007 to 2009, therefore evaluation of a longer period following PMB was impossible for the majority of cases. Hence, medical records were only reviewed for two years as this allowed a standardised period of time for all participants to be followed up.

In addition, it can be suggested a follow-up period greater than two years would not be beneficial as the majority of uterine malignancies are diagnosed within the two years following the PMB episode. This notion is substantiated by findings from the systematic review, in which a study conducted by Sharon et al. (1977) reported 50% of malignancies were detected within one month of the initial presentation of the symptom. A study conducted by Jones et al. (2007) also demonstrated the majority of malignancies are diagnosed shortly after the "alarming" presenting symptom. When a patient presented to their GP with an "alarm symptom" for a cancer, a cancer diagnosis was most frequently made within the first three months after symptom onset. Only a minority of cancers were diagnosed after three years from symptom onset.

The questionnaires in the PRIMROSE study do not date the last menstrual period. Women were deemed to have experienced amenorrhoea by their response to the question "Have you had a period in the last 6 months?". A woman stating she had had a menstrual period in the last six months on one questionnaire and no menstrual period in the last six months on the subsequent questionnaire is known to have at least six months amenorrhoea but may have had up to 11 months of amenorrhoea due to the retrograde nature of the question. This is also the case for those reporting no menstrual period on two consecutive questionnaires. Such women are known to have at least 12 months amenorrhoea but may have experienced up to 17 months amenorrhoea dependent upon the date of their last menstrual period. Therefore the PRIMROSE questionnaires cannot provide precise data regarding the length of amenorrhoea a woman experienced. This is not of great significance as women are known to have at least 6 or 12 months of amenorrhoea therefore fulfil definitions of being "postmenopausal" and "PMB" outlined in Table 3.1.

Women from the PRIMROSE cohort reporting no menstrual period on either one or two consecutive questionnaires were only included in the analysis if they were “natural”. The criteria for classifying women as “natural” were outlined in subsection 3.3.1.1 and involved excluding, among others, those using an intrauterine contraceptive device. This included hormonal (Mirena) and copper intrauterine devices. Hormonal intrauterine systems such as Mirena are known to cause spotting and irregular bleeding, symptoms that may be interpreted as PMB (NICE 2005b). Therefore, including women with such a device could have affected results. Women suffering from spotting due to the device alone could have been deemed to have a PMB episode, overestimating the incidence of PMB and therefore underestimating the PPV. Hence excluding women with such an intrauterine device was acceptable.

However, copper intrauterine devices are not known to cause symptoms that could be interpreted as PMB, such as spotting and irregular bleeding but instead cause heavy menstrual bleeding (NICE 2005b). Therefore including women with a copper intrauterine device would have a neutral effect on the PPV estimate and hence such women should be included. Not including women with an intrauterine device however reduces the generalisability of results as the PPV estimated cannot be applied to those with a device.

However, between the years 2003 and 2004 it was estimated in the UK approximately 8% of women aged 16 to 49 years had some form of long acting reversible contraception, not only an intrauterine contraceptive device (NICE 2005b). Therefore it is likely there are not a substantial number of individuals in the population that the PPV estimate will not be applicable to.

The criteria for classifying women as “natural” did not exclude those that were breastfeeding. Breastfeeding is known to cause amenorrhoea, therefore could be a reason for women reporting no menstrual period on a questionnaire. Data regarding breastfeeding was not however recorded on PRIMROSE questionnaires; hence exclusion of such women could not be achieved. However, it is unlikely to have affected the results to a great extent, as a minority of women aged 45 to 54 years have infants and of those that do 19% breastfed (Office for National Statistics 2005).

The fact women were only included in analysis if they were “natural” throughout all the follow-up questionnaires could be a limitation. It can be argued that providing women were “natural” on the questionnaires on which they reported amenorrhoea they should have been included for analysis as a subsequent postmenopausal bleed, whether in a “natural” woman or not, could have been due to a uterine malignancy. However, the use of some of the medical interventions women were excluded for such as HRT and the Mirena coil can cause irregular bleeding (NICE 2005b) and therefore could have been the cause of the PMB. Excluding women using such interventions ensured only those with PMB due to “natural” causes were analysed, not only those with “natural” amenorrhoea.

In addition interventions such as HRT have been shown to increase the risk of endometrial cancer dependent upon the regimen used (Judd et al. 1996). Hence this possibility is removed when women taking HRT are excluded. Excluding such women was consistent with methods used in eight of the studies identified in the systematic review, including the community based study (Astrup & Olivarius 2004), that excluded participants using HRT and other exogenous hormones.

For ethical reasons only those from the PRIMROSE study that consented to their medical records being viewed were used to test the derived PPV. There were no explanations as to why women did not consent to their medical records being viewed. However, it may be argued women that gave consent could be healthier and those with more severe illness did not favour their medical records being viewed. Therefore, women that did not have their medical records reviewed may be more likely to have a recorded uterine malignancy diagnosis than those consenting to their records being reviewed. Therefore, including only women consenting to medical record review may have led to bias in the sample and an inaccurate representation of the true PPV in a community population.

The PRIMROSE participants were a representative community population as the study gathered participants from the entire registered population of seven general practices covering urban and rural areas with affluent and deprived patients. Despite participants being obtained from primary care practices they remain representative of a community population as the majority of individuals in the UK are registered with a general practice even if they do not attend for health care (Lis & Mann 1995).

However, there are concerns regarding the representativeness of the sample obtained from the PRIMROSE cohort. It may be those women that had previously experienced gynaecological problems would be more likely to respond to the questionnaire as it something they have an increased awareness of. This could result in such women being more likely to have a positive response on the questionnaire and therefore an increased rate of PMB in the PRIMROSE cohort compared to the community population.

It may also be possible that women that are illiterate did not respond to the questionnaire. This may have been women with low literary skills, health illiterate or unable to understand the English language. This could therefore result in a sample not representative of the general community population as those with low literacy skills were not included in analysis. This possible lack of representativeness could lead to selection bias in the sample used to calculate the PPV and hence a PPV not applicable to a general community population.

A further strength of the methods employed was the thorough review of patient records. Both Read codes and free text were examined. Additional information regarding relevant contact with secondary care and investigation requests or findings was also sought using docman. Therefore, it is highly unlikely a relevant cancer diagnosis, investigation or referral for PMB was overlooked.

3.5 Summary

This Chapter had demonstrated how a cohort of women with PMB from a community population was established and assessed for the presence of a subsequent uterine cancer diagnosis. The aim of doing so was to ascertain whether the resulting PPV of PMB for uterine cancer was consistent with that derived from the systematic review. Despite the inability to obtain a PPV, the lack of cancer diagnosis indicates the PPV obtained would be very small. Whether this can therefore be considered consistent with the PPV for a community population obtained in Chapter 2 will be discussed in the following Chapter.

Chapter 4. Discussion

4.1 Overview

The previous Chapters have presented findings regarding the PPV of PMB for uterine malignancy. This Chapter will discuss the resultant PPVs and their possible implications for both decision making in primary care and more generally. Previous Chapters additionally indicated that those with PMB do not always consult their GP and that GPs do not always investigate or refer women with PMB. The consequences of these findings in conjunction with the PPVs obtained will also be discussed.

A further point of discussion in this Chapter will be the current definitions of PMB. The definition of PMB was not a topic this thesis set out to investigate however, in both the systematic review and in analysis of PRIMROSE data, varied and inconsistent definitions of PMB have arisen. The question of whether a more precise and accurate definition is therefore required will be addressed.

4.2 Positive Predictive Value of Postmenopausal Bleeding for Uterine Malignancy

PPVs have been established for community, primary and secondary care populations independently by searching available literature to identify studies providing PPVs and collecting data to derive a PPV when necessary. It was determined in Chapter 2 that despite possible concerns regarding the PPVs established for the community and primary care they can, overall, be

considered reliable estimates. The quantity of studies identified in secondary care allowed for meta-analysis and therefore, a reliable single pooled estimate of the PPV, something not before achieved. The associations between the PPVs obtained and their implications are discussed below.

The derived PPV for a community population in the systematic review was found to be low (0.51% for uterine cancer and 0.46% for endometrial cancer). In an attempt to test the derived PPV analysis of data from the PRIMROSE study was conducted. However, a PPV was not obtained due to none of those with PMB having a uterine cancer diagnosis.

Nevertheless, the lack of malignancy in the 75 women with PMB indicates the PPV in such a community population would also be low. If only one of the women from the PRIMROSE cohort with PMB were found to have a uterine cancer a PPV of 1.33% would have been produced, which would have been notably greater than that derived from the systematic review. Consequently, the finding from the PRIMROSE cohort may be assumed consistent with the derived PPV in Chapter 2 and provides further evidence that uterine malignancy is rare in women with PMB from the community.

The low PPV provided for a community population indicates a public health programme promoting awareness of PMB and aiding detection of uterine malignancy to be unwarranted for those aged 45 to 54 years. The WHO developed ten “Principles of Screening” that act as criteria for assessing whether a disease and its related tests are suitable for a screening programme (Wilson & Jungner 1968). One of these principles states the cost of finding a case should be economically balanced against the total medical expenditure. The low PPV provided from the

review for a community population suggests the cost of implementing a screening programme would potentially outweigh the benefits as it is doubtful a large number of women with cancer would be identified.

A public health programme raising awareness of PMB could potentially produce a negative effect. Raising public awareness of PMB as a possible symptom of cancer could create undue anxiety about a symptom that is unlikely, in the community, to have a sinister cause. However, it can only be stated a public health programme would be unwarranted for those aged 45 to 54 years as no data has been available regarding the risk of malignancy in those aged 55 years and over in a community population. This highlights the deficits in current research.

The PPV provided for a primary care population was also relatively low. The PPV for endometrial cancer in women aged 35 and over in primary care is 1.68% (95% CI 1.43-1.93), which is greater than the 0.47% (95% CI 0.24-0.70) in the community. This increase could reflect the findings in both the systematic review and analysis of PRIMROSE data that suggest not all women with PMB in the community present to their GP with the symptom. Those more likely to have a malignancy may be more likely to be those that present. The main reason women consult primary care with increased vaginal bleeding has been found to be interference with life (Shapley et al. 2002). Therefore, the symptoms interfering with life that cause a woman to consult could also be those that increase the risk of malignancy and therefore the PPV.

However, this apparent increase in PPV from the community to primary care is a largely irrelevant finding as the figures are not comparable. The community PPV is applicable to women aged 45 to 54 years whereas the primary care PPV encompasses all women over 35 years. The age-stratified

figure for women aged 45 to 54 years in primary care as shown in Table 2.9 is 0.35% (95% CI 0.13-0.55). Therefore the PPV of PMB for endometrial cancer in primary care has been demonstrated to be less than that in the community for women of the same age. This is unexpected as the PPV has been demonstrated to ordinarily increase from a community to primary care population (Fijten et al. 1994). An explanation for this could therefore be an overestimation of the PPV in the community population or an underestimation in the primary care population.

There are possible explanations as to why the PPV derived for the community could lead to an inaccurate estimate. The study used to derive the PPV reporting the incidence of PMB was based in Denmark (Astrup & Olivarius 2004), and of those estimating the proportion of women with cancer that presented with PMB, three were conducted in Israel (Krissi et al. 1996, Piura et al. 1997, Sharon et al. 1977), one in Austria (Seebacher et al. 2009) and one in the UK (Redman 2000). The National Statistics cancer incidence data was based upon a UK population (Office for National Statistics 2012).

The differing origins of the data could therefore have led to a PPV which is not representative of a community population in the UK, accounting for an unexpected overestimate of the PPV compared to the solely UK based primary care PPV. As highlighted in Chapter 2 the incidence rate used to derive the community PPV may also have led to an overestimation of the PPV. As a PPV could not be provided from the PRIMROSE cohort, the concept of an overestimated PPV cannot be substantiated. The data from the PRIMROSE study does confirm a low PPV would be observed in a community population but not how low. If it is the community PPV that is overestimated, the low value of the PPV is further emphasised, reinforcing the assumption no action is required to raise awareness of PMB as a potential symptom of cancer in the community.

However, rather than an overestimation of the PPV in the community there may be an underestimation in the primary care result. As highlighted in Chapter 2 the study conducted by Parker et al. (2007) was dependent on GPs recording an appropriate Read Code and that it is possible that some women did not have a necessary cancer diagnosis Read coded. Therefore, the resulting PPVs calculated would be underestimated. There is no means of determining which, if either, of these possible explanations accounts for the unexpected differences in the PPVs but the findings do imply further research is required in order to gain improved understanding.

The relatively low PPV provided for a primary care population suggests of those presenting with PMB a minority will have an underlying malignancy. In current UK guidelines it is advised to refer all women presenting with PMB to secondary care or for investigation (NICE 2005a, SIGN 2002). However, as highlighted in Chapter 1 a criticism of such guidelines is that they are not based upon reliable epidemiological data (Rubin et al. 2011). The results of the systematic review support this as the low PPV established does not justify urgent referral of all women presenting with PMB in primary care. The risk of malignancy cannot be deemed great enough to warrant all women in primary care with PMB undergoing potentially invasive procedures, women would be over investigated. It would also be detrimental to the health economy as funding would be wasted on unnecessary investigations and specialist outpatient appointments.

Additional findings from the systematic review and PRIMROSE data analysis have however established that GPs do not necessarily adhere to guidelines, not urgently referring all women with PMB. The study in the review found 40% of those with PMB are referred (Parker et al. 2007) while of the PRIMROSE participants presenting to primary care with PMB, 50% were referred. A

study by McBride et al. (2010) confirms this further, reporting that 61.4% of women with PMB are referred to secondary care.

It has now been established that it may not be necessary to refer all women presenting with PMB and it appears, in practice, GPs do not. This is confirmed by the increase in PPV from primary to secondary care. The PPVs for primary and secondary care are comparable as they likely deal with women of the same age-range. An overall PPV for endometrial cancer in women aged 35 years and over in primary care, as stated previously, was 1.68% (95% CI 1.43-1.93). The pooled estimates for PPVs in secondary care were obtained from studies using differing age-ranges of participants. As shown in Table 2.7 the youngest of the participants in the studies used to pool PPVs was 37 years and the oldest 94 years. The resulting pooled estimate for the PPV for endometrial cancer was 8.4% (95% CI 6.9-9.9) and 19.6% (95% CI 13.8-25.5) for uterine cancer.

The pooled estimates for the PPVs are substantially greater than that for primary care, indicating secondary care are receiving patients with an increased risk of malignancy. As the majority of patients seen in secondary care are received by referrals from primary care it may be that GPs are somehow "selecting" women with an increased risk of malignancy for referral. This implies that GPs are apt at discriminating between those with PMB that have a high or low risk of malignancy. However, other than the observed increase in PPV from primary to secondary care there are no means to verify this. The methods used by GPs for selecting patients and how effective they are also remain unclear.

The study by McBride et al. (2010) discovered that referral rates for PMB decreased significantly with advancing age and may be attributed to GPs and patients deciding that investigations and

their outcomes may not benefit older individuals. Age may therefore be a factor GPs account for when referring patients with PMB. Additional factors to consider when deciding to refer a patient may be other signs and symptoms. A study by Fijten et al. (1995) identified patient characteristics, signs and symptoms related to rectal bleeding that aided discrimination between those with a high and low probability of colorectal cancer. This suggests there may be clinical indicators for PMB that can discriminate between high risk and low risk patients. If such factors were to be identified their presence would increase the PPV of PMB and consequently aid GPs in their selection of patients for referral.

Several of the studies in the systematic review investigated the association between the characteristics of PMB and risk of malignancy development. Three studies found the quantity, characteristics and duration of bleeding did not indicate the presence of malignancy (Linasmita 1983, Liaquat & Noorani 2000, Ewies & Musonda 2010), while one study demonstrated PMB was significantly associated with malignancy the longer the onset from the menopause (Lee et al. 1995). This indicates current research provides diverse information and a study investigating patient characteristics, signs and symptoms related to PMB such as that conducted by Fijten et al. (1995) for rectal bleeding may be beneficial.

There is an apparent difference between the secondary care PPVs for uterine and endometrial cancer, possible explanations for which were discussed in Chapter 2. The difference between the PPVs does not hold significant implications as they both suggest the risk of malignancy is great enough in women presenting with PMB for all to be investigated. As there is an increased risk of malignancy, not investigating a woman with PMB in secondary care could result in a uterine cancer remaining undiagnosed.

4.3 Implications of Results

The findings in the thesis have implications for clinical practice, education and training, and further research. The implication for clinical practice in primary care specifically, is that it may not be necessary for GPs to refer all women with PMB as the risk of malignancy in those presenting to primary care is not great enough to warrant investigation in all. This would be important to communicate to clinicians as part of education and training. However, this finding raises the question of which patients to refer, as there are no methods for GPs to use to identify women with an increased risk of malignancy. Therefore it may also be useful as part of future training to advise clinicians in primary care to perform a gynaecological examination in all of those with PMB. This would establish whether there is an obvious benign cause of the PMB such as atrophic vaginitis. Such conditions could be treated prior to referral in order to ascertain whether the PMB subsides and hence may ensure women are not over investigated.

The finding regarding the low PPV in primary care and resulting implication of not needing to refer all women with PMB also holds implications for future research. There is the possibility of designing a decision making tool to differentiate between patients with a high and low risk of uterine malignancy. This could be produced after quantitative research. As alluded to previously, a study could be conducted to identify signs and symptoms, including characteristics of PMB, that could essentially increase the PPV of the symptom.

The findings also imply that future qualitative research may be beneficial. Results have shown patients to not always seek medical advice regarding their PMB symptom and it was suggested interference with life is the reason for individuals presenting to primary care. However, a group of individuals in the community with PMB could be identified, both those that present to primary

care and those that do not, and interviews conducted to ascertain common themes that may help explain their health seeking behaviour.

A qualitative study exploring GPs' perspectives and decision-making around referral would also be useful. However, this may be difficult as clinicians may provide answers in interviews that they believe they should give. Instead, it may therefore be beneficial to analyse video recordings of consultations between clinicians and those with PMB. This highlights several ways in which there may be future developments from findings in this thesis and the importance of the research conducted.

4.4 Definition of Postmenopausal Bleeding

The definition of PMB was not a topic originally intended to be examined during this thesis however it has emerged as recurrent issue. There is an apparent lack of consensus and clarity regarding a definition of PMB in research and clinically.

In the systematic review studies were identified that defined PMB as vaginal bleeding occurring after six, 12 or 24 months of amenorrhoea. It can be argued that this is not an adequate definition of PMB but rather a description of the time frame applied to diagnosing the menopause. As highlighted in Chapter 1, the menopause is defined as the final menstrual period and can only be known in retrospect after the event has occurred (WHO 1996). The time that must have elapsed since the final menstrual period for it to be defined as the menopause, as highlighted by studies in the review varies. However, the most commonly used by studies in the review and by clinicians appears to be the WHO definition of 12 months of amenorrhoea.

As definitions of PMB used by studies in the review included a required period of amenorrhoea, women that had experienced their final menstrual period and were hence postmenopausal were adequately identified. However, the definition of PMB used by the studies appears to only encompass bleeding occurring after this. The question arises of whether PMB should refer to any vaginal bleeding after the final menstrual period rather than vaginal bleeding after a period of amenorrhoea used to define the menopause. This would therefore include vaginal bleeding during amenorrhoea in addition to after it.

However, some may argue that bleeding episodes during amenorrhoea cannot be deemed PMB as it would contradict the concept of amenorrhoea. However, if amenorrhoea is defined as the absence of a menstrual period then providing the vaginal bleed is not a menstrual period it is bleeding after the menopause and hence PMB.

This then leads to the question of how a menstrual period can be defined. Ascertaining an adequate definition of a menstrual period is challenging. In a study investigating the use of menstrual diaries by Belsey et al. (1986) a “bleeding episode” was defined rather than a menstrual period and consisted of one or more consecutive days of bleeding or separated by only one bleeding free day, bounded at each end by two or more bleeding free days. Therefore, providing vaginal bleeding experienced after the menopause does not fulfil this definition, bleeding should be defined as PMB.

The information above suggests a more appropriate definition for PMB may be “vaginal bleeding other than a menstrual period in the first 12 months after the final menstrual period or any vaginal bleeding occurring 12 months after the final menstrual period”. A challenge that does

arise with this definition is that vaginal bleeding other than a menstrual period in the first 12 months after the final menstrual period will be a retrospective diagnosis as the menopause is. Such bleeding can only be known to have occurred once the final menstrual period has been established, 12 months from when it is experienced. Therefore, this part of the definition may not always be useful clinically but could be useful in research. Retrospective studies that identify women who have experienced the menopause could look back at the year from the date of the final menstrual period to establish whether any PMB was experienced.

This new definition of PMB suggested would therefore more accurately encompass all bleeding experienced after the final menstrual period as PMB and provide a definition that can be used clinically and in research, ensuring all have the same understanding of PMB.

4.4 Summary

This Chapter has discussed the PPVs obtained and the associations between them. The possible implications they may have for patient management have additionally been outlined. Current difficulties with the definition of PMB have been addressed and a new definition of PMB suggested overcoming these. The following Chapter will assess whether the thesis has met the objectives originally set.

Chapter 5. Conclusions

The aim of this thesis was to obtain a PPV of PMB for uterine malignancy. Independent PPVs were established for community, primary and secondary care populations. This was achieved by conducting a systematic review identifying studies providing a PPV or allowing a PPV to be derived. Results were pooled where possible by meta-analysis to obtain a single reliable estimate for the PPV. The PPV obtained for a community population was tested by analysis of participants with PMB from the PRIMROSE study.

The systematic review did not identify a community based study which directly provided a PPV therefore one was derived using additional data gathered. The low PPV derived was therefore tested on the PRIMROSE cohort and results found to be consistent, suggesting risk of malignancy in women with PMB in the community is low.

One study was identified from a primary care setting providing a PPV which was also relatively low. This indicates the risk of malignancy in women presenting to primary care with PMB is not great enough to justify investigating all women for malignancy as advised in current UK guidelines. Additional findings from analysis of the PRIMROSE data and from the systematic review suggest that GPs are in fact not referring all women with PMB, instead "selecting" women for referral. Methods for doing so were unclear but appear successful as there is an apparent increase in PPV from primary to secondary care. The higher PPVs for secondary care indicate the risk of malignancy in those with PMB presenting to secondary care is great enough to warrant investigations to assess for the presence of malignancy in all.

In summary the main findings of this thesis have been:

- PPV of PMB for uterine and endometrial cancer is 0.51% (95% CI 0.27-0.75) and 0.47% (95% CI 0.24-0.70) respectively for a community population aged 45 to 54 years
- PPV of PMB for endometrial cancer in women aged 35 years and over in primary care is 1.68% (95% CI 1.43-1.93)
- In secondary care the pooled estimate via random effects meta-analysis for the PPV of PMB for endometrial cancer is 8.4% (95% CI 6.9-9.9) and 19.6% (95% CI 13.8-25.5) for uterine cancer
- Current definitions of PMB are inconsistent and at times unclear, an improved definition of PMB has therefore been suggested to be “vaginal bleeding other than a menstrual period in the first 12 months after the final menstrual period or any vaginal bleeding occurring 12 months after the final menstrual period”

Chapter 6. Reflection

This Chapter will outline my personal reflections on the highlights and challenges faced whilst completing this MPhil. The MPhil was undertaken as an intercalated degree, between my fourth and fifth year as an undergraduate medical student. Therefore, the possible implications completing the MPhil may hold for my future career will additionally be discussed.

6.1 Highlights

Prior to commencing this MPhil I had never before completed research other than small tasks organised by the medical school and possessed limited knowledge of what research entailed. Whilst completing the MPhil I have attended courses regarding research methodologies and a seminar series given by experts in their research fields. Such opportunities have allowed me to develop an increased understanding of research methodologies and feel I have gained a wider appreciation of the implications research holds.

A particular experience of highlight was attending a symposium at the Research Institute I have been based. This provided me with an insight into the variety of research conducted by fellow MPhil and PhD students and also gave me the opportunity to present my own research to students, clinicians and academics. As a result I feel my oral presentation skills and confidence in public speaking have improved. I have also been given the opportunity to present my research at an international conference which will improve such skills further and allow me to share the research I have completed with a wider audience.

6.2 Challenges

Despite the MPhil being a rewarding process, there have also been challenges to face. The greatest challenge has been writing a coherent and succinct thesis as I had only previously written small essays forming part of my undergraduate studies. When I began to write the thesis I came to realise how taxing it was going to be to ensure my writing had clarity and a logical flow. However, after guidance from my supervisory team and persistence, my writing skills improved and I consequently feel more confident in my scientific writing ability.

In the initial stages it was also a challenge to conduct the research required in order to write the thesis. I had previously come across systematic reviews in my medical education and understood their purpose. However, when I came to learn my MPhil would consist of a systematic review I would be conducting I did not know where to begin. Nevertheless, with the advice of supervisors and knowledge gained by reading and attending courses, I soon came to understand what would be required. This again demonstrates the knowledge I have gained during the MPhil.

Apart from the challenges faced in writing the thesis and conducting research there were also general challenges which would be applicable to any intercalated degree. After spending four years as an undergraduate medical student, spending one year as a postgraduate research student was a welcome opportunity, with the chance to manage my own time and become an improved self-directed learner. However, I feel returning to the fifth year of my medical degree may be challenging to begin with after not being in a clinical setting for a year. Nevertheless, I believe I will soon resume my former level of clinical knowledge and skills, being fully prepared for my finals when they arrive.

6.3 Implications for the Future

As highlighted this MPhil has provided me with the opportunity to improve my knowledge of research methodologies, enhance my oral presentation skills and scientific writing ability. These will all be beneficial skills for my future career in medicine. I now feel I will have the ability to practice evidence based medicine, obtaining the most appropriate scientific evidence available to aid my clinical decision making.

The qualification in itself will also hopefully improve my career prospects. During my time in medical school I have concluded that I wish to pursue a career in general practice. However, the MPhil has enlightened me to the prospect of incorporating academia in my medical career and applying for an Academic Foundation Year 1 post is something I am now strongly considering.

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Appendix 1 Medline Database Search

1. postmenopaus*.ti,ab
2. (post ADJ menopaus*).ti,ab
3. post-menopaus*.ti,ab
4. exp POSTMENOPAUSE/
5. (after adj2 menopause).ti,ab
6. 1 OR 2 OR 3 OR 4 OR 5
7. bleed*.ti,ab
8. hemorrhag*.ti,ab
9. haemorrhag*.ti,ab
10. exp HEMORRHAGE/
11. 7 OR 8 OR 9 OR 10
12. 6 AND 11
13. endometri*.ti,ab
14. exp ENDOMETRIUM/
15. cervi*.ti,ab
16. (uterus OR uterine).ti,ab
17. exp UTERUS/
18. 13 OR 14 OR 15 OR 16 OR 17
19. neoplasm*.ti,ab
20. exp NEOPLASMS/
21. cancer*.ti,ab
22. carcinoma*.ti,ab
23. malignan*.ti,ab

24. lesion*.ti,ab
25. (tumour OR tumor*).ti,ab
26. 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25
27. exp ENDOMETRIAL NEOPLASMS/
28. exp UTERINE CERVICAL NEOPLASMS/
29. 18 AND 26
30. 27 OR 28 OR 29
31. prevalen*.ti,ab
32. exp PREVALENCE/
33. inciden*.ti,ab
34. exp INCIDENCE/
35. epidemiolog*.ti,ab
36. exp EPIDEMIOLOGY/
37. frequen*.ti,ab
38. cross-sectional.ti,ab
39. longitudinal.ti,ab
40. prospective.ti,ab
41. retrospective
42. survey.ti,ab
43. cohort.ti,ab
44. exp EPIDEMIOLOGIC STUDIES/
45. 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44
46. 12 AND 30
47. 12 AND 45
48. 46 [Limit to: English Language]
49. 47 [Limit to: English Language]

Appendix 2 PRIMROSE Baseline Questionnaire

SECTION 1: INTRODUCTION

These questions are about whether or not you have had a period or been pregnant recently.

1. Have you had a period in the **last 6 months**?

   (Please tick either the Yes or No box)

   Yes ☐ **(continue with question 2)**

   No ☐ **(go to question 39 on page 12)**

2. Are you currently pregnant or have you been pregnant during the **last 6 months**?

   (Please tick either the Yes or No box)

   Yes ☐ **(go to question 39 on page 12)**

   No ☐ **(continue with question 3)**

SECTION 2: MEDICINES AND OPERATIONS

These questions are about any medicines or devices you have **used or stopped using** in the last 6 months and about gynaecological operations

3. We are interested in the following medicines that contain female hormones and devices that are used in the womb.

   HRT (hormone replacement therapy)
   The contraceptive pill
   The mini-pill
   The contraceptive injection
   Contraceptive hormone implants
   The hormone coil (Mirena)
   The coil (copper/plastic IUCD)
   Female hormones
   Female hormone suppressors or blockers (e.g. zoladex injections)

   Have you **used** any of the above in **the last 6 months?**

   (Please tick either the Yes or No box)

   Yes ☐ **(go to question 39 on page 12)**

   No ☐ **(continue with question 4)**

4. Have you **ever** had an operation to try to permanently thin the lining of your womb (endometrial ablation)?

   (Please tick either the Yes or No or Unsure box)

   Yes ☐ **(go to question 39 on page 12)**

No ☐ **(continue with question 5)**

Unsure ☐ **(continue with question 5)**

5. Have you had any gynaecological operations in the **last 6 months?**

(Please tick either the Yes or No box)

Yes ☐ **(continue with question 6)**

No ☐ **(go to question 7)**

6. Please **list the gynaecological operations** you have had in the **last 6 months.**

……..

……..

(Please continue with question 7)

SECTION 3: MENSTRUAL PERIODS

These are questions for women who are having menstrual periods. They are some general questions about your periods.

7. Over the **last 6 months** how do you regard your periods?

(Please tick one box only)

Very light	☐
Fairly light	☐
Neither heavy nor light	☐
Fairly heavy	☐
Very heavy	☐
Variable	☐

(Please continue with question 8)

8. Over the **last 6 months** has the **heaviness** of your periods interfered with your life?

(Please tick either the Yes or No box)

Yes ☐ **(continue with question 9)**

No ☐ **(continue with question 9)**

(Please continue with question 9)

9. Over the **last 6 months** have you had a period **within 3 weeks** (21 days) of the **start of the previous** period?

(Please tick either the Yes or No box)

Yes ☐ **(continue with question 10)**

No ☐ **(go to question 11)**

10. How many times has this happened during the **last 6 months**?

(*Please tick one box only)*

Once ☐

Twice ☐

Three or more ☐

(Please continue with question 11)

11. Over the **last 6 months** what is the **usual** time from the start of one period to the start of the next?

(Please tick one box only)

Less than 21 days	☐
21 to 35 days	☐
More than 35 days	☐
Too variable to say	☐

(Please continue with question 12)

12. Over the **last 6 months** have you missed or skipped a period?

(Please tick either the Yes or No box)

Yes	☐	**(continue with question 13)**
No	☐	**(go to question 14)**

13.How many times has this happened during the **last 6 months**?

(*Please tick one box only)*

Once ☐

Twice ☐

Three or more ☐

(Please continue with question 14)

14. Over the **last 6 months** have you bled between periods?

(Please tick either the Yes or No box)

Yes ☐ **(continue with question 15)**

No ☐ **(go to question 16)**

15. How many times has this happened during the **last 6 months**?

(*Please tick one box only)*

Once ☐

Twice ☐

Three or more ☐

(Please continue with question 16)

16. Over the **last 6 months** have you bled during or after sexual intercourse (making love) when you were not on a period?

(Please tick either the Yes or No box)

Yes ☐ **(continue with question 17)**

No ☐ **(go to question 18)**

Not applicable ☐ **(go to question 18)**

17. How many times has this happened during the **last 6 months**?

(*Please tick one box only)*

Once ☐

Twice ☐

Three or more ☐

(Please continue with question 18)

18. Over the **last 6 months** have **irregular periods, bleeding between periods or bleeding after making love** when you were not on a period interfered with your life?

(Please tick either the Yes or No box)

Yes ☐ **(continue with question 19)**

No ☐ **(continue with question 19)**

SECTION 4: CONTACT WITH DOCTORS AND NURSES

These are questions about consultations during the last 6 months with doctors or nurses about the **heaviness** of your periods.

19. Have you consulted a doctor or nurse during the **last 6 months** about the **heaviness** of your periods?

(Please tick either the Yes or No box)

Yes ☐ **(continue with question 20)**

No ☐ **(continue with question 21)**

*20. Which type of doctor and/or nurse did you consult regarding the **heaviness** of your periods?*

(Please tick one or more boxes)

General practice doctor or practice nurse	☐
Family planning doctor or family planning nurse at the clinic	☐
A gynaecologist or gynaecological nurse at the hospital or clinic	☐
Other doctor or nurse	☐

If other doctor or nurse please describe the type of doctor or nurse

……

(Please continue with question 21)

*21. Are you waiting to see a gynaecologist at the hospital or clinic about the **heaviness** of your periods?*

(Please tick either the Yes or No box)

Yes ☐ **(continue with question 22)**

No ☐ **(continue with question 22)**

22. Have you had any tests because of the **heaviness** of your periods during the **last 6 months?** (for example blood tests, x-rays, scans, biopsies)

(Please tick either the Yes or No box)

Yes ☐ **(continue with question 23)**

No ☐ **(continue with question 23)**

(Please continue with question 23)

These are questions about consultations during the last 6 months with doctors or nurses about **irregular periods, bleeding between periods or bleeding after making love** when you were not on a period.

23. Have you consulted a doctor or nurse during the **last 6 months** about **irregular periods, bleeding between periods or bleeding after making love** when you were not on a period?

(Please tick either the Yes or No box)

Yes ☐ **(continue with question 24)**

No ☐ **(go to question 25)**

*24. Which type of doctor and/or nurse did you consult regarding **irregular periods, bleeding between periods or bleeding after making love** when you were not on a period?*

(Please tick one or more boxes)

General practice doctor or practice nurse ☐

Family planning doctor or family planning nurse at the clinic ☐

A gynaecologist or gynaecological nurse at the hospital or clinic ☐

Other doctor or nurse ☐

If other doctor or nurse please describe the type of doctor or nurse

……

(Please continue with question 25)

25. Are you waiting to see a gynaecologist about ***irregular periods, bleeding between periods or bleeding after making love*** *when you were not on a period?*

(Please tick either the Yes or No box)

Yes ☐ **(continue with question 26)**

No ☐ **(continue with question 26)**

(Please continue with question 26)

26. Have you had any tests because of the **irregular periods, bleeding between periods or bleeding after making love** when you were not on a period during the **last 6 months?** (for example blood tests, x-rays, scans, biopsies)

(Please tick either the Yes or No box)

Yes ☐ **(continue with question 27)**

No ☐ **(continue with question 27)**

SECTION 5: TREATMENTS

These questions are about treatments for heaviness of periods, irregular periods, bleeding between periods and bleeding after making love when not on a period in the last 6 months.

27. Have you used any treatments for the **heaviness** of your periods in the **last 6 months?**

(Please tick either the Yes or No box)

Yes ☐ **(continue with question 28)**

No ☐ **(go to question 29)**

*28. Please **list the treatments** you have used in the **last 6 months** for the **heaviness** of your periods.*

……..

……..

(Please continue with question 29)

29. Have you used any treatments for **irregular periods, bleeding between periods or bleeding after making love** when you were not on a period in the **last 6 months?**

(Please tick either the Yes or No box)

Yes ☐ **(continue with question 30)**

No ☐ **(go to question 31)**

*30. Please **list the treatments** you have used in the **last 6 months** for **irregular periods, bleeding between periods or bleeding after making love** when you were not on a period.*

……..

……..

(Please continue with question 31)

SECTION 6: GENERAL QUESTIONS

These are general questions about you.

31. Have you ever smoked cigarettes?

(Please tick either the Yes or No box)

Yes ☐ **(continue with question 32)**

No ☐ **(go to with question 33)**

32. Do you currently smoke cigarettes?

(Please tick either the Yes or No box)

Yes ☐ **(continue with question 33)**

No ☐ **(continue with question 33)**

33. What is your current marital status?

(*Please tick one box only)*

Currently married ☐

Cohabiting with partner ☐

Single ☐

Divorced /separated ☐

Widowed ☐

(Please continue with question 34)

34. Are you currently working?

(Please tick either the Yes or No box)

Yes ☐

No ☐

If working, what is your occupation?.....

If not working, what was your last occupation?.....

If retired, what was your last occupation?.....

(Please continue with question 35)

35. Do you have a spouse or partner who is currently living with you?

(Please tick either the Yes or No box)

Yes ☐

No ☐

If working, what is their occupation?.....

If not working, what their last occupation?.....

If retired, what was their last occupation?.....

(Please continue with question 36)

36. What is your ethnic origin?

(Please tick only one box)

White UK or European ☐

Afro-Caribbean ☐

African ☐

Asian ☐

Chinese ☐

Other ☐

If “other”, please write in your ethnic origin .....

(Please continue with question 37)

37. What is your weight?

		Stones			lbs	or				kgs

(Please continue with question 38)

38. What is your height?

	Feet			inches	or				cms

(Please continue with question 39)

39. What is your date of birth?

Day		Month		Year	

(Please continue with question 40)

40. What is today's date?

Day	Month	Year

(Please continue with SECTION 7)

SECTION 7: CONTINUING TO HELP WITH OUR STUDY

This is a continuing study. We would like to ask for your help with work that we need to do later. It is very important for this study to find out how your symptoms change over the next 2 years. We would like to ask your permission to send you 4 further questionnaires in order to find this out.

May we send you a further 4 follow-up questionnaires over the next 2 years (one every 6 months)?

(Please tick either the Yes or No box)

Yes ☐

No ☐

It is also important for us to see how you have consulted doctors and nurses at your Practice. We would like to ask your permission to review your medical records. When the records are reviewed your name will not be attached to any information released by the Practice so that you will not be identified personally away from your Surgery. We can assure you that any information will be held in the **strictest confidence**.

May we review your medical records for research purposes?

(Please tick either the Yes or No box)

Yes ☐

No ☐

Signed…….. Date……

Please print your name and address –

……

……

……

……

Appendix 3 PRIMROSE Follow-up Questionnaire

SECTION 1: MEDICINES AND OPERATIONS

These questions are about any medicines or devices you have **used or stopped using** in the last 6 months and about gynaecological operations

1. We are interested in the following medicines that contain female hormones and devices that are used in the womb.

   HRT (hormone replacement therapy)
   The contraceptive pill
   The mini-pill
   The contraceptive injection
   Contraceptive hormone implants
   The hormone coil (Mirena)
   The coil (copper/plastic IUCD)
   Female hormones
   Female hormone suppressors or blockers (e.g. zoladex injections)

   Have you **used** any of the above in **the last 6 months?**

   (Please tick either the Yes or No box)

   Yes ☐ **(continue with question 2)**

   No ☐ **(go to question 3)**

2. Which medicines or devices have you used in **the last 6 months**?

   (Please tick one or more boxes)

   HRT (hormone replacement therapy) ☐
   The contraceptive pill ☐
   The mini-pill ☐
   The contraceptive injection ☐
   Contraceptive hormone implants ☐
   The hormone coil (Mirena) ☐
   The coil (copper/plastic IUCD) ☐
   Female hormones ☐
   Female hormone suppressors or blockers ☐

(Please continue with question 3)

3. Have you had any gynaecological operations in the **last 6 months?**

(Please tick either the Yes or No box)

Yes ☐ **(continue with question 4)**

No ☐ **(go to question 5)**

4. Please **list the gynaecological operations** you have had in the **last 6 months.**

……..

……..

(Please continue with question 5)

SECTION 2: DO YOU HAVE PERIODS?

These questions are about whether or not you have had a period or been pregnant recently.

5. Are you currently pregnant or have you been pregnant during the **last 6 months**?

(Please tick either the Yes or No box)

Yes ☐ **(go to question 41 on page 12)**

No ☐ **(continue with question 6)**

6. Have you had a period in the **last 6 months**?

(Please tick either the Yes or No box)

Yes ☐ **(continue with question 7)**

No ☐ **(go to question 31 on page 10)**

SECTION 3: MENSTRUAL PERIODS

These are questions for women who are having menstrual periods. They are some general questions about your periods.

7. Over the **last 6 months** how do you regard your periods?

(Please tick one box only)

Very light	☐
Fairly light	☐
Neither heavy nor light	☐
Fairly heavy	☐
Very heavy	☐
Variable	☐

(Please continue with question 8)

8. Over the **last 6 months** has the **heaviness** of your periods interfered with your life?

(Please tick either the Yes or No box)

Yes ☐ **(continue with question 9)**

No ☐ **(continue with question 9)**

9. Over the **last 6 months** have you had a period **within 3 weeks** (21 days) of the **start of the previous** period?

(Please tick either the Yes or No box)

Yes ☐ **(continue with question 10)**

No ☐ **(go to question 11)**

10. How many times has this happened during the **last 6 months**?

(*Please tick one box only)*

Once	☐
Twice	☐
Three or more	☐

(Please continue with question 11)

11. Over the **last 6 months** what is the **usual** time from the start of one period to the start of the next?

(Please tick one box only)

Less than 21 days	☐
21 to 35 days	☐
More than 35 days	☐
Too variable to say	☐

(Please continue with question 12)

12. Over the **last 6 months** have you missed or skipped a period?

(Please tick either the Yes or No box)

Yes	☐	**(continue with question 13)**
No	☐	**(go to question 14)**

13. How many times has this happened during the **last 6 months**?

(*Please tick one box only)*

Once	☐
Twice	☐
Three or more	☐

(Please continue with question 14)

14. Over the **last 6 months** have you bled between periods?

(Please tick either the Yes or No box)

Yes ☐ **(continue with question 15)**

No ☐ **(go to question 16)**

15. How many times has this happened during the **last 6 months**?

(*Please tick one box only)*

Once ☐

Twice ☐

Three or more ☐

(Please continue with question 16)

16. Over the **last 6 months** have you bled during or after sexual intercourse (making love) when you were not on a period?

(Please tick either the Yes or No box)

Yes ☐ **(continue with question 17)**

No ☐ **(go to question 18)**

Not applicable ☐ **(go to question 18)**

17. How many times has this happened during the **last 6 months**?

(*Please tick one box only)*

Once ☐

Twice ☐

Three or more ☐

(Please continue with question 18)

18. Over the **last 6 months** have **irregular periods, bleeding between periods or bleeding after making love** when you were not on a period interfered with your life?

(Please tick either the Yes or No box)

Yes ☐ **(continue with question 19)**

No ☐ **(continue with question 19)**

SECTION 4: CONTACT WITH DOCTORS AND NURSES

These are questions about consultations during the last 6 months with doctors or nurses about the **heaviness** of your periods.

19. Have you consulted a doctor or nurse during the **last 6 months** about the **heaviness** of your periods?

(Please tick either the Yes or No box)

Yes ☐ **(continue with question 20)**

No ☐ **(continue with question 21)**

20. Which type of doctor and/or nurse did you consult regarding the **heaviness** of your periods?

(Please tick one or more boxes)

General practice doctor or practice nurse ☐

Family planning doctor or family planning nurse at the clinic ☐

A gynaecologist or gynaecological nurse at the hospital or clinic ☐

Other doctor or nurse ☐

If other doctor or nurse please describe the type of doctor or nurse

……

(Please continue with question 21)

21. Are you waiting to see a gynaecologist at the hospital or clinic about the **heaviness** of your periods?

(Please tick either the Yes or No box)

Yes ☐ **(continue with question 22)**

No ☐ **(continue with question 22)**

22. Have you had any tests because of the **heaviness** of your periods during the **last 6 months?** (for example blood tests, x-rays, scans, biopsies)

(Please tick either the Yes or No box)

Yes ☐ **(continue with question 23)**

No ☐ **(continue with question 23)**

These are questions about consultations during the last 6 months with doctors or nurses about **irregular periods, bleeding between periods or bleeding after making love** when you were not on a period.

23. Have you consulted a doctor or nurse during the **last 6 months** about **irregular periods, bleeding between periods or bleeding after making love** when you were not on a period?

(Please tick either the Yes or No box)

Yes ☐ **(continue with question 24)**

No ☐ **(go to question 25)**

24. Which type of doctor and/or nurse did you consult regarding **irregular periods, bleeding between periods or bleeding after making love** when you were not on a period?

(Please tick one or more boxes)

General practice doctor or practice nurse	☐
Family planning doctor or family planning nurse at the clinic	☐
A gynaecologist or gynaecological nurse at the hospital or clinic	☐
Other doctor or nurse	☐

If other doctor or nurse please describe the type of doctor or nurse

……

(Please continue with question 25)

25. Are you waiting to see a gynaecologist about **irregular periods, bleeding between periods or bleeding after making love** when you were not on a period?

(Please tick either the Yes or No box)

Yes ☐ **(continue with question 26)**

No ☐ **(continue with question 26)**

26. Have you had any tests because of the **irregular periods, bleeding between periods or bleeding after making love** when you were not on a period during the **last 6 months?** (for example blood tests, x-rays, scans, biopsies)

(Please tick either the Yes or No box)

Yes ☐ **(continue with question 27)**

No ☐ **(continue with question 27)**

(Please continue with question 27)

SECTION 5: TREATMENTS

These questions are about treatments for heaviness of periods, irregular periods, bleeding between periods and bleeding after making love when not on a period in the last 6 months.

27. Have you used any treatments for the **heaviness** of your periods in the **last 6 months?**

    (Please tick either the Yes or No box)

    Yes ☐ **(continue with question 28)**

    No ☐ **(go to question 29)**

28. Please **list the treatments** you have used in the **last 6 months** for the **heaviness** of your periods.

    ……..

    ……..

(Please continue with question 29)

29. Have you used any treatments for **irregular periods, bleeding between periods or bleeding after making love** when you were not on a period in the **last 6 months?**

    (Please tick either the Yes or No box)

    Yes ☐ **(continue with question 30)**

    No ☐ **(go to question 41 on page 12)**

30. Please **list the treatments** you have used in the **last 6 months** for **irregular periods, bleeding between periods or bleeding after making love** when you were not on a period.

    ……..

    ……..

    (Please continue with SECTION 7 question 41 on page 12)

SECTION 6: BLEEDING IN WOMEN WHO DO NOT HAVE PERIODS

These questions are for women who have not had a period in the last 6 months. They are about bleeding unrelated to periods.

31. Over the **last 6 months** have you bled during or after sexual intercourse (making love)?

(Please tick either the Yes or No box)

Yes ☐ **(continue with question 32)**

No ☐ **(go to question 33)**

Not applicable ☐ **(go to question 33)**

32. How many times has this happened during the **last 6 months**?

(*Please tick one box only)*

Once ☐

Twice ☐

Three or more ☐

(Please continue with question 33)

33. Over the **last 6 months** have you had any other vaginal bleeding (excluding periods and after sexual intercourse)?

(Please tick either the Yes or No box)

Yes ☐ **(continue with question 34)**

No ☐ **(go to question 35)**

34. How many times has this happened during the **last 6 months**?

(*Please tick one box only)*

Once ☐

Twice ☐

Three or more ☐

(Please continue with question 35)

35. Have you consulted any doctor or nurse during the **last 6 months** about bleeding during or after sexual intercourse (making love) or other vaginal bleeding (excluding periods)?

(Please tick either the Yes or No box)

Yes ☐ **(continue with question 36)**

No ☐ **(go to question 37)**

36. Which type of doctor and/or nurse did you consult regarding bleeding during or after sexual intercourse (making love) or other vaginal bleeding (excluding periods)?

(Please tick one or more boxes)

General practice doctor or practice nurse	☐
Family planning doctor or family planning nurse at the clinic	☐
A gynaecologist or gynaecological nurse at the hospital or clinic	☐
Other doctor or nurse	☐

If other doctor or nurse please describe the type of doctor or nurse

……

(Please continue with question 37)

37. Are you waiting to see a gynaecologist at the hospital or clinic about bleeding during or after sexual intercourse (making love) or other vaginal bleeding (excluding periods)?

(Please tick either the Yes or No box)

Yes ☐ **(continue with question 38)**

No ☐ **(continue with question 38)**

(Please continue with question 38)

38. Have you had any tests because of the bleeding during or after sexual intercourse (making love) or other vaginal bleeding (excluding periods) during the **last 6 months**? (for example blood tests, x-rays, scans, biopsies)

(Please tick either the Yes or No box)

Yes ☐ **(continue with question 39)**

No ☐ **(continue with question 39)**

39. Have you used any treatments for bleeding during or after sexual intercourse (making love) or other vaginal bleeding (excluding periods) in the **last 6 months**?

(Please tick either the Yes or No box)

Yes ☐ **(continue with question 40)**

No ☐ **(go to question 41)**

40. Please **list the treatments** you have used in the **last 6 months** for the bleeding during or after sexual intercourse (making love) or other vaginal bleeding (excluding periods).

……..

……..

(Please continue with question 41)

SECTION 7: GENERAL QUESTIONS

These are general questions about you.

41. Do you currently smoke cigarettes?

(Please tick either the Yes or No box)

Yes ☐ **(continue with question 42)**

No ☐ **(continue with question 42)**

(Please continue with question 42)

42. What is your weight?

☐☐ stones ☐☐ lbs or ☐☐☐ kgs

(Please continue with question 43)

43. What is your date of birth?

Day	Month	Year
☐☐	☐☐	☐☐

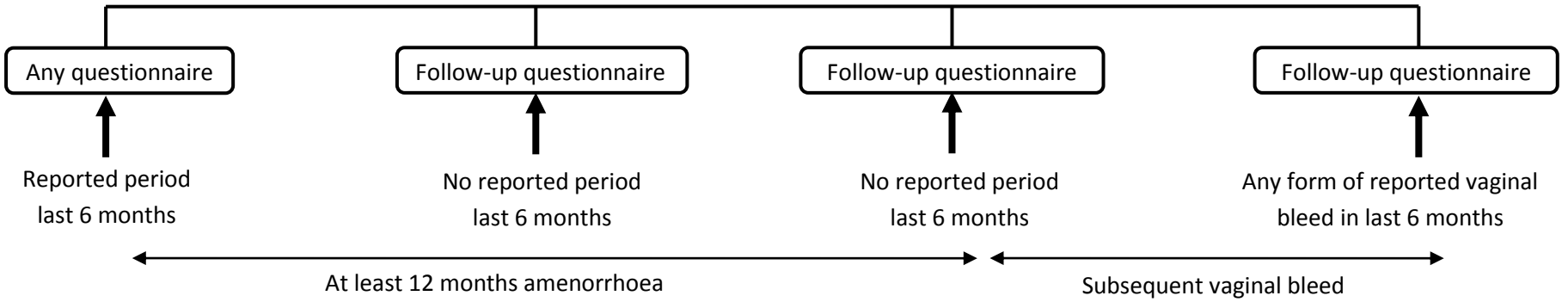
(Please continue with question 44)

44. What is today's date?

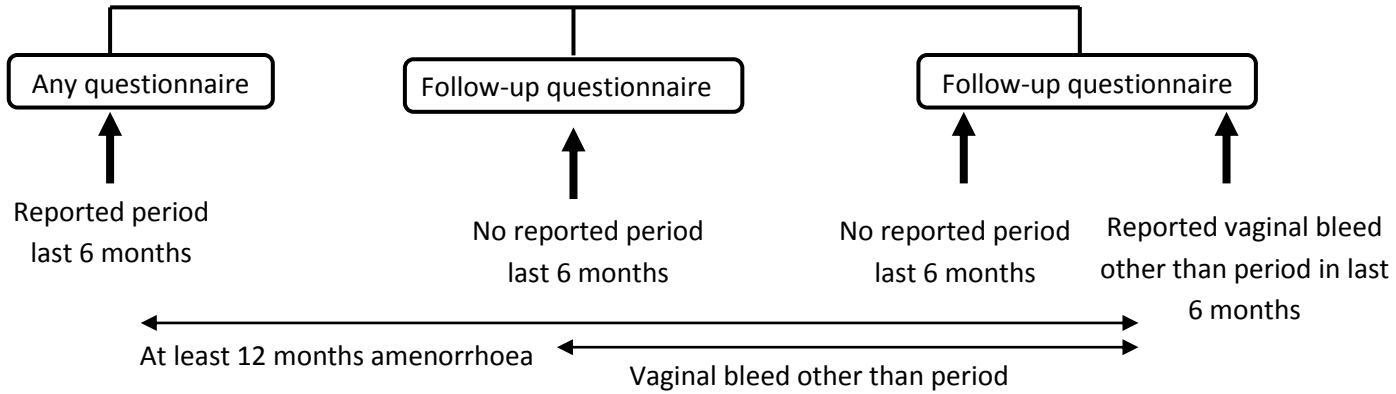
Day	Month	Year
☐☐	☐☐	☐☐

Appendix 4 Examples of PRIMROSE Groups

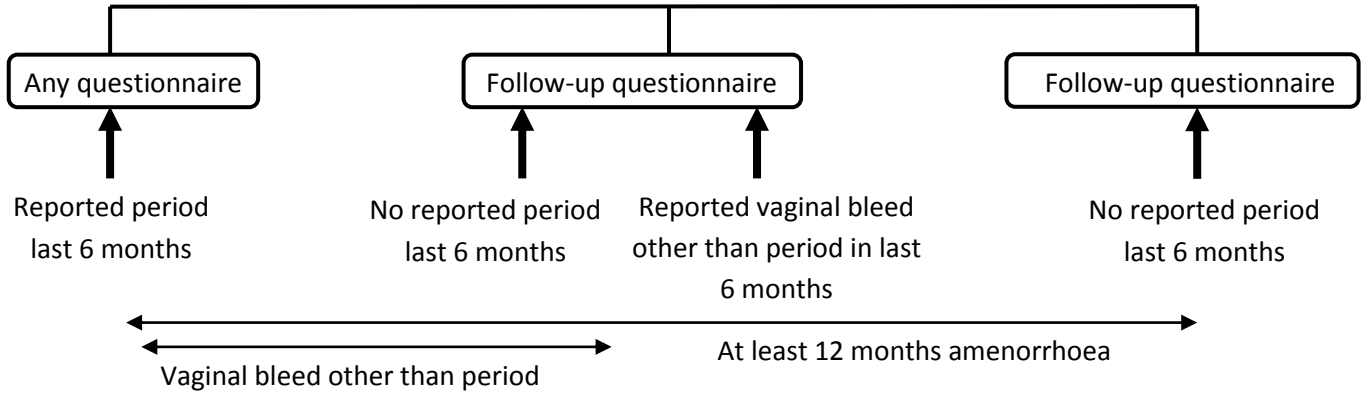
Example of Definition A – at least 12 months with no menstrual period and any form of vaginal bleeding in the following 6 months



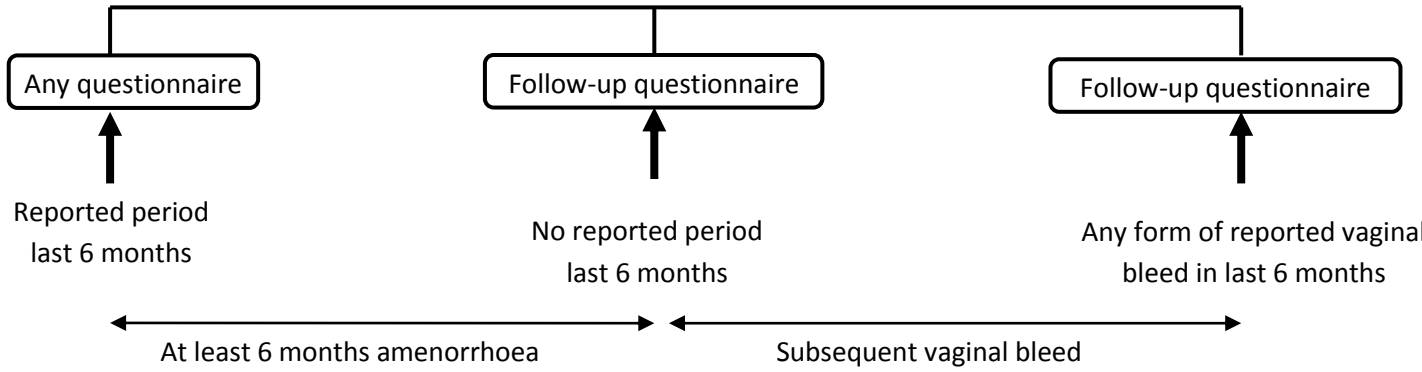
Example of Group B - at least 12 months with no menstrual period and vaginal bleeding other than a period within the last six months



Example of Group C– at least 12 months with no menstrual period and vaginal bleeding other than a period in the first six months



Example of Definition D – at least 6 months with no menstrual period and any form of vaginal bleeding in the following 6 months



Example of Definition E – at least 6 months with no menstrual period and vaginal bleeding other than a period within same 6 months