

CRANFIELD UNIVERSITY

S M NICHOLSON

**INVESTIGATING THE IMPACT OF NHS BASED
OVARIAN CANCER SCREENING**

CRANFIELD HEALTH

MSc by Research

MSc Thesis

Supervisors: Dr S.L. Morgan and Mr K. Sehdev

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ABSTRACT

In the UK ovarian cancer is the fifth most common cancer in females and after uterine cancer, the second most common gynaecological cancer. There were 6,596 new cases diagnosed in the UK in 2006. The majority of women who develop ovarian cancer have few symptoms until the cancer has spread. A systematic review of published literature was performed to include randomised control trials, case control or cohort studies. It is apparent from the literature on ovarian cancer screening that internationally extensive research is performed however, there is lack of consensus on who to offer screening to, and the most efficacious way of offering it. Annual screening was found to be inadequate for early cancer detection as several studies report advanced stage disease or found that women were developing symptoms in the interim period of screening visits.

The retrospective studies performed at Milton Keynes Hospital demonstrated that ovarian cancer affects a wide age range with many women having no family history of ovarian or breast cancer. Many cases were found to have early stage ovarian cancer however, the largest group of women were found to have extensive metastatic disease at time of diagnosis. 80% of cases reviewed experienced abdominal or pelvic pains often with distension. Five patients were found to have a CA125 value in the normal range, one of which had advanced disease, indicating the limitations of this biomarker. The impact and costs associated with screening in the NHS setting vary considerably with inclusion criteria used. The UK National Screening Committee will have to decide once the findings of UKCTOCS are published in 2010/11 as to the cost benefit of offering NHS based ovarian cancer screening. An annual cost of at least £1.3 million should be expected per NHS trust, in addition to individual trusts needs for equipment, staff and additional facilities required to offer such screening.

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Table of Contents

ABSTRACT	iii
ACKNOWLEDGEMENTS	iv
LIST OF FIGURES	4
LIST OF TABLES.....	5
LIST OF ABBREVIATIONS	6
1 BACKGROUND.....	7
1.1 What is Cancer?	8
1.2 Ovarian Cancer	11
1.2.1 Classification and Stages of Disease	12
1.2.2 Incidence, Mortality and Symptoms.....	14
1.2.3 Familial and Sporadic Ovarian Cancer.....	17
1.3 Detection and Diagnosis of Ovarian Cancer.....	19
1.3.1 Imaging Diagnosis	19
1.3.2 Biomarkers	22
1.4 Screening	24
1.4.1 Sensitivity and Specificity	25
1.4.2 Ovarian Cancer Screening	26
1.4.3 Screening Population	27
1.4.4 Treatment.....	28
1.4.5 Milton Keynes Hospital NHS Foundation Trust	28
1.5 Aims and Objectives	29
1.6 Thesis Methodology	31
2 SCREENING FOR OVARIAN CANCER: A Systematic literature review ...	32
2.1 Benefit of Systematic Literature Reviews	33
2.1.1 Characteristics of Systematic Reviews.....	34
2.2 Study Design.....	35
2.2.1 Search Terms	36
2.2.2 Study Dates to be Included.....	36
2.3 Results of Systematic Literature Review	37
2.3.1 Cochrane Library Database Search	37
2.3.2 SCOPUS Database Search	40
2.4 Discussion of Systematic Literature Review	42

2.4.1	Evaluation of Included Studies in Literature Review.....	42
2.4.2	Ovarian Cancer Screening Studies	43
2.4.3	Screening Methods	44
2.4.4	Ovarian Cancer Screening using Ultrasound Imaging alone.....	47
2.4.5	Ovarian Cancer Screening Studies using Ultrasound combined with serum tumour markers.....	48
2.4.6	Compliance in Ovarian Cancer Screening Studies.....	49
2.5	Conclusion of Systematic Literature Review	52
2.6	Recommendations from Systematic Literature Review	54
3	RETROSPECTIVE STUDY OF CONFIRMED AND SUSPECTED OVARIAN CANCER CASES.....	56
3.1	Introduction.....	57
3.2	Design of Retrospective Studies	58
3.3	Results of First Retrospective Study.....	61
3.3.1	Age at Diagnosis.....	61
3.3.2	Menopausal Status.....	62
3.3.3	Stage of Ovarian Cancer.....	62
3.3.4	Presenting Symptoms	63
3.3.5	Diagnostic Findings.....	64
3.3.6	CA125 Analysis.....	65
3.3.7	Documented History of Cancer	67
3.4	Results of Second Retrospective Study	68
3.4.1	Age Range	68
3.4.2	Imaging Findings.....	68
3.4.3	Outcome of Cases.....	69
3.5	Discussion of Retrospective Studies.....	71
3.5.1	Strengths and Limitations of Retrospective Studies performed	73
3.5.2	Conclusion of Retrospective Studies.....	74
4	COST ANALYSIS of Ovarian cancer screening.....	75
4.1	Cost Analysis Introduction	76
4.2	NHS Based Cancer Screening Programmes	79
4.2.1	Breast Cancer Screening.....	79
4.2.2	Cervical Cancer Screening	80
4.2.3	Bowel Cancer Screening	80

4.2.4	Comparison of ovarian cancer screening with currently offered cancer-screening programmes	81
4.3	NHS Screening Programme for Ovarian Cancer	84
4.3.1	Inclusion Criteria	84
4.3.2	Scenario One.....	86
4.3.3	Scenario Two.....	86
4.3.4	Scenario Three.....	86
4.3.5	Screening Method.....	88
4.3.6	Quality Control of a Screening Programme	89
4.4	Proposed Cost Analysis for NHS Implementation of Screening	91
4.5	The Impact on Milton Keynes Hospital in offering an ovarian cancer-screening programme.....	95
4.5.1	Impact of Scenario One	96
4.5.2	Impact of Scenario Two	97
4.5.3	Impact of Scenario Three	99
4.6	Conclusion of Cost Analysis.....	100
5	DISCUSSION.....	101
5.1	Ovarian Cancer Screening	102
5.1.1	Why offer ovarian cancer screening?	102
5.1.2	Who should be offered screening?	103
5.1.3	How to screen for ovarian cancer	104
5.1.4	How often to screen for ovarian cancer.....	105
5.1.5	Impact to a local NHS Trust.....	106
5.2	Conclusion	108
	REFERENCES	111
	APPENDICES.....	118

LIST OF FIGURES

Figure 1.1 Features of normal and cancer glandular epithelium (King, 2000)	9
Figure 1.2 Main structure of a healthy ovary and ovulation (Herbrandson, 2005)	11
Figure 1.3 Number of new cases and age-specific incidence rates in UK, 2006 (Cancer Research UK, 2009)	14
Figure 1.4 Correlation of Stage and 5-year survival in ovarian cancer (Menon and Jacobs, 2002)	16
Figure 1.5 Age at diagnosis and five-year survival rates (Cancer Research UK, 2009)	16
Figure 1.6 Ultrasound image of a normal appearing ovary (Harris, 2002)	20
Figure 1.7 Ultrasound image of a complex adnexal mass with multiple septations, solid components and abnormal vascularity suggesting malignancy (Fishman et al, 2005) ..	20
Figure 1.8 Transvaginal scan of a solid ovarian mass with low impedance flow (Fleischer, 2009)	21
Figure 1.9 Screening Strategies for Ovarian Cancer (Menon and Jacobs, 2002)	26
Figure 1.10 Performance characteristics of ovarian cancer screening strategies (Menon and Jacobs, 2002)	27
Figure 2.1 Flow Diagram of Cochrane Library Database Search	39
Figure 2.2 Flow Diagram of SCOPUS Database Search	41
Figure 2.3 Population screened for ovarian cancer in studies analysed	44
Figure 3.1 Method of First Retrospective Study	58
Figure 3.2 Method of Second Retrospective Study	60
Figure 3.3 FIGO Classification of Disease and Age at Diagnosis	61
Figure 3.4 FIGO Classification of disease and number of cases	63
Figure 3.5 Boxplot of FIGO Classification of Disease and CA125	66
Figure 3.6 How a diagnosis of benign pathology was reached	69
Figure 4.1 Framework for cost-effectiveness and health-related quality of life measurements (Miller et al, 2001)	77
Figure 4.2 Screening Population in Scenario Three	87

LIST OF TABLES

Table 1.1 Comparison of benign and malignant growths (King, 2000).....	9
Table 1.2 FIGO Staging System for Ovarian Cancer (International Federation of Gynaecology and Obstetrics, 2010).....	13
Table 1.3 Number of deaths and mortality rates of ovarian cancer (Cancer Research UK, 2009).....	15
Table 1.4 Brief overview of genes implicated in hereditary ovarian cancer (Kasprzak et al, 1999).....	17
Table 1.5 Main differences in BRCA mutation between sporadic and inherited ovarian cancer (Wong, 2003)	18
Table 1.6 Causes of elevated CA125 levels (Menon and Jacobs, 2002).....	22
Table 1.7 Calculating the performance of a screening test (Bell et al., 1998)	25
Table 2.1 Levels of Evidence (Scottish Intercollegiate Guidelines Network, 2001)	35
Table 2.2 Cochrane Library Database Search	37
Table 2.3 Cochrane Library Database Search Resources	37
Table 2.4 Excluded studies from Cochrane Library Database search.....	38
Table 2.5 SCOPUS database search results.....	40
Table 2.6 Excluded studies from SCOPUS database search.....	40
Table 2.7 Ovarian Cancer Screening Studies using Ultrasound alone	45
Table 2.8 Ovarian Cancer Screening Studies using Ultrasound combined with serum tumour markers.....	46
Table 3.1 Menopausal Status of Ovarian Cancer Cases	62
Table 3.2 Outcome of suspected ovarian pathology diagnosis	70
Table 4.1 Explanation of each numbered node (Miller et al, 2001)	78
Table 4.2 Cost Analysis for Scenario One – Based on UKCTOCS.....	92
Table 4.3 Cost Analysis for Scenario Two – Based on UKFOCSS.....	93
Table 4.4 Cost Analysis for Scenario Three.....	94

LIST OF ABBREVIATIONS

ANN – Artificial Neural Network

BRCA – Breast Cancer gene

CA125 – Cancer Antigen 125

CE – Cost Effectiveness

CT – Computerised Tomography

DNA – Deoxyribonucleic acid

FASP – Fetal Anomaly Screening Programme

FIGO – International Federation of Gynaecology and Obstetrics

HRQL – Health Related Quality of Life

HTA – Health Technology Assessment

MESH – Medical Subject Headings

MM – Multimodal screening

MRC – Medical Research Council

MRI – Magnetic Resonance Imaging

NHS – National Health Service

NICE – National Institute for Health and Clinical Excellence

NSC – National Screening Committee

PLCO – Prostate Lung Colorectal and Ovarian Trial

PPV – Positive Predictive Value

PSO – Prophylactic Salpingo-oophorectomy

ROC – Risk of Cancer

SIGN – Scottish Intercollegiate Guidelines Network

TVS – Transvaginal Ultrasound

UKCTOCS – United Kingdom Collaborative Trial of Ovarian Cancer Screening

UKFOCSS – United Kingdom Familial Ovarian Cancer Screening Study

1 BACKGROUND

1.1 What is Cancer?

Cancer is broadly characterised by unregulated cell growth leading to invasion of surrounding tissues and occasionally with metastatic spread (King, 2000). Any growth of one or, occasionally, a few cell types at the expense of others that disrupt the normal interrelationships between different cell types and their extracellular matrix, is cancer. The acquisition of invasive properties is what distinguishes malignant cells from benign cells, whilst the primary cause of clinical problems and death is due to metastatic disease. At a molecular level, animal and cell biological experiments have identified DNA (deoxyribonucleic acid) sequences and proteins directly relevant to human cancers. However, no single model explains the pathogenesis of all human cancers.

The terms cancer, tumour and neoplasm are often used in an interchangeable way often causing confusion. It is important to understand that neoplasm means new growth without qualifying the nature of that growth whereas tumour can be applied to both benign and malignant growths. A clinician would consider an increased cell mass on its own to be a benign, easily controllable growth and not cancer. An abnormal mass of tissue that is uncontrolled and progressive resulting from excessive cell division is a process of tumorigenesis. Tumorigenesis is considered a compilation of complex genetic diseases that regulate cell growth, proliferation and differentiation (King, 2000). Benign growths are sometimes, but not always precursors of malignant growths. Colon and thyroid cancer are examples where benign growths turn malignant, whereas benign prostate and breast growths are not precursors of malignant growths. Table 1.1 provides distinctions between benign and malignant growths.

Table 1.1 Comparison of benign and malignant growths (King, 2000)

Feature	Benign	Malignant
Edges	Encapsulated	Irregular
Metastasis	No	Yes
Invasion	No	Yes
Comparison to normal	Good	Variable, often none
Growth rate	Low	High
Nuclei	Normal	Variable, irregular
Life-threatening	Unusual	Usual

Diagnostic imaging is the routine method of detecting a cancer and staging of disease, with histopathology characterisation following an excision or biopsy. Diagnosis of cancer not only relies on the appearance of the cells but also on the tissue architecture as summarised in Figure 1.1.

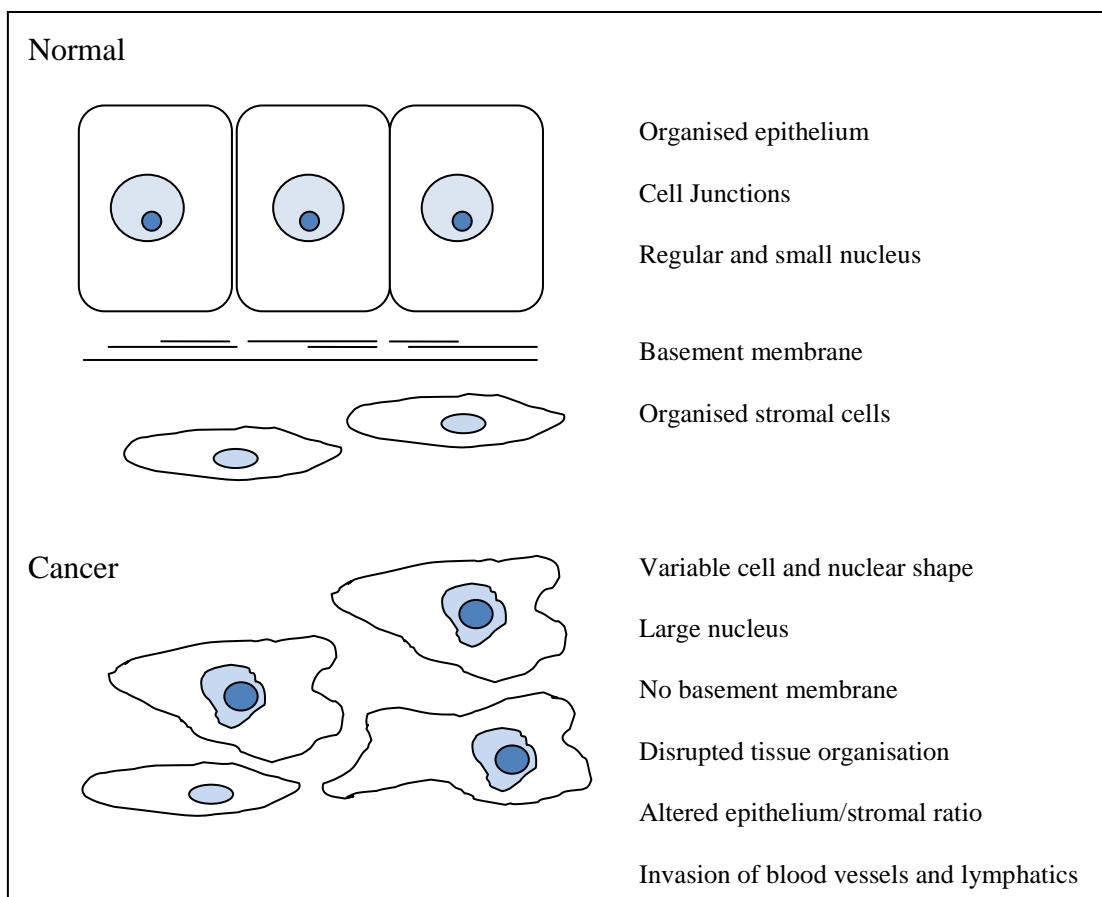


Figure 1.1 Features of normal and cancer glandular epithelium (King, 2000)

Cancers are described according to their cell origin and the tissue in which they arise:

Epithelium (carcinoma)

- Glandular eg. Prostate: adenocarcinoma
- Squamous eg. Cervix: carcinoma

Mesenchyme (sarcoma)

- Smooth muscle: leiomyosarcoma – benign hyperproliferation is called a leiomyoma (fibroid).
- Bone: Osteosarcoma
- Fat cells: Liposarcoma – benign hyperproliferation is called a lipoma.

Nervous system

- Eye: retinoblastoma
- Astrocytes: astrocytoma

White blood cells (leukaemia)

- Myeloid cells: myelocytic leukaemia
- Lymphocytes: lymphocytic leukaemia
- Lymphoma: solid tumour derived from B and T lymphocytes

Carcinogenesis involves a series of changes that are reflected in an increasing departure from normal morphology with uncontrolled and often rapid proliferation of cells leading to malignant tumours. Pathology helps to define boundaries in this sequence of events, but as changes continue to occur after a cancer has formed, cell characterisation also has a role to play as a prognostic tool to determine the likely course of the disease. Pathology can also be used for monitoring the completeness of surgery as cancers can have ill-defined margins, microscopic analysis of an excised lump can tell whether or not cancer cells occur at its edges and provide evidence as to efficiency of removal.

1.2 Ovarian Cancer

It is important to realise that ovarian cancer is not a single disease as there are many types, each with their own characteristics and behaviour from an assortment of different cell types. Its pathogenesis is still indefinite but it is possible to catalogue tumours into three groups benign, intermediate and malignant. Surface epithelial carcinomas are the most common type of ovarian cancer with Figure 1.2 providing identification of a healthy ovary structure and stages of ovulation.

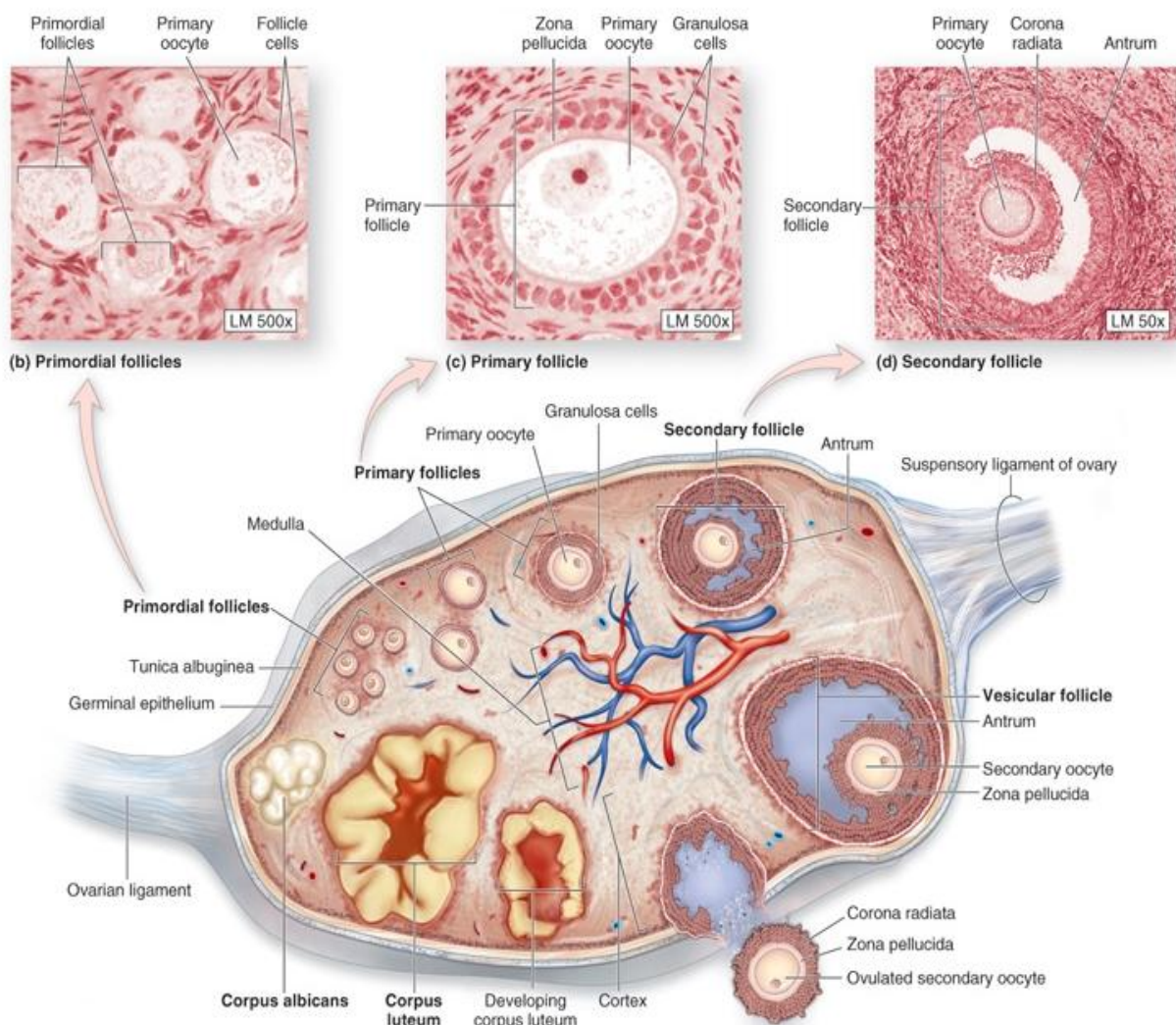


Figure 1.2 Main structure of a healthy ovary and ovulation (Herbrandson, 2005)

1.2.1 Classification and Stages of Disease

Ovarian cancer is classified according to the histology of the tumour. Lesions differ significantly in clinical features, management and prognosis. There are three different types of ovarian cancer. The type is determined by the location in the ovary where the cancer develops (Mougeot et al, 2006):

Epithelial

Cancer that develops on the surface of the ovary

85-95% of all ovarian cancers

Serous

Mucinous

Endometrioid

Clear cell

Papillary serous

Brenner cell

Undifferentiated adenocarcinomas and sarcomas

Germ Cell

Cancer that develops in the supportive tissue of the ovary

5-8% of all ovarian cancers

Teratomas

Mature teratomas

Immature teratomas

Struma ovarii

Carcinoid

Dysgerminoma

Embryonal cell carcinoma

Endodermal sinus tumour

Primary choriocarcinoma

Gonadoblastoma

Specialised stromal cell cancers

Cancer that develops in an egg cell produced in the ovary

Most typically occurs in young girls / women

<5% of all ovarian cancers

Granulosa cell tumour

Theca cell tumour

Sertoli-leydig cell tumour

Hilar cell tumour

Epithelial ovarian cancer is staged using the International Federation of Gynaecology and Obstetrics (FIGO) stage at initial presentation as shown in Table 1.2. In the first stage of the disease the tumour is concentrated only in the ovaries, Stage II the growth is limited to the ovaries with pelvic extensions, Stage III the growth involves the ovaries with peritoneal implants outside the pelvis and finally, Stage IV the growth involves the ovaries with distant metastases.

Table 1.2 FIGO Staging System for Ovarian Cancer (International Federation of Gynaecology and Obstetrics, 2010)

Stage	Definition
I	Growth Limited to the Ovaries
IA	Limited to one ovary; no ascites; no tumour on external surfaces; capsule intact.
IB	Limited to both ovaries; no ascites; no tumour on external surfaces, capsule intact.
IC	Tumour either stage IA of IB but with tumour on the surface of one or both ovaries, or with capsule ruptured, or with ascites containing malignant cells, or with positive peritoneal washings.
II	Growth involving one or both ovaries with pelvic extension
IIA	Extension or metastases to the uterus or tubes
IIB	Extension to other pelvic tissues
IIC	Tumour either stage IIA or IIB but with tumour on the surface of one or both ovaries, or with capsule ruptured, or with ascites containing malignant cells, or with positive peritoneal washings.
III	Tumour involving one or both ovaries with peritoneal implants outside the pelvis or positive retroperitoneal or inguinal nodes; superficial liver metastases; tumour limited to the true pelvis but with histologically verified malignant extension to small bowel or omentum.
IIIA	Tumour grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces.
IIIB	Tumour of one or both ovaries; histologically confirmed implants of abdominal peritoneal surfaces, none exceeding 2cm in diameter, nodes negative.
IIIC	Abdominal implants greater than 2cm in diameter or positive retroperitoneal or inguinal nodes.
IV	Growth involving one or both ovaries with distant metastases; if pleural effusion is present, there must be positive cytological test results to allot a case to Stage IV; parenchymal liver metastases equals Stage IV.

The stage of disease is determined through diagnostic imaging and at surgery through examination of the primary tumour, assessing lymph node involvement and whether the cancer has metastasised to other parts of the body. The prognosis based on the type of tumour, stage of cancer and patient's overall health means a health professional can recommend the most effective treatment options (International Federation of Gynaecology and Obstetrics, 2010).

1.2.2 Incidence, Mortality and Symptoms

In the UK ovarian cancer is the fifth most common cancer in females and after uterine cancer, the second most common gynaecological cancer. There were 6,596 new cases diagnosed in the UK in 2006 and it has been estimated, based on incidence and mortality data from 2001-2005 (Cancer Research UK, 2009), that the lifetime risk of developing ovarian cancer is 1 in 50 for women in the UK. Over 80% of ovarian cancer cases are diagnosed in women over 50yrs of age with a steep increase in incidence in postmenopausal women (aged 55yrs and over), as seen in Figure 1.3.

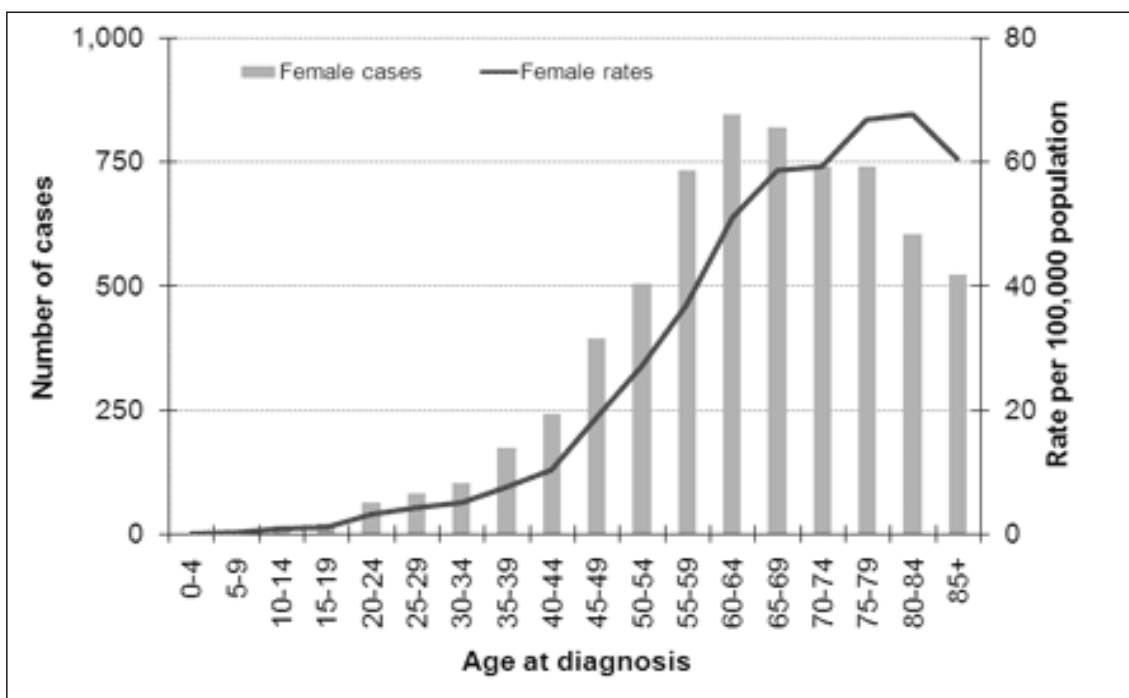


Figure 1.3 Number of new cases and age-specific incidence rates in UK, 2006 (Cancer Research UK, 2009)

Ovarian cancer accounts for more deaths than all the other gynaecological cancers combined. 4,317 UK women died from ovarian cancer in 2007, accounting for around 6% of all female deaths from cancer (Cancer Research UK, 2009). The number of deaths and the rates for the constituent countries of the UK are shown below in Table 1.3.

Table 1.3 Number of deaths and mortality rates of ovarian cancer (Cancer Research UK, 2009)

	England	Wales	Scotland	N.Ireland	UK
Deaths					
Females	3,554	255	392	116	4,317
Crude rate per 100,000 population					
Females	13.7	16.7	14.7	12.9	13.9
Age-Standardised rate (European) per 100,000 population					
Females	9.7	11.0	10.1	10.5	9.8

The majority of women who develop ovarian cancer have few symptoms until the cancer has spread and by then treatment is more difficult. It used to be believed that ovarian cancer had no symptoms at all, however, the symptoms experienced are vague and difficult to recognise particularly in the early stages of the disease. Symptoms known to be related with the disease include (Rufford et al., 2007):

- Pelvic pain / bloating
- Pain during intercourse
- Urinary urgency or frequency of micturition
- Nausea / weight loss
- Constipation / irregular periods
- Loss of appetite / tiredness

Research has shown that the advanced stage at diagnosis of ovarian cancer is thought to be directly responsible for the high case fatality ratio, as early-stage disease (FIGO Stage I) is associated with a five-year survival of over 85% as shown in Figure 1.4. For women diagnosed with distant metastases (FIGO Stage IV) the five-year survival rate is around 15%.

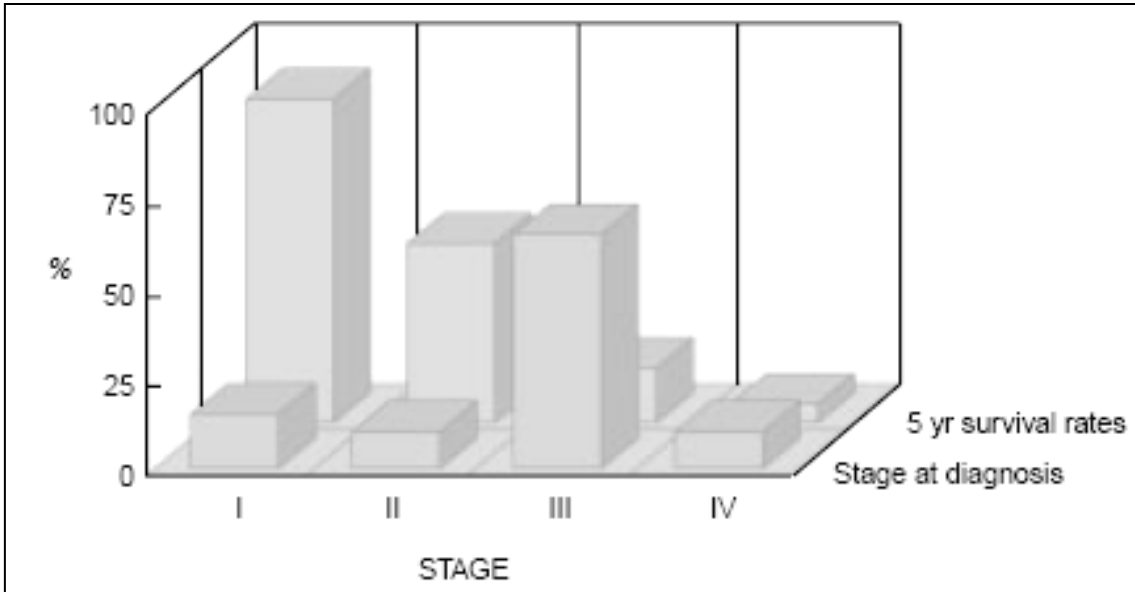


Figure 1.4 Correlation of Stage and 5-year survival in ovarian cancer (Menon and Jacobs, 2002)

Five-year survival rates are also related to the age at which the disease is diagnosed with women under the age of 50 years likely to be diagnosed with local disease and women over 65 years are more likely to have distant metastases. Figure 1.5 demonstrates the difference from women aged 15-39 having a five-year survival rate of nearly 70% to that of 12% survival if diagnosed between 80-89 years of age.

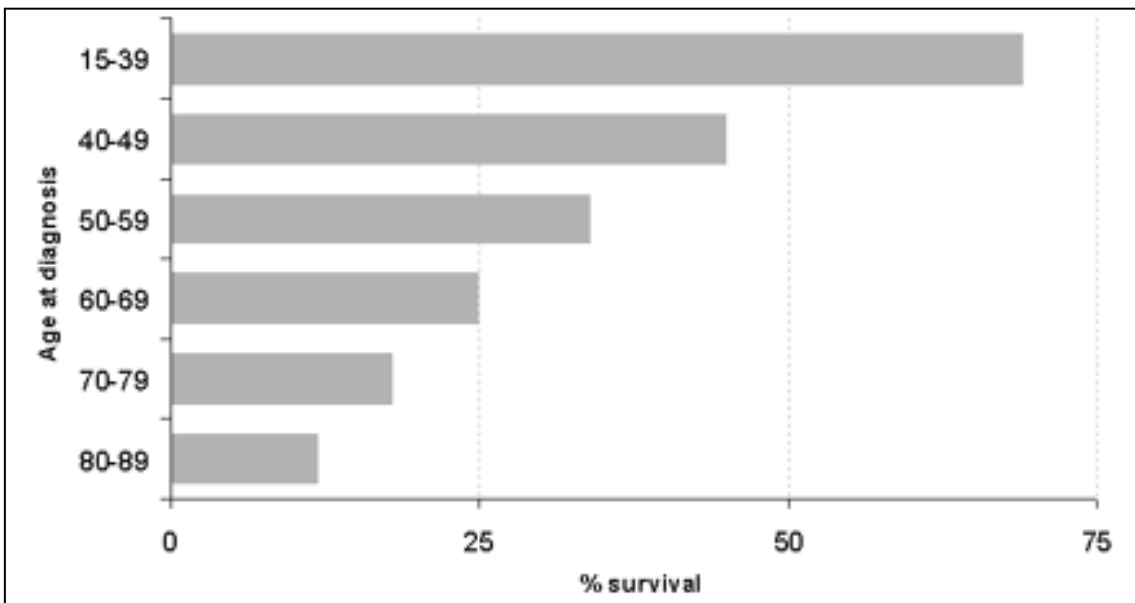


Figure 1.5 Age at diagnosis and five-year survival rates (Cancer Research UK, 2009)

1.2.3 Familial and Sporadic Ovarian Cancer

Around 5 – 10% of all cases of ovarian cancer are the result of an inherited gene or genes. There are three types of family history of ovarian cancer (Sekine, 2001):

- Hereditary site-specific
- Lynch syndrome II (MSH2 and MLH1)
- Hereditary breast / ovarian carcinoma (BRCA1 and BRCA2 tumour suppressor genes).

Breast cancer genes (BRCA) are tumour suppressor genes that inhibit the growth of cancer cells. Mutations of BRCA1 or BRCA2 genes express proteins that have different functions in ovarian carcinogenesis. Nearly all site specific hereditary ovarian carcinoma is a result of BRCA1 and BRCA2 mutations. BRCA1 is implicated in up to 90% of breast-ovarian cancer families with two or more cases of early onset breast cancer and two or more cases of ovarian carcinoma. BRCA2 mutations account for fewer than 10% of cases of hereditary breast-ovarian carcinoma. The risk of developing ovarian cancer to age 70 in those BRCA1 carriers is up to 50%. An overview of the genes implicated in hereditary ovarian cancer is provided in Table 1.4.

Table 1.4 Brief overview of genes implicated in hereditary ovarian cancer (Kasprzak et al, 1999)

Gene (syndrome name)	% of inherited cases associated with gene mutation	Type of ovarian cancer	Risk of ovarian cancer to age 70 (%)	Other features of syndrome
BRCA1 (hereditary breast and ovarian cancer)	75	Serous ovarian carcinoma	20-50	Cancer of breast, fallopian tube
BRCA2 (hereditary breast and ovarian cancer)	10	Serous ovarian carcinoma	10-30	Cancer of breast, prostate, pancreas, head and neck
MMR genes (hereditary non-polyposis colorectal cancer)	5-10	Ovarian carcinoma – all types	<10	Cancer of colorectum, endometrium, stomach, urinary tract and small bowel
STK11 (Peutz-Jeghers)	<1	Granulosa cell tumour	<2	Mucosal freckles, gastrointestinal polyps and breast cancer
PTEN (Cowden disease)	<1	Ovarian carcinoma	<2	Mucocutaneous lesions, breast cancer, thyroid cancer
PTC (Gorlin syndrome)	<1	Ovarian fibrosarcoma	<1	Basal cell carcinoma
EXT1, EXT2, EXT3 (Ollier's disease)	<1	Granulosa cell tumour	<1	Osteochondromatosis

Kasprzak (1999) found that hereditary forms of ovarian carcinoma occur at an earlier age than sporadic disease, with a mean age of five years younger onset in hereditary ovarian carcinoma found. Sporadic ovarian cancer and hereditary ovarian cancer are not significantly different as shown in Table 1.5. Kasprzak (1999) also found similar prognosis in hereditary and sporadic ovarian carcinoma.

Table 1.5 Main differences in BRCA mutation between sporadic and inherited ovarian cancer (Wong, 2003)

Sporadic Ovarian Cancer	Inherited Ovarian Cancer
May result also in loss of BRCA functions through inactivation of these genes.	Ovarian cancers arising from BRCA1 or BRCA2 mutations positive families are more likely to be invasive high grade and of serous histological type.
Mutations are rare	
Loss of BRCA function	

No strong environmental risk factors are known, and after age, the most important risk factor is a family history of the disease. However, factors known to be associated with the development of epithelial ovarian cancer include (Sekine, 2001):

- Reproductive Factors**
 - Early menarche
 - Late menopause
 - Infertility, null parity
- Demographics**
 - White or European
 - Jewish descent
 - Residence in industrialised nation (except Japan)
- Diet**
 - High fat intake
 - High coffee intake
 - Low fibre
 - Low vitamin A
- Environmental exposure**
 - Perineal talc use
 - Asbestos radiation
 - Viral infection

1.3 Detection and Diagnosis of Ovarian Cancer

Ovarian cancer may be suspected if any of the previously described symptoms are experienced or a pelvic mass is felt by a clinician. Typically in the NHS setting there are two main methods of investigating ovarian pathology with the aim of detecting ovarian cancer, an imaging modality and serum based biomarker analysis.

1.3.1 Imaging Diagnosis

Several modalities exist capable of imaging normal and abnormal ovaries, including ultrasound, computerised tomography (CT), magnetic resonance imaging (MRI), radioimmunoscinotography and positron-emission tomography scanning. At present ultrasound is widely available for diagnostic use as a non-ionising and cost effective imaging modality. Particularly through the introduction of transvaginal ultrasound (TVS), image quality has greatly improved with higher frequencies used during scanning (Van Nagell et al, 2007). Ultrasound examinations are easily referred for by general practitioners and gynaecologists as a first-line imaging modality for suspected gynaecological pathology. The size, appearance and vascularity of the ovary can be assessed without the need of intravenous contrast as used in CT and MRI. Normal physiological events can be observed, particularly in premenopausal women during active ovarian follicle formation. Ultrasound detects both benign and malignant lesions and therefore, appearances and criteria for diagnosis of an abnormal ovary can therefore, vary with menopausal status and age. Currently standardised ultrasound criteria for distinguishing between benign and malignant conditions has not been universally accepted (DePriest and DeSimone, 2003); however, through the morphological characteristics of the ovary being imaged, many investigators have developed diagnostic criteria scoring systems to systematically assess the risk of malignancy. Commonly used complex ovarian morphology classification criteria

include measurements of the ovary, echogenicity of solid masses, cyst wall thickness, presence of septae or papillary growths, with an example of this shown in Appendix G. Figures 1.6 and 1.7 provide ultrasound examples of normal and abnormal appearing ovaries on transvaginal scanning. Follicular detail in the normal appearing ovary can be seen in Figure 1.6, whilst in Figure 1.7 there is evidence of a large complex part-solid / part-cystic tumour with abnormal vascularity.

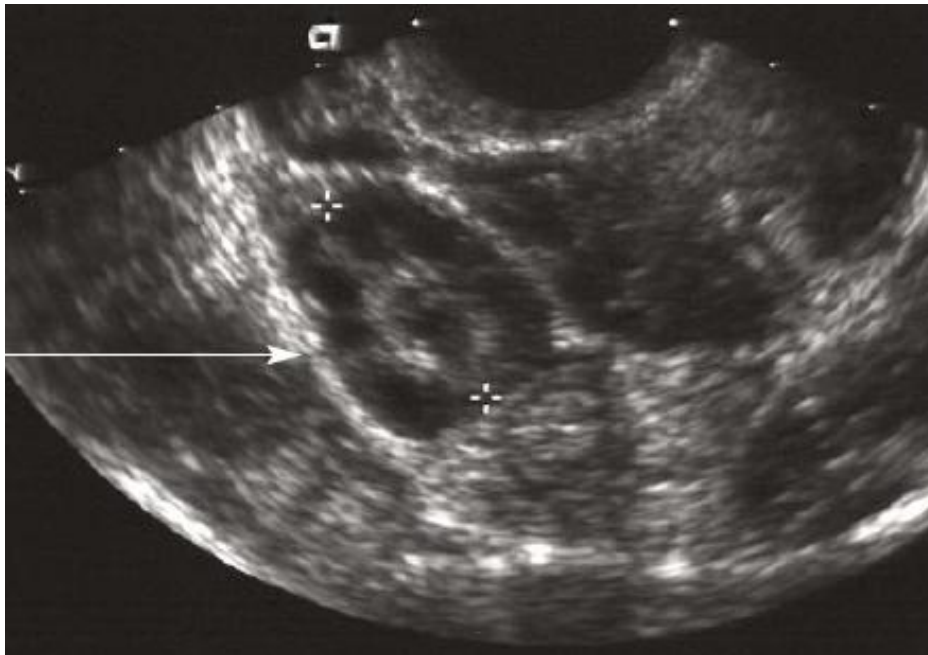


Figure 1.6 Ultrasound image of a normal appearing ovary (Harris, 2002)

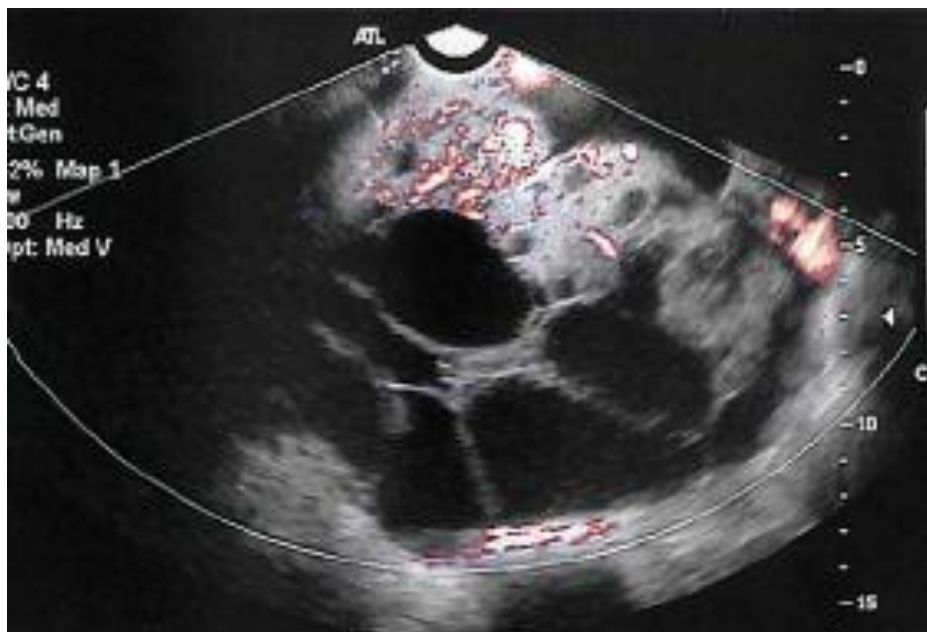


Figure 1.7 Ultrasound image of a complex adnexal mass with multiple septations, solid components and abnormal vascularity suggesting malignancy (Fishman et al, 2005)

Colour Doppler imaging is a recently developed tool used in addition to grey-scale ultrasound that enables blood flow imaging in vessels and a trace of the pattern of flow. This technique can provide additional important information regarding the risk of malignancy as ovarian neoplasm angiogenesis leads to the formation of abnormal vessels with a lower impedance to blood flow. This second-line technique can improve the specificity of ultrasound by enhancing the ability to discriminate benign from malignant ovarian pathology (Fishman et al, 2005). Figure 1.8 provides a transvaginal scan image of a solid ovarian mass with low impedance flow using colour Doppler imaging, which is a clear cell carcinoma of the ovary.

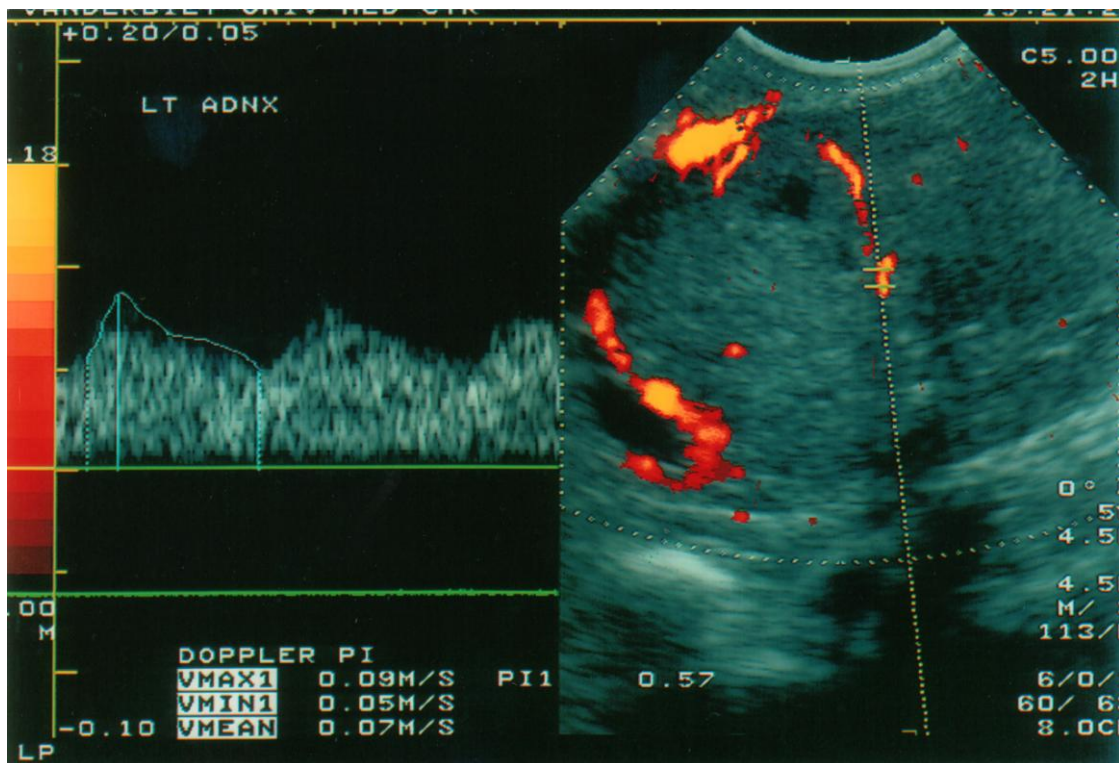


Figure 1.8 Transvaginal scan of a solid ovarian mass with low impedance flow (Fleischer, 2009)

Following an abnormal pelvic tumour detected by ultrasound a CT or MRI is routinely performed to stage the disease and / or to investigate the tumour further prior to biopsy or surgical removal.

1.3.2 Biomarkers

An ideal tumour marker would change in concentration with the amount of malignant tissue present and be specific for the cancer for which it is testing, without being present in any other conditions. A marker can be a protein, gene, proteomic pattern, a cell type or an abnormality. Tumour markers can be detected in elevated amounts in serum (blood or plasma), body tissues and urine (Gogoi et al, 2006).

Ovarian tumours are known to produce a number of cell-surface antigens and serum proteins that can be measured through a blood test and laboratory assay of the serum. The most common serum based biomarker for ovarian cancer detection is cancer antigen 125 (CA125). This tumour marker is a chemical that is secreted by cancer cells and circulates in the blood stream. Women with ovarian cancer tend to have higher levels of CA125 in their blood, compared to women who do not have ovarian cancer. However, CA125 has known limitations with elevated levels found in 61-96% of routinely diagnosed epithelial ovarian cancers and in 29-75% of cancers diagnosed at the earliest stage (Menon & Jacobs, 2002). The specificity of CA125 is also often limited with elevated levels found in other cancers and benign diseases as outlined in Table 1.6.

Table 1.6 Causes of elevated CA125 levels (Menon and Jacobs, 2002)

Cancers	Benign Disease
Ovarian	Benign ovarian disease
Endometrial	Uterine leiomyomas
Cervical	Endometriosis
Lung	Pregnancy
Breast	Menstruation
Colorectal	Pelvic inflammatory disease
Pancreatic	Pancreatitis
	Hepatitis
	Hypothyroidism

It is clear from Menon & Jacobs (2002) that premenopausal women may often have elevated levels of CA125 due to benign ovarian disease, fibroids, endometriosis and pelvic inflammatory disease. Therefore, to summarise what CA125 offers:

- Around 61-96% of all women with ovarian cancer will have elevated CA125.
- Around 29-75% of all women with early stage ovarian cancer will have elevated CA125.
- Premenopausal women may also have elevated CA125 due to other benign causes.

Despite these limitations CA125 is the most common and routinely used biomarker in clinical practice for the detection of ovarian cancer. Extensive research is ongoing for new and clinically more useful biomarkers for early ovarian cancer detection (Gogoi et al, 2006).

1.4 Screening

When investigating the impact of screening it is important to understand what certain terminology means. The UK National Screening Committee (2009) defines screening as “a process of identifying apparently healthy people who may be at increased risk of a disease or condition. They can then be offered information, further tests and appropriate treatment to reduce their risk and/or any complications arising from the disease or condition.”

In order for screening to have the potential to save lives and improve quality of life, early diagnosis of serious conditions is paramount. Diagnosis is defined as the process of identifying a medical condition or disease by its signs, symptoms, and from the results of various diagnostic procedures (Harris, 2002). Several criteria that must be satisfied in the design and clinical application of an early-detection programme are described by Teneriello and Park (1995):

- The cancer has an identifiable phase of early invasive disease, such that the outcome of patients is improved if the disease is detected at an early stage.
- The disease itself must pose a significant medical threat to justify the expense and effort of a population-based screening programme.
- The testing modality should be sensitive enough to detect small-volume disease states, cost efficient, widely available for use and relatively easy to perform.
- Specificity must be maintained so that individuals without disease can be accurately identified.

1.4.1 Sensitivity and Specificity

Establishing the benefits and harms of a screening test is related to its ability to distinguish between those who have a certain condition and those who do not. This can be expressed as the sensitivity and specificity of the test. When the test is undertaken, four outcomes are possible in the context of cancer screening:

1. True-positive(a): the test correctly identifies those people with cancer.
2. False-positive(b): the test is positive when in fact the person does not have cancer.
3. False-negative(c): the test is negative when in fact the person has cancer.
4. True-negative(d): the test is negative and the person does not have cancer.

Table 1.7 provides an overview of calculating the performance of a screening test. A high sensitivity and specificity of a screening test is achieved through discriminating well between diseased and healthy participants.

Table 1.7 Calculating the performance of a screening test (Bell et al., 1998)

	Disease		
	Present	Absent	
Test: Positive	a	b	a + b
Negative	c	d	c + d
	a + c	b + d	a + b + c + d
Sensitivity – proportion of those with the disease testing positive $a / (a+c)$			
Specificity – proportion of those without the disease testing negative $d / (b+d)$			

The **Positive Predictive Value (PPV)** is the percentage of patients with a positive result who actually have the condition. The PPV can be calculated by:

$$\frac{\text{Number of true positives}}{\text{Number of true positives} + \text{Number of false positives}}$$

1.4.2 Ovarian Cancer Screening

The current position of the UK National Screening Committee (2009) is that ovarian cancer screening should not be offered except in the context of the Medical Research Council randomised controlled trial. This policy is due to be reviewed in 2010/11 following the report of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). The aim of ovarian cancer screening is to reduce mortality and morbidity from ovarian cancer by detecting it at an early stage when treatment may be more effective. Two screening tests have evolved through years of research for the early detection of ovarian cancer (Menon and Jacobs, 2002):

1. Detection of ovarian morphological abnormalities by transvaginal ultrasound.
2. Measurement of serum tumour markers produced by, or in response to, ovarian cancer.

Based on these two screening tests, three ovarian cancer screening strategies have emerged as shown in Figure 1.9.

	Primary Test		Secondary Test
Multimodal Strategy	CA125	If primary test is abnormal	TVS + CA125
Ultrasound Strategy	TVS		Repeat TVS
Combined Strategy	CA125 + TVS		Repeat TVS + CA125 or TVS or CA125 alone

Figure 1.9 Screening Strategies for Ovarian Cancer (Menon and Jacobs, 2002)

The detection of ovarian cancer regardless of screening strategy must aim for a high sensitivity ($\geq 90\%$) and an acceptable false-positive rate. As shown in Figure 1.10, the data from prospective studies of ovarian cancer screening in the general population suggest that ultrasound offers greater sensitivity as a first-line test and multimodal screening (MM) particularly using a risk of cancer algorithm (ROC), has superior specificity and positive predictive values.

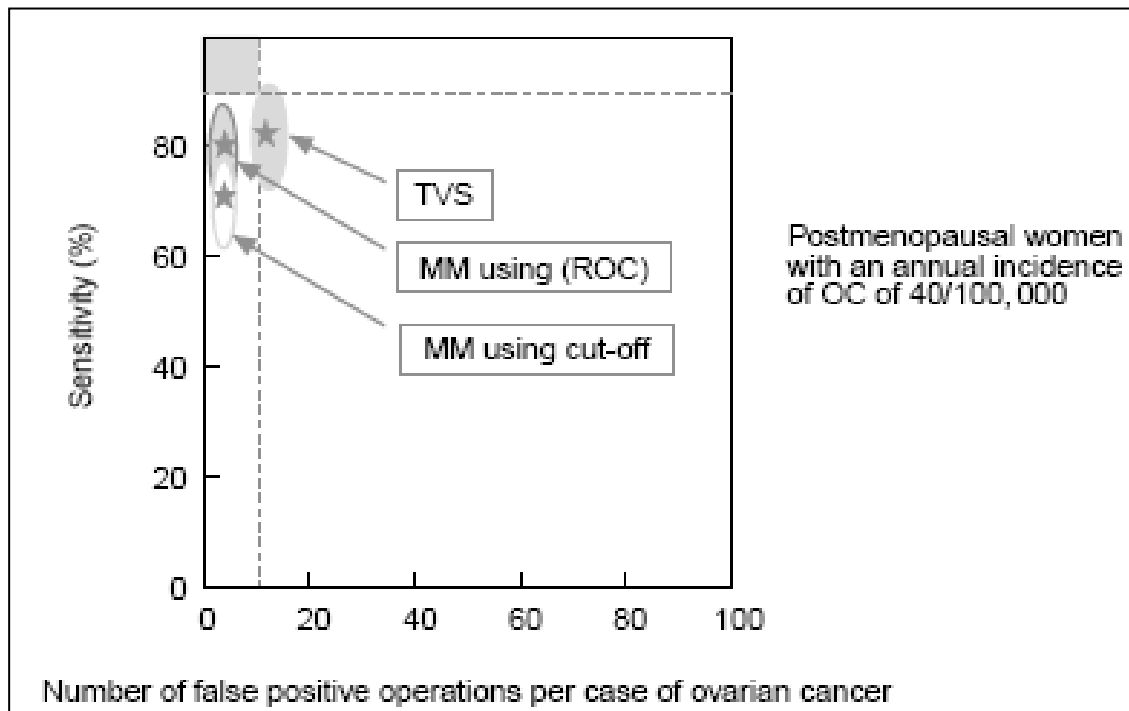


Figure 1.10 Performance characteristics of ovarian cancer screening strategies (Menon and Jacobs, 2002)

1.4.3 Screening Population

Women in the United Kingdom who are determined to be at high risk of developing ovarian cancer and who are unsuitable or unwilling to undergo prophylactic bilateral salpingo-oophorectomy are currently being offered annual screening for ovarian cancer through the UK Familial Ovarian Cancer Screening Study (UKFOCSS) led by the University College London. There are two main groups of women who are at increased risk of developing ovarian cancer. Firstly, women over the age of 50 with no significant family history of ovarian cancer and secondly, women with a strong family history of breast and/or ovarian cancer. The median age for diagnosis of ovarian cancer in women over the age of 50 with no significant family history of the disease is 59, with a lifetime risk of developing the cancer being 1.3% in this population. Those with a strong family history of the disease will usually have a lifetime risk of developing ovarian cancer of >15% with a median age for diagnosis being 51.9 years (Drescher et al., 2004). Menon and Jacobs (2002) recommend screening women at increased risk from the age of 35, even though screening premenopausal women is associated with an increase in false-positive CA125 levels and benign ultrasound abnormalities.

1.4.4 Treatment

Treatment options available vary with the type of ovarian cancer, stage at diagnosis and patient's general health. Almost all women with ovarian cancer will need surgery and the amount required will vary with stage and type of ovarian cancer. Women with borderline tumours or low-grade FIGO Stage I disease may need no further treatment, although some may have radiotherapy to the pelvic area. Chemotherapy is used in most other cases. Despite aggressive treatment 70% of patients who present initially with a FIGO Stage III or IV disease, at best will have a five year survival rate in the range of 15-25% (Menon and Jacobs, 2002). Chemotherapy is often used in Stage IV disease prior to surgery to attempt to reduce the size of the tumour or if surgery is not appropriate, to relieve symptoms.

1.4.5 Milton Keynes Hospital NHS Foundation Trust

Approximately 228,400 people live and over 130,000 people work in Milton Keynes. In 2007 Milton Keynes Hospital became a Foundation Trust, meaning that its patients, the public and staff can now be more responsive to the needs and wishes of people living in Milton Keynes and the surrounding areas. Services offered by the Trust include all medical, surgical and child health emergency admissions with increasing specialist services, including cancer, cardiology, oral surgery and neonatal care. Over 300,000 people every year are provided a broad range of general medical and surgical services, including accident and emergency. Screening currently offered at Milton Keynes Hospital includes breast, cervical and bowel cancer, fetal anomaly, infectious diseases in pregnancy and newborn hearing. The Department of Health and South Central Strategic Health Authority provide strategic direction for this medium sized hospital.

1.5 Aims and Objectives

The aim of this project is to investigate the feasibility of an NHS based ovarian cancer screening programme with regard to current clinical evidence, resources required, costs involved and implications for a local NHS Foundation Trust. In order to achieve this aim a systematic literature search will be performed analysing variations in methods used for screening and inclusion criteria adhered to. A retrospective study of ovarian cancer cases diagnosed at Milton Keynes Hospital will provide an overview of the clinical problem that ovarian cancer presents in its stage at diagnosis and symptoms experienced by women. Confirmed and suspected cases of ovarian cancer at Milton Keynes Hospital will be analysed with key findings and cases documented where initial imaging was unable to confirm benign ovarian lesions. Finally, through exploring recommended NHS costings, the financial impact of offering ovarian cancer screening will be predicted at a local level based on literature reviewed and findings from the retrospective study of confirmed ovarian cancer cases at Milton Keynes Hospital.

The objectives of this thesis have been listed using their chapter headings:

Chapter 2 – Screening for Ovarian Cancer: A Systematic Literature Review

1. Perform a systematic literature review of available publications investigating ovarian cancer screening and critically appraise studies included.
2. Compare ovarian cancer screening with currently offered cancer-screening programmes.
3. Investigate variations in screening methods used.
4. Investigate variations in high risk of ovarian cancer classification / study inclusion criteria.
5. Investigate psychosocial constructs associated with participants involved in ovarian cancer screening studies.

Chapter 3 – Retrospective Study of Confirmed and Suspected Ovarian Cancer Cases

6. Perform a retrospective study of patients diagnosed with ovarian cancer at Milton Keynes Hospital to establish stage at diagnosis, age and family history of the disease.
7. Investigate the role and diagnostic accuracy of imaging when suspecting ovarian cancer to establish how many cases with suspected malignancy through imaging alone resulted in benign pathology.

Chapter 4 – Cost Analysis of Ovarian Cancer Screening

8. Investigate NHS based cancer screening programme costs.
9. Provide a proposed cost analysis of NHS implemented ovarian cancer screening.
10. Incorporate experience from a current ovarian cancer screening study.
11. Investigate the impact on Milton Keynes Hospital in offering an ovarian cancer-screening programme.

1.6 Thesis Methodology

To investigate the impact of NHS based ovarian cancer screening several research methods have been used in order to provide evidence based conclusions and justified recommendations. As NHS based ovarian cancer screening is not currently recommended by the UK National Screening Committee a systematic literature review has been performed of published studies investigating ovarian cancer screening with variations in methods used analysed. A systematic literature review was chosen as this research method provides a comprehensive appraisal of large quantities of research, which as part of the systematic process is subject to a critical appraisal meaning evidence that is of an inadequate quality is excluded from further review. The literature review provides recent high quality ovarian cancer screening studies and an overview of variations in screening methods and inclusion criteria used.

To establish the impact of NHS based ovarian cancer screening at a local level in Milton Keynes Hospital NHS Foundation Trust, a retrospective study of patients diagnosed with ovarian cancer at Milton Keynes Hospital was performed. This study was firstly, aimed to provide up to date information into the clinical problem that ovarian cancer presents in its stage at diagnosis, age and the number of women diagnosed with the disease in a local Hospital. Secondly, as ovarian cancer diagnosis involves an imaging modality a further retrospective study investigated the diagnostic accuracy of ovarian pathology detection and possible diagnostic limitations of lesion characterisation. Finally, through performing the systematic literature review and local retrospective studies, a cost analysis based on current NHS recommendations has been provided with scenarios based on current UK screening studies and literature reviewed. The impact at a local level and cost associated with ovarian cancer screening have been explored should implementation within the NHS begin.

2 SCREENING FOR OVARIAN **CANCER: A SYSTEMATIC** **LITERATURE REVIEW**

2.1 Benefit of Systematic Literature Reviews

Detection of early serious conditions provides the opportunity to start effective treatment or intervention before the disease or condition progresses. Women who have screen detected ovarian cancer have the potential for their outcome to be improved with effective treatment, prior to presenting with symptoms. The National Health Service has a number of screening programmes in place proving successful in the early identification of diseases and conditions including breast cancer, bowel cancer, cervical cancer, cystic fibrosis, sickle cell anaemia, Down's syndrome and Chlamydia. The National Screening Committee (NSC) was created in 1996 to assess proposed new screening programmes and advise government health ministers on all aspects of screening policy. This advice is often based on Health Technology Assessment (HTA) reports, part of the National Institute for Health Research, providing independent scientific research. The HTA programme aims to ensure that high quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and work in the NHS (National Institute for Health Research, 2010). As ovarian cancer screening is not currently recommended by the NSC except in the context of the Medical Research Council randomised control trial, a systematic literature review evaluating ovarian cancer screening would be of interest in providing a current overview of screening methods used by high quality studies and what sensitivity and specificity levels were able to be achieved.

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation responsible for providing national guidance on promoting good health and preventing and treating ill health. NICE guidance aims to ensure that the promotion of good health and patient care in local health communities is in line with the best available evidence of effectiveness and cost effectiveness. Therefore, a systematic literature review investigating ovarian cancer screening would be of interest to NICE as the evidence provided could lead to patient benefit through improved patient outcomes and efficient use of NHS resources through analysis of screening studies performed.

2.1.1 Characteristics of Systematic Reviews

There is a growing requirement that clinical practice is based on evidence due to the vast array of health care literature and products available. There are therefore, difficulties in ensuring that clinicians base decisions on reliable sources of research, as often studies produce contradictory results. Systematic reviews provide a comprehensive appraisal of large quantities of research, which as part of the systematic process is subject to a critical appraisal. There are certain key characteristics of a systematic review that increase the power and decrease the bias of research findings. This is because a systematic review (Trinder and Reynolds, 2000):

- Is based on an exhaustive search for all the relevant literature.
- Uses explicit and validated criteria for excluding evidence that is of inadequate quality.
- Cites the evidence that has been excluded.
- Uses valid and explicit methods for combining data, a process called meta-analysis.

2.2 Study Design

The search for published literature involves two main electronic bibliographic databases with studies found subject to a critical appraisal as part of the systematic process. The two electronic bibliographic databases were chosen due to their extensive coverage of scientific, technical, medical and social sciences research. The **Cochrane Library** provides a collection of databases containing high-quality independent evidence to inform healthcare decision-making. Current evidence is available through sources in systematic reviews, technology assessments, economic evaluations and clinical trials. **SCOPUS** offers the world's biggest abstract and citation database covering all areas of science, technology and medicine. 36 million abstracts from over 14,000 titles across 4,000 publishers are available through this database including complete coverage of Medline titles.

The quality of the studies in this review were graded using the Scottish Intercollegiate Grading Network 2001 (SIGN) grading system as shown in Table 2.1, based on their appropriate study design assessment criteria. It was decided that in order to provide conclusions based on a high level of evidence, non-analytical or studies based on expert opinion (SIGN levels three and four) will be excluded from this literature review.

Table 2.1 Levels of Evidence (Scottish Intercollegiate Guidelines Network, 2001)

1++	High quality meta analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well conducted meta analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High quality systematic reviews of case-control or cohort studies High quality case-control or cohort studies with a very low risk of confounding bias, or chance and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Non-analytic studies e.g. case reports, case series
4	Expert opinion

2.2.1 Search Terms

The Cochrane Handbook suggests multiple search terms that describe the health condition of interest can be joined together with the Boolean ‘OR’ operator, enabling retrieval of articles containing at least one of the search terms. A second set of terms for example intervention can then be applied with the Boolean ‘AND’ operator (Higgins and Green, 2008). To optimise the results from searches performed and minimise the chance of a relevant paper being missed firstly, the terms searched were mapped to their subject headings (MeSH). This was performed using the database being searched so that suitable terms recognised by that database were used.

1. The term ovarian cancer was mapped to the subject heading *Ovarian Neoplasm*. Defined as tumours or cancer of the ovary. These neoplasms can be benign or malignant. They are classified according to the tissue of origin, such as the surface epithelium, the stromal endocrine cells, and the germ cells.
2. The term screening was mapped to the subject heading *Mass Screening*. Defined as organized periodic procedures performed on large groups of people for the purpose of detecting disease.

2.2.2 Study Dates to be Included

Through a brief literature search of published literature, an extensive systematic literature review performed by Bell et al (1998) was found with no other more recent publication investigating literature evidence of ovarian cancer screening to date. Therefore, this systematic review will exclude studies published prior to 1998 as these will have already been evaluated and thus, provide the reader with findings and recommendations based on more recent studies.

2.3 Results of Systematic Literature Review

2.3.1 Cochrane Library Database Search

The Cochrane Library Database was searched on 1st June 2008 using the term *ovarian neoplasms* (explode all trees) that produced 971 results and *mass screening* (explode all trees) that produced 3748 results. Once both search terms were combined 86 results were found, as shown in Table 2.2.

Table 2.2 Cochrane Library Database Search

Search Terms	N° of Results
#1. Ovarian Neoplasms (Explode)	971
#2. Mass Screening (Explode)	3748
#3. #1 AND #2	86

Table 2.3 demonstrates the range of results from the resources available through the Cochrane Library Database. Through reviewing the title and abstract of the 86 possible relevant studies for inclusion 71 studies were excluded. Reasons why studies were excluded consisted of the study being of no relevance to this review, study being based on expert opinion or being published in 1998 or earlier.

Table 2.3 Cochrane Library Database Search Resources

Cochrane Resources	Results
Cochrane Reviews	1
Other Reviews	8
Clinical Trials	53
Methods studies	0
Technology assessments	10
Economic evaluations	14
Cochrane Groups	0

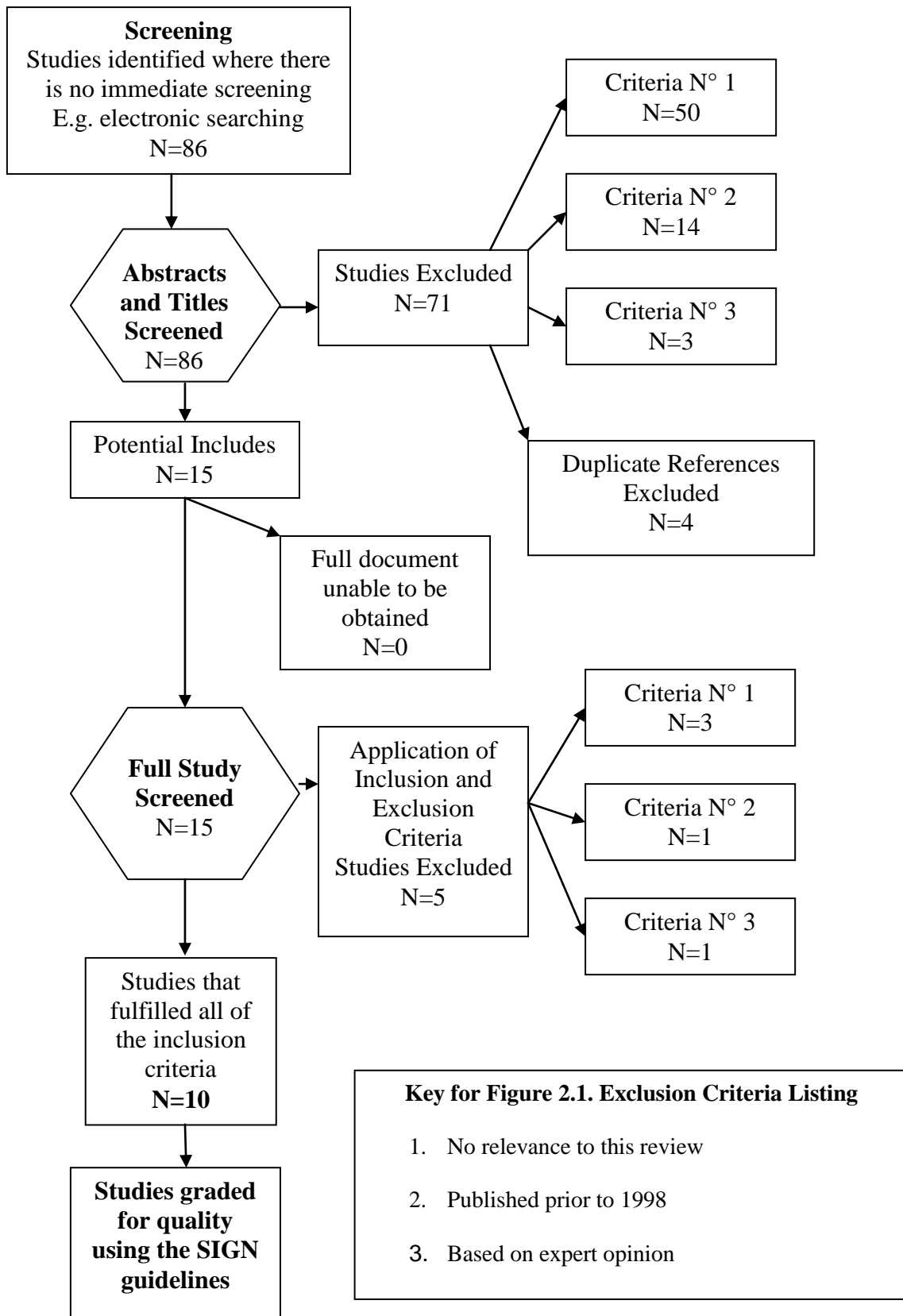
Table 2.4 summaries the reasons why studies were excluded based on their title and abstract. Therefore, through the Cochrane Library Database search 15 studies were found to be of relevance to this review and their full text screened.

Table 2.4 Excluded studies from Cochrane Library Database search

Reasons for studies being excluded	N° of Results
Study not relevant to this review	50
Study based on expert opinion	3
Study published in 1998 or earlier	14
Study already found - duplicate	4

Figure 2.1 provides an overview of the Cochrane Library Database search and what stages studies were excluded and why, resulting in the final 10 studies that were included in this review. Each study included has been reviewed with Appendix A providing an analysis of each study objectives, design, SIGN grading and key findings, with studies organised in alphabetical order of study author.

Figure 2.1 Flow Diagram of Cochrane Library Database Search



2.3.2 SCOPUS Database Search

The SCOPUS Database was searched on 1st June 2008 using the term *ovarian neoplasms* that produced 23594 results and *mass screening* that produced 47407 results.

Once both search terms were combined 527 results were found, as shown in Table 2.5.

Table 2.5 SCOPUS database search results

Search Terms	N° of Results
#1. Ovarian Neoplasms	23,594
#2. Mass Screening	47,407
#3. #1 AND #2	527

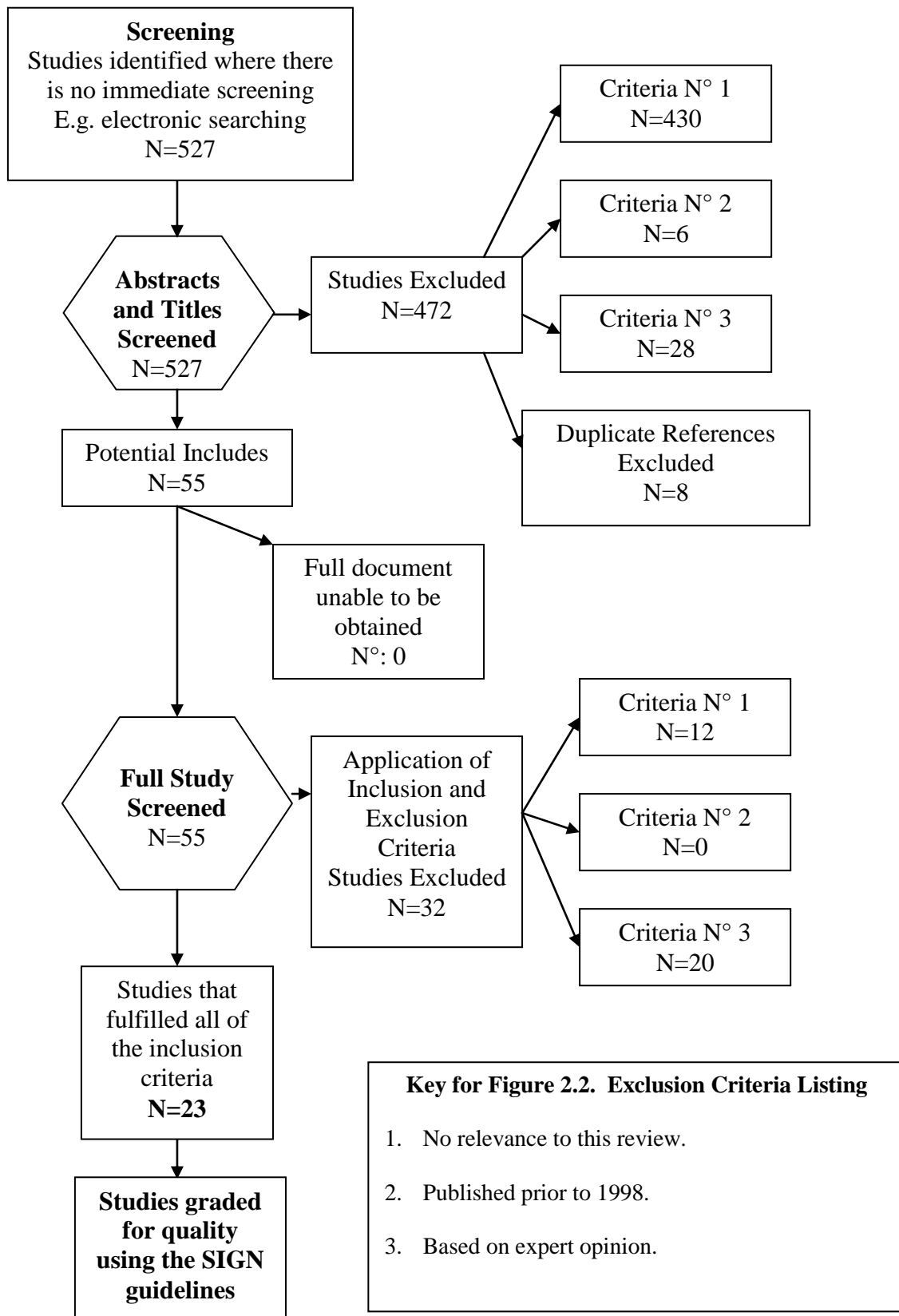
Through reviewing the title and abstract of the 527 studies found through searching SCOPUS, 55 possible studies were found to be eligible for review. Reasons for studies excluded are shown in Table 2.6.

Table 2.6 Excluded studies from SCOPUS database search

Reasons for studies being excluded	N° of Results
Study not relevant to this review	430
Study based on expert opinion	28
Study published in 1998 or earlier	6
Study already found - duplicate	8

Figure 2.2 provides an overview of the SCOPUS Database search and what stages studies were excluded and why, resulting in the final 23 studies that were included in this review. Each study included has been reviewed, with Appendix B providing an analysis of each study objectives, design, SIGN grading and key findings, with studies organised in alphabetical order of study author.

Figure 2.2 Flow Diagram of SCOPUS Database Search



2.4 Discussion of Systematic Literature Review

2.4.1 Evaluation of Included Studies in Literature Review

Through the systematic literature searches performed using the Cochrane Library and SCOPUS database 33 relevant studies were found and subject to a critical appraisal. Appendix A and B provide an overview of each study included in the review. Relevant studies included were performed in developed countries primarily in the United Kingdom and America but also include Croatia and Japan. Studies investigated various ovarian cancer screening techniques, compliance of screening participants and costs involved in offering an ovarian cancer screening service. As shown by Figure 2.1 and Figure 2.2 more potential studies were found by searching SCOPUS with 527 studies in comparison to the Cochrane Library Database providing 86 potential studies for inclusion. Following screening of the abstract and full text 23 studies were found to fulfil all of the inclusion criteria from the SCOPUS search with the majority (20 studies from the 32 studies excluded) being excluded as being based on expert opinion or on a low level of evidence. The Cochrane Library provided 10 studies that fulfilled all of the inclusion criteria with just three full text studies being excluded due to no relevance to this review. Only one study in the Cochrane Library was found to be based on a low level of evidence.

2.4.2 Ovarian Cancer Screening Studies

It is apparent from the literature on ovarian cancer screening that internationally extensive research is performed however, there is lack of consensus on who to offer screening to, and the most efficacious way of offering it. Through investigating the 17 studies that aimed to determine the benefit or usefulness of ovarian cancer screening a wide variation in screening methods used was found. Six different inclusion criteria were used in the 17 studies to decide what participants were offered screening with variations in their age, menopausal status and associated risk of developing ovarian cancer due to family history of the disease, as follows:

1. Peri and postmenopausal women.
2. Postmenopausal women.
3. Postmenopausal women with raised CA125.
4. Premenopausal and postmenopausal women.
5. Premenopausal and postmenopausal women at high risk of developing ovarian cancer.
6. Women >50yrs of age and women >25 yrs of age at high risk of developing ovarian cancer.

As shown in Figure 2.3 the largest number of studies (six of the 17) decided to focus on pre and postmenopausal women at high risk of developing ovarian cancer due to family history of the disease. The second largest number of studies focused on all postmenopausal women. Other studies analysed varied in including premenopausal women or screening all women regardless of family history of ovarian cancer.

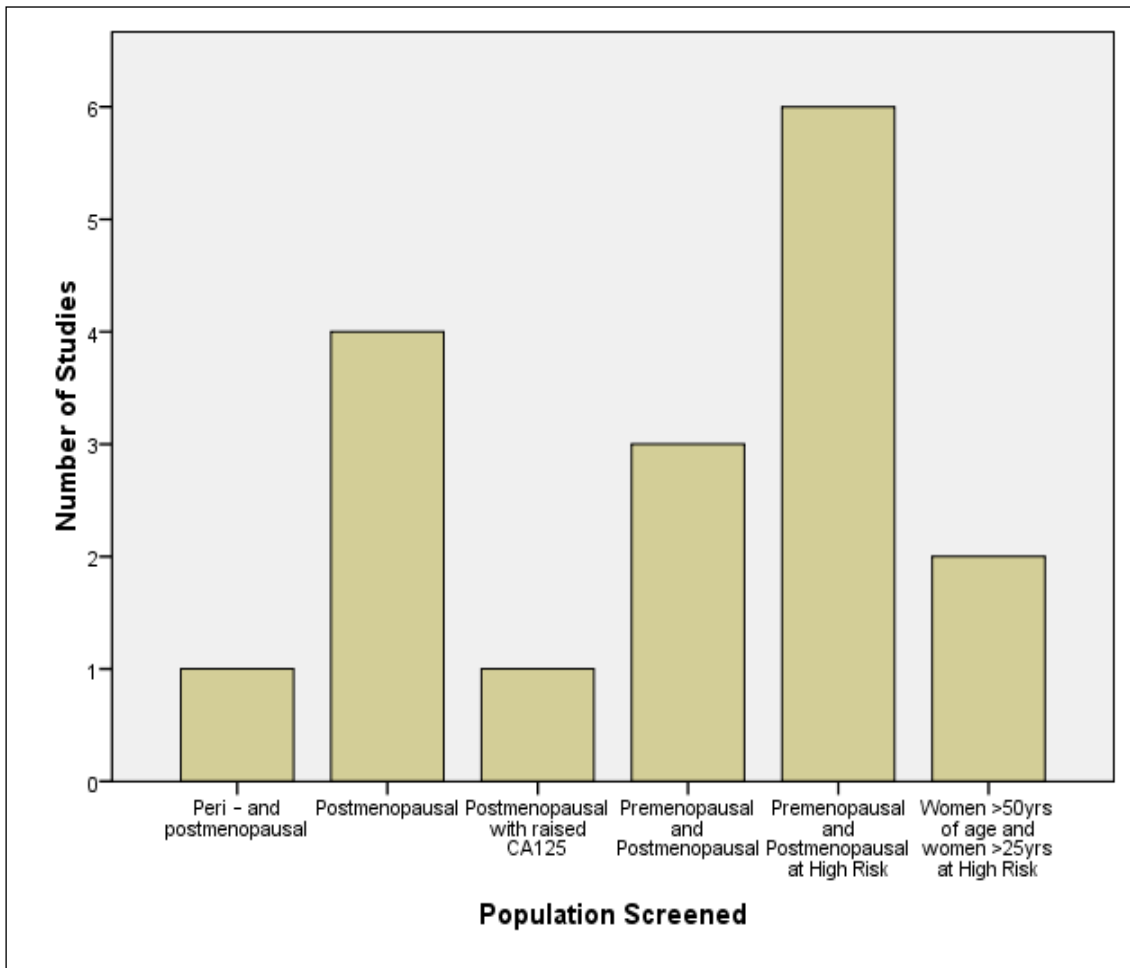


Figure 2.3 Population screened for ovarian cancer in studies analysed

2.4.3 Screening Methods

Two different screening methods were found in the 17 studies analysed. Firstly, screening through the use of ultrasound examination alone and secondly, using ultrasound imaging alongside tumour markers, typically CA125. Tables 2.7 and 2.8 provide an overview of these two screening methods in alphabetical order of study author with inclusion criteria, screening method and results analysed.

Table 2.7 Ovarian Cancer Screening Studies using Ultrasound alone

Author and Year of Publication	Study Inclusion Criteria	Screening Method	Screening Results
(DePriest and DeSimone, 2003)	University of Kentucky Programme 14,469 Women 50yrs or older and Women 25yrs or older with family history of ovarian cancer	Transvaginal ultrasound	Sensitivity of 81% Specificity 98.9% PPV 9.4% NPV 99.97%
(Fishman et al., 2005)	4,526 Premenopausal and postmenopausal women at high risk of ovarian cancer	Transvaginal ultrasound	Of the 2 primary ovarian cancers detected both women had normal ultrasound examinations 6/12 months prior to the diagnosis.
(Kurjak et al., 2005)	3,201 Peri / Postmenopausal women	Three- dimensional with power Doppler ultrasound	Sensitivity of 100% Specificity 99.4% PPV 20% NPV 100%
(Marchetti et al., 2002)	4,350 Pre and Postmenopausal women	Transvaginal Ultrasound	Sensitivity 100% Specificity 99.81% PPV 20%
(Van Nagell Jr. et al., 2007)	25,327 Women 50yrs or older and 25yrs or older with a family history of ovarian cancer	Transvaginal Ultrasound	Sensitivity 85% Specificity 98.7% PPV 14.01% NPV 99.9%
(Tailor et al., 2003)	2500 women at increased risk of developing ovarian cancer	Transvaginal ultrasound	15 of the 20 cancers occurred in premenopausal women Sensitivity 92% Specificity 97.8%

Table 2.8 Ovarian Cancer Screening Studies using Ultrasound combined with serum tumour markers

Author and Year of Publication	Study Inclusion Criteria	Screening Method	Screening Results
(Bosse et al., 2006)	Women at high risk of ovarian cancer	Transvaginal ultrasound and CA125	Specificity of 98.7% Positive predictive value 10%
(Buys et al., 2005)	28,816 Postmenopausal women	Transvaginal ultrasound and CA125	PPV of Ultrasound alone 1.0% PPV of CA125 alone 3.7% Ultrasound and CA125 23.5%
(DePriest and DeSimone, 2003)	Hirosaki University Programme 183,043 Women 30yrs or older	Transvaginal ultrasound and serum tumour evaluation	PPV 6.8%
(Gaarenstroom et al., 2006)	269 women at high risk of ovarian cancer	Transvaginal ultrasound and CA125	Efficacy of screening women at high risk seems poor as the majority of cancers were detected at an advanced stage
(Jacobs et al., 1999)	Postmenopausal women above 45yrs - Screened group 10,958	Transvaginal ultrasound and CA125	Positive predictive value 20.7
(Lacey et al., 2006)	28,460 Women with a family history of ovarian cancer	Transvaginal ultrasound and CA125	Probabilities of abnormal CA125 and TVS were similar across the groups. Women at higher family history-based risk more likely to be diagnosed with ovarian cancer.
(Menon et al., 2000)	741 Postmenopausal women with a raised CA125	Transvaginal ultrasound following a raised CA125	Sensitivity 100% Specificity 97% and PPV 37.2% Using complex morphology criteria
(Menon et al., 2005)	13,582 Postmenopausal women	Transvaginal ultrasound following an elevated CA125 level	Specificity 99.8% PPV 19%
(Roupa et al., 2004)	120 Postmenopausal women	Transvaginal ultrasound and CA125	Sensitivity 81.7% Specificity 100%
(Sato et al., 2000)	183,034 Premenopausal and Postmenopausal	30 Second Transvaginal Ultrasound examination followed by tumour markers	Surgery performed on 324 participants 22 Tumours found 77% of which were classified as Stage 1.
(Stirling et al., 2005)	1,110 women at increased risk of developing ovarian cancer	Annual transvaginal ultrasound and CA125	Three cancers not detected by screening – two stage III and one stage IV. Sensitivity 50% PPV 17%

2.4.4 Ovarian Cancer Screening using Ultrasound Imaging alone

Through the 6 studies found that use ultrasound alone for ovarian cancer screening interestingly only one does not include premenopausal women. It is widely accepted that screening premenopausal women for ovarian cancer will increase the false positive screening rate due to benign gynaecological conditions including endometriosis, functional ovarian cysts and fibroids (Jacobs, 2009). However, the clear benefit of this inclusion was found by Tailor et al (2003) with 15 of the 20 cancers detected in premenopausal women.

The screening results from each study all vary in their sensitivity and specificity values as follows:

- The sensitivity ranges from 81% (DePriest and DeSimone, 2003) to 100% (Marchetti et al., 2002; Kurjak et al., 2005).
- The specificity ranges from 97.8% (Tailor et al., 2003) to 99.8% (Marchetti et al., 2002).
- The positive predictive values range from 9.4% (DePriest and DeSimone, 2003) to 20% (Marchetti et al., 2002; Kurjak et al., 2005).

Transvaginal ultrasound has been recognised for several years as the ‘gold standard’ of ultrasound clinical practice, offering improved image resolution and visualisation of the female pelvis. Kurjak et al (2005) incorporates the use of three-dimensional ultrasound and power Doppler ultrasound. Three-dimensional ultrasound is not commonly used in routine NHS clinical practice however, this study reports a sensitivity of 100%, specificity of 99.4% and one of the highest positive predictive values of 20%.

2.4.5 Ovarian Cancer Screening Studies using Ultrasound combined with serum tumour markers

The majority of the screening studies analysed incorporated the use of tumour markers alongside ultrasound examination with 11 studies included. Variations in study populations were again found with nine studies using CA125 as the biomarker of choice. The two other studies (DePriest and DeSimone, 2003; Sato et al., 2000) incorporated the use of tumour makers still being evaluated.

The sensitivity and specificity values from each study are as follows:

- The sensitivity ranges from 50% (Stirling et al., 2005) to 100% (Menon et al., 2000)
- The specificity ranges from 97% (Menon et al., 2000) to 100% (Roupa et al., 2004)
- The positive predictive values range from 10% (Bosse et al., 2006) to 37.2% (Menon et al., 2000)

The studies analysed showed that incorporate serum tumour markers have a large variation in their sensitivity and positive predictive values. The benefit of incorporating biomarker analysis into screening for ovarian cancer was clearly found by Buys et al (2005) with a positive predictive value of 1% with ultrasound alone, 3.7% with CA125 alone and a combined positive predictive value of 23.5%. Menon et al (2000) provides the most ‘successful’ screening study of the 17 analysed, which involved postmenopausal women undergoing a transvaginal ultrasound using complex morphological ultrasound criteria following a raised CA125 result. The highest positive predictive value of all studies analysed was achieved at 37.2% with a sensitivity of 100% and specificity of 97%.

2.4.6 Compliance in Ovarian Cancer Screening Studies

It was decided that in order to investigate the impact and feasibility of an NHS based ovarian cancer screening programme, inclusion of studies investigating the compliance of a population and psychological constructs associated with screening will be included. Firstly, to determine rates of compliance with an ovarian cancer screening strategy, particularly one incorporating transvaginal ultrasound and secondly, to acknowledge the psychological distress participants in a screening study may experience and what impact that may have.

Through analysis of the screening studies performed with variations in screening methods used it is important to note that annual screening seems inadequate for early ovarian cancer detection. Firstly, Stirling et al (2005) concluded that annual surveillance with ultrasound and CA125 is ineffective in detecting tumours at a sufficiently early stage to influence prognosis with three cancers (two Stage III and one Stage IV) not being detected by screening and presenting in the interim screening period. Secondly, Gaarenstroom et al (2006) found the majority of cancers were detected at an advanced stage. Thirdly, Fishman et al (2005) detected two primary ovarian cancers both of which had normal ultrasound examinations 6/12 months prior to the diagnosis. This therefore, suggests that the disease is often aggressive and monitoring of ovarian appearance and biomarker analysis is required more frequently than every 12 months. It is accepted as current imaging practice that ultrasound examinations incorporate a transvaginal scan due to the improvement of image quality achieved through high resolution probes in close proximity to the ovaries. However, if this intensive screening is required Drescher et al (2004) found that compliance of average and intermediate risk women to an ovarian cancer screening protocol requiring semi-annual screening diminished rapidly

and a screening method incorporating transvaginal ultrasound may be too intensive for use in this population. Similar low compliance of women returning for repeat screening was found by Andrykowski et al (2007) with over 25% of the sample population not returning for repeat ultrasound screening within 24 months of their baseline examination. In comparison, Pavlik et al (2000) found high levels of continuation through annual ultrasound screening with 96% of women returning for visits within two years, indicating that women take ovarian cancer disease seriously and it is of consequence to them through continuing with screening. Hensley et al (2003) found that the perception of ovarian cancer risk and risk-related anxiety was higher in premenopausal women along with increased false-positive results in comparison to postmenopausal women. However, Tailor et al (2003) highlights the need for screening premenopausal women as 15 of the 20 cancers detected in this study were in this population.

It is important to address the efficacy of subjecting asymptomatic participants to screening, particularly involving transvaginal ultrasound. Salsman et al (2004) found that nearly all women both in the healthy comparison group and those already involved in an ovarian cancer screening trial endorsed positive beliefs in the ability of transvaginal ultrasound to detect ovarian cancer and the curability of ovarian cancer if detected early. More importantly to this literature review, the groups did not differ regarding beliefs concerning the efficacy of transvaginal ultrasound screening for ovarian cancer. Salsman et al (2004) found 88.3% of women invited to undergo screening provided informed consent. Those who declined screening cited reasons as too busy or too stressed. This aspect of stress and cancer worry was addressed by Andersen et al (2007) who found that ovarian cancer screening does not have significant

negative effects on participants, at least when they do not receive abnormal results. For those who receive abnormal results, screening may have long-term effects and increase worry about cancer risk. A previous study by Andersen et al (2002) highlights that most women over-estimated their risk of developing ovarian cancer with those at risk of the disease due to family history experiencing particularly worry and anxiety. Their study also found that a significant percentage of women at high risk of developing ovarian cancer fail to get recommended screening.

2.5 Conclusion of Systematic Literature Review

The conclusions and recommendations made in this review are based on the best available evidence taken only from well conducted randomised control trials, case control or cohort studies. Non analytic studies and expert opinion publications were excluded.

Bell et al (1998) performed a systematic literature review to provide the HTA programme with an overview of the results of research evaluating screening for ovarian cancer. Similar findings were observed in studies performed prior to 1998 as in this review, with wide variations in inclusion criteria and modalities used for screening study participants. Bell et al (1998) concluded that uncontrolled screening studies could not provide reliable evidence concerning the effect of ovarian cancer screening on health outcomes such as mortality and quality of life. It is clear that there is a level of uncertainty as to which women to offer screening to from studies analysed in this review from 1998 to 2008. However, even though there is variability in screening inclusion criteria used, this review suggests that ovarian cancer is often aggressive and monitoring of ovarian appearance and biomarker analysis is required more frequently than every 12 months. Annual screening was found to be inadequate for early cancer detection by Stirling et al (2005) and Gaarenstroom et al (2006) who reported that the majority of cancers were either detected at an advanced stage or presented in the interim screening period. Fishman et al (2005) detected two primary ovarian cancers both of which had normal ultrasound examinations six months prior to the diagnosis. It is important to also note that Andrykowski et al (2007) and Drescher et al (2004) found that participant compliance was often low when screening within a 12 month period particularly when involving transvaginal ultrasound examinations. This aspect of

participant compliance to a screening protocol raised in this review is important, as assuming the effectiveness of cancer screening is predicted on timely screening then only through a high rate of participation can early ovarian cancer detection be proposed.

As previously mentioned it is widely accepted that screening premenopausal women for ovarian cancer will increase the false positive screening rate due to benign gynaecological conditions including endometriosis, functional ovarian cysts and fibroids (Jacobs, 2009). However, the clear benefit of this inclusion was found in Taylor et al (2003) study with 15 of the 20 cancers detected in premenopausal women. This has an implication for ovarian cancer screening in the NHS setting as potentially more women may need to be offered screening rather than focusing entirely on postmenopausal women.

The most successful screening study of the 17 analysed was performed by Menon et al (2000) and agrees with literature evidence that ovarian cancer screening involving multimodal screening has superior specificity and positive predictive value. Menon et al (2000) focused on postmenopausal women undergoing a transvaginal ultrasound using complex morphological ultrasound criteria following a raised CA125 result. This screening method resulted in the highest positive predictive value of all studies analysed at 37.2% with a sensitivity of 100% and specificity of 97%. However, it is important to remember the possible low compliance of women to a screening protocol that involves semi-annual screening with transvaginal ultrasound should CA125 levels indicate more frequent ultrasound examinations are necessary (Drescher et al., 2004).

2.6 Recommendations from Systematic Literature Review

Based on this systematic literature review the main recommendation that must be made particularly when the NHS National Screening Committee is due to evaluate their opinion on ovarian cancer screening, is that currently there is no agreed method of screening or inclusion criteria being adhered to. This aspect of screening in the NHS setting must be decided upon with justification based on clinical evidence as screening methods and inclusion criteria used will have varying cost implications.

It is clear that ultrasound and CA125 both have limitations in their sensitivity and specificity of diagnosing ovarian cancer and therefore, further work must be recommended in these areas as both are required in clinical practice to reach a diagnosis and screening for early detection of the disease. The benefit of incorporating biomarker analysis into screening for ovarian cancer was clearly found by Buys et al (2005) with a positive predictive value of 1% with ultrasound alone, 3.7% with CA125 alone and a combined positive predictive value of 23.5%. Biomarker research may provide new and more clinically useful markers to aid practitioners in the early detection of ovarian cancer and more specific to stage at diagnosis. Further research into imaging particularly in the field of ultrasound due to this modality being the first line investigation is suggested. Complex morphological ultrasound criteria as used by Menon et al (2000) achieved the highest positive predictive value of all studies analysed and could therefore, provide a useful and robust method of deciding the likelihood of malignancy in a systematic way for all practitioners performing gynaecological ultrasound. An example of a transvaginal ultrasound classification algorithm as used in UKFOCSS is provided in Appendix G and is particularly appropriate for premenopausal women in whom functional cysts are common but a risk of developing ovarian cancer still exists. (Tailor et al, 2003).

Kurjak et al (2005) incorporates the use of three-dimensional ultrasound and power Doppler ultrasound not commonly used in routine NHS clinical practice. However, this study reports a sensitivity of 100%, specificity of 99.4% and one of the highest positive predictive values of 20% suggesting a possible very useful advancement in the field of imaging and ultrasound characterisation of ovarian lesions. This literature review highlights the need for screening more frequently than on an annual basis, however, it is important to note the low compliance found by Andrykowski et al (2007) and Drescher et al (2004) to a frequent screening protocol particularly one using transvaginal ultrasound. Therefore, research into a more sensitive and clinically useful biomarkers present in blood would provide a cost-effective and possibly more acceptable method of screening during the interim period of annual transvaginal ultrasound examinations.

3 RETROSPECTIVE STUDY OF CONFIRMED AND SUSPECTED OVARIAN CANCER CASES

3.1 Introduction

In order to investigate the impact of introducing ovarian cancer screening and to gain an insight into the clinical problem that ovarian cancer presents at a local level, a retrospective study was performed at Milton Keynes Hospital NHS Foundation Trust. Ethical approval was applied for and granted from Milton Keynes Research Ethics Committee on 14th July 2008 (REC reference 08/H0603/14).

Two searches were performed differing in their objectives:

1. Perform a retrospective study of patients diagnosed with ovarian cancer at Milton Keynes Hospital over a five year timescale from 2004 to 2009 regardless of presentation or method of diagnosis, to establish the stage at diagnosis, age and family history of the disease.
2. Investigate the role and diagnostic accuracy of imaging when suspecting ovarian pathology to establish how many cases with suspected malignancy or pathology undetermined through imaging alone resulted in benign pathology.

3.2 Design of Retrospective Studies

The first retrospective study aimed to find the maximum number of patients diagnosed with ovarian cancer at Milton Keynes Hospital through implementing two search methods. Firstly, all patients referred for treatment following a diagnosis of ovarian cancer are seen by a Consultant Oncologist at Northampton Hospital, contact was made for a list of patients referred from 2004 to 2009 and the National Cancer Registry searched. Secondly, in order to find those patients not given treatment as palliative care may have been appropriate or follow-up care provided in a different region, a keyword search of medical reports held on the radiology database used at Milton Keynes Hospital was performed to establish a diagnosis. Figure 3.1 provides an overview of how the total number of patients diagnosed with ovarian cancer at Milton Keynes Hospital was found.

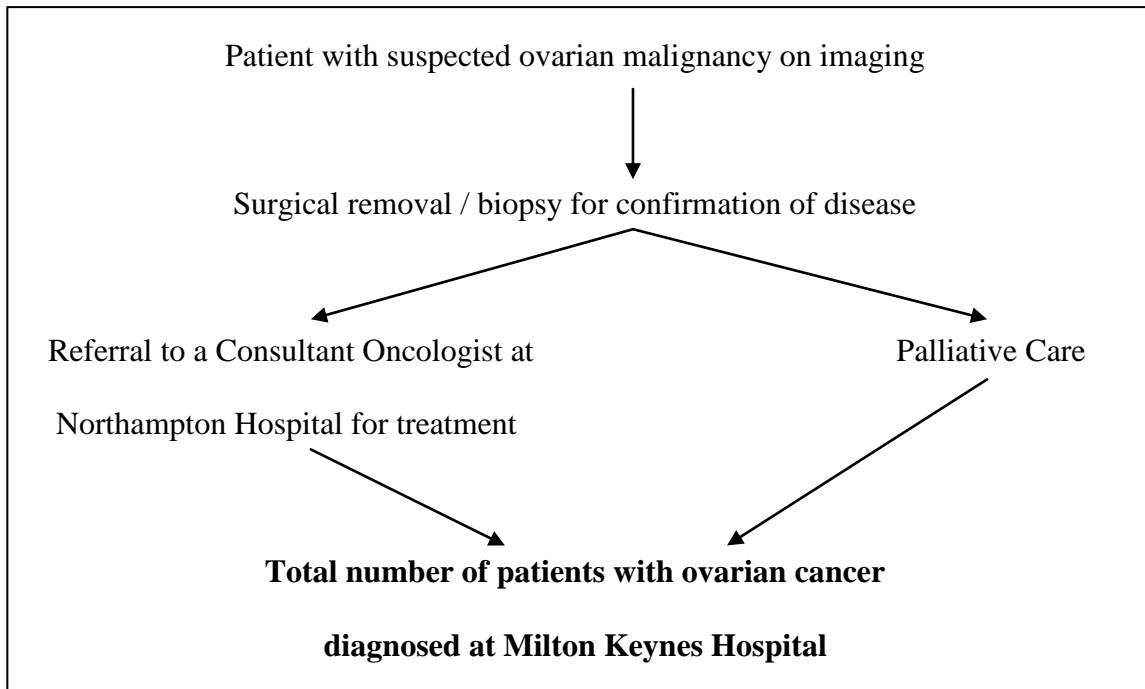


Figure 3.1 Method of First Retrospective Study

Once all patients diagnosed at Milton Keynes Hospital with ovarian cancer were found the following information was collected through examining their medical notes and incorporating data held on the radiology or histology database when required:

- Age at diagnosis
- Menopausal status
- Stage of ovarian cancer – FIGO classification of disease
- Presenting symptoms and diagnostic findings
- CA125 level
- Documented medical history or family history of cancer

As detection of ovarian cancer involves an imaging modality alongside biomarker analysis, a second retrospective study was performed in order to investigate the challenges that imaging face in the characterisation of ovarian pathology. The aim of this second retrospective study was to establish how many cases with suspected malignancy through imaging alone resulted in benign pathology (false-positive results) and establish the outcome of cases with complex ovarian pathology unable to be characterised as benign on first-line imaging. This aspect of imaging diagnostic accuracy is key when investigating the impact of ovarian cancer screening, as a modality that offers a high sensitivity and specificity level is vital in detecting small-volume disease states and accurately identify individuals without disease (Teneriello and Park, 1995).

The current radiology information system at Milton Keynes Hospital has been in use for 18 months and therefore, the search was performed over this timescale incorporating all female patients of any age and of any imaging modality. Figure 3.2 provides an overview of the second retrospective study design.

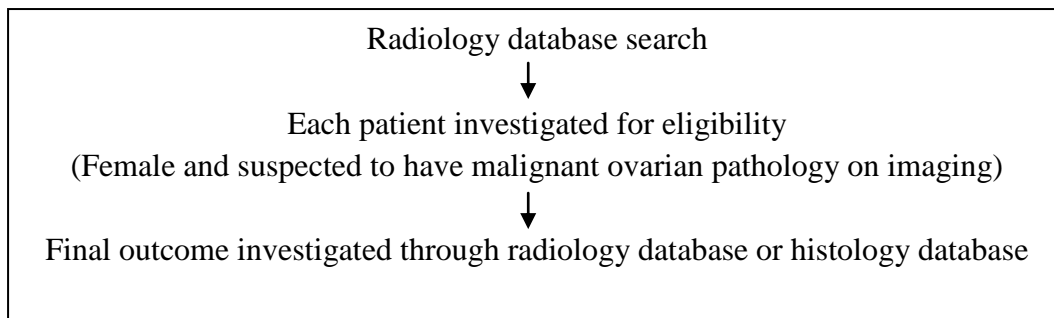


Figure 3.2 Method of Second Retrospective Study

As both Consultant Radiologists and Reporting Sonographers perform imaging examinations in the field of general medical and gynaecology ultrasound there is a variation in how medical reports are structured and described by the practitioner. Therefore, to maximise the number of patients found in this search several Radiologists and Reporting Sonographers were approached to find how they describe and report on ovarian pathology to develop a list of search terms used. Search terms decided upon were as follows and all were used with the Boolean OR operator for the database search:

- Ovarian mass
- Ovarian carcinoma
- Complex mass
- Adnexal mass
- Ovarian malignancy
- Ovarian tumour
- Complex cyst
- Adnexal cyst

Cases eligible for inclusion in this second study were as follows:

- Any case where ovarian pathology has been detected but not able to be characterised by the practitioner as benign using one imaging modality.
- Any case where ovarian pathology has been detected and incorrectly characterised as benign using one imaging modality (false-negative result).
- Any case where surgical intervention was required for histology analysis of ovarian tumour resulting in a final diagnosis of a benign nature (false-positive result).

3.3 Results of First Retrospective Study

A total of 75 cases of ovarian cancer were found through implementing the two search methods described with all sets of medical notes found and examined. Interestingly all medical notes had excellent and detailed documentation meaning that all of the key information set out to gather was achievable. Information from Milton Keynes Hospital radiology database and histology reports were used to confirm the diagnosis or provide additional information to cases analysed.

3.3.1 Age at Diagnosis

The age range of patients diagnosed with ovarian cancer was found to be from 30 to 87 years of age. The median age calculated was 59. A dispersion of age range was found through calculating the first quartile and third quartile equalling 53 to 70 years of age. Figure 3.3 provides a box-plot of age at diagnosis and FIGO classification of disease, as shown; both young and older women were diagnosed in all four stages of disease.

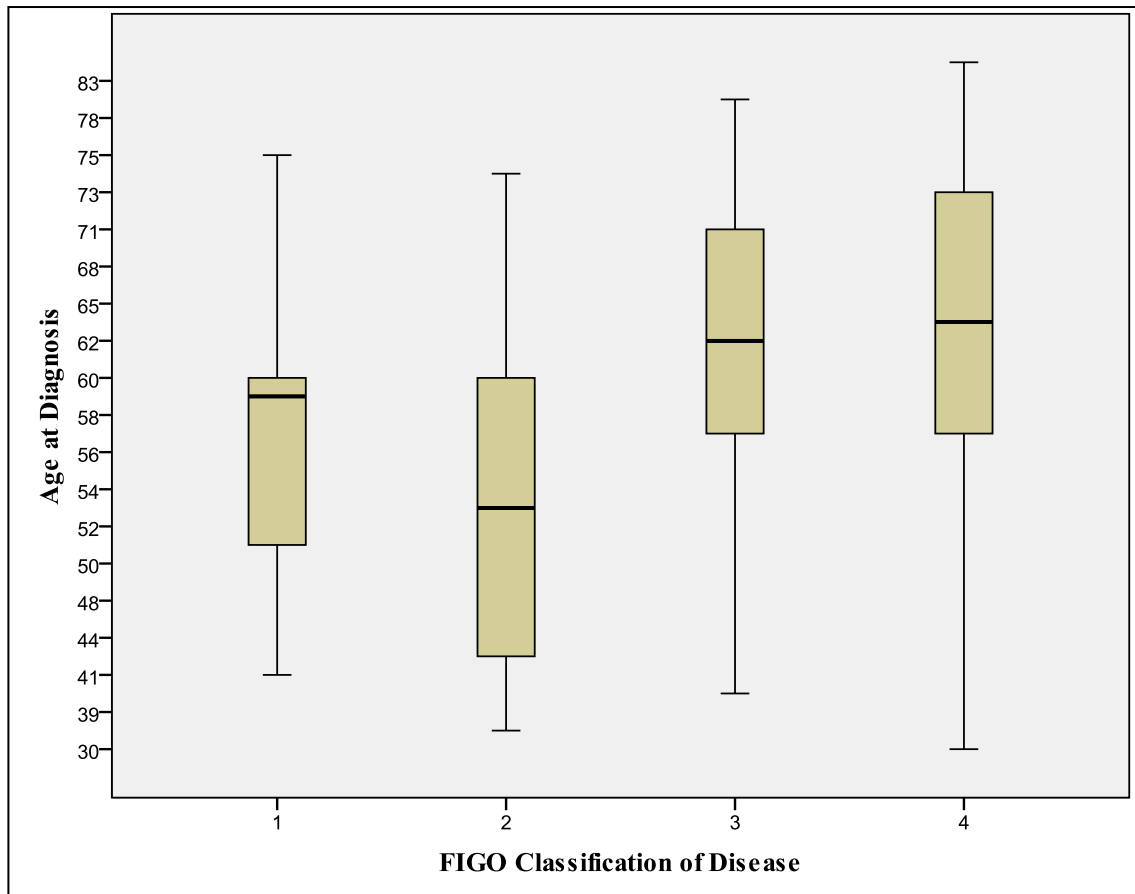


Figure 3.3 FIGO Classification of Disease and Age at Diagnosis

A statistically significant difference was found between each group using the ANOVA test, resulting in a p-value of 0.000554. These findings suggest that although each stage does have a wide age range, older women tend to have more advanced disease (Stage III or IV) at time of diagnosis with younger women more likely to be diagnosed with early disease (Stage I or II).

3.3.2 Menopausal Status

Through reviewing medical notes, reasons why patients were referred for imaging and symptoms experienced, the menopausal status was recorded resulting in the majority of women (77%) diagnosed with ovarian cancer found to be postmenopausal. However, from the 75 cases found, 17 patients were premenopausal and often referred due to irregular vaginal bleeding and pain.

Table 3.1 Menopausal Status of Ovarian Cancer Cases

Number of Cases	Menopausal Status
17	Premenopausal
58	Postmenopausal

3.3.3 Stage of Ovarian Cancer

Through reviewing the medical notes and post-surgical oncology review once the stage of ovarian disease was decided, each case was documented. This retrospective analysis found the largest group of patients (23 of the 75 cases) were found to have advanced FIGO Stage IV disease at time of diagnosis. Therefore, these women were found to have ovarian cancer along with distant metastatic disease. The second largest group of patients (20 of the 75) were found to have early FIGO Stage I disease at time of diagnosis. Figure 3.4 demonstrates the variability in FIGO classification of disease that patients presented with at time of diagnosis at Milton Keynes Hospital.

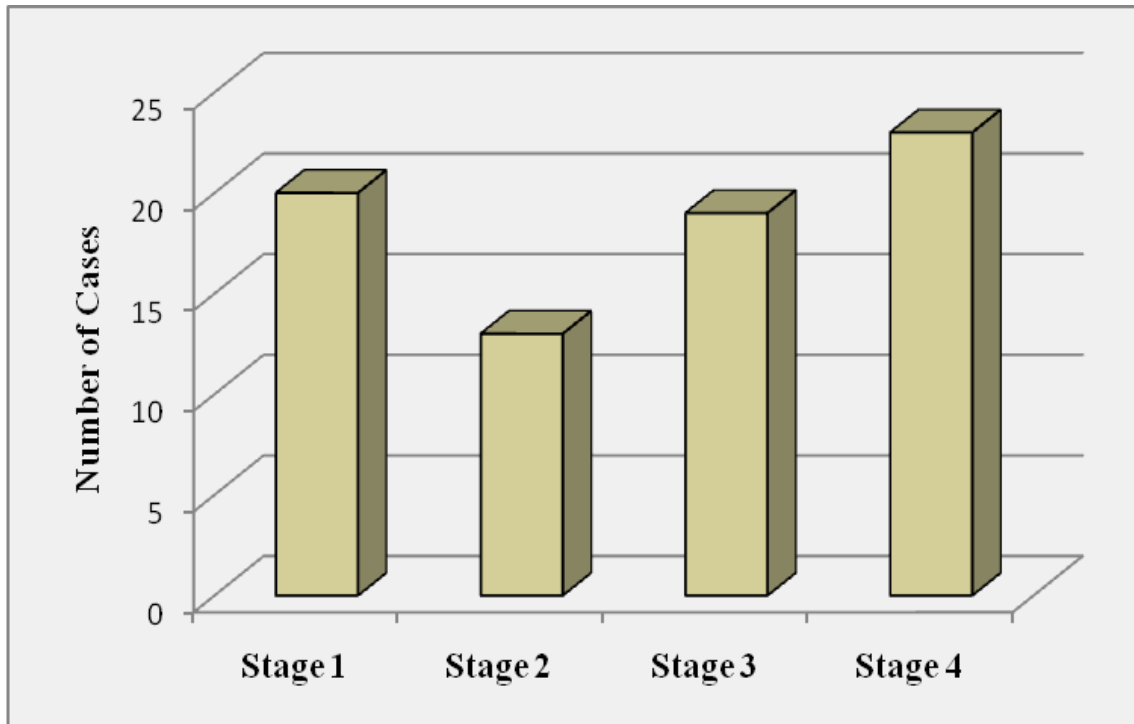


Figure 3.4 FIGO Classification of disease and number of cases

3.3.4 Presenting Symptoms

As previously mentioned the symptoms of ovarian cancer are often vague and difficult to recognise particularly in the early stages of the disease. Similar presenting symptoms from the 75 cases were found with 57% of the cases reviewed experiencing at least two or more of these symptoms:

- Abdominal or pelvic pain / distension
- Change in bowel habit
- Weight loss
- Abnormal vaginal bleeding
- Urinary symptoms / frequency of micturition

The most common symptom found was abdominal or pelvic pain often with distension, with 80% of the cases reviewed having this symptom documented. From evaluating the medical notes it was clear that due to the variability in presentation and often non-specific symptoms, patients with underlying ovarian cancer were often initially referred

to clinicians in gastrointestinal medicine in cases 17, 39, 42 and 49 as these patients experienced change in bowel habit with weight loss and often abdominal pains, meaning the referring general practitioner was suspecting bowel pathology rather than ovarian disease (Appendix D). Other key cases include:

- Case 38 that presented with a pleural effusion on a medical ward under the chest physicians who found adenocarcinoma in the fluid drained and therefore, requested imaging resulting in a final diagnosis of advanced Stage IV ovarian cancer.
- Case 29 is of particular interest as this patient was experiencing pelvic pain and found to have FIGO Stage III disease on surgical laparoscopy. However, just four months prior had a normal CT examination. This case provides a key example of how quickly ovarian cancer can develop and spread.

3.3.5 Diagnostic Findings

The majority of cases (93%) in this retrospective study had ovarian pathology first diagnosed by an ultrasound examination. This modality is routinely used as first line imaging for gynaecologists and general practitioners suspecting gynaecological pathology at Milton Keynes Hospital. The size of the ovaries and morphology can be assessed for the presence of cysts, cyst septae, solid areas and solid papillations. An abnormal ultrasound is classified as cysts above 5cm in diameter, multiple cysts or all complex morphology (non-uniform echogenicity). Following an ultrasound examination demonstrating a pelvic or abdominal complex cyst or mass, all patients underwent a CT examination to aid in staging the disease. Several patients also had an MRI examination for further investigation prior to surgical intervention. 97% of ovarian cancer cases in this retrospective study had a pelvic or abdominal mass / cyst diagnosed by imaging prior to surgical intervention.

Cases 10 and 48 were found to have peritoneal metastatic disease and omental thickening without a definite ovarian tumour visualised by imaging. In all other 73 cases a complex mass / tumour or enlarged abnormal ovaries were visualised with tumour ranging from 6cm up to 16cm in size. Other diagnostic features also detected on imaging included:

- Omental spread / peritoneal deposits
- Liver / lung metastasis
- Ascites / pleural effusion
- Bowel / uterus / cervical / fallopian tube involvement
- Lymphadenopathy
- Deposits under the diaphragm

Case 63 provides a key finding from this retrospective study as a false negative result based on ultrasound examination in a patient who presented with a palpable pelvic mass of unknown cause was found. This was reported as an enlarged fibroid uterus on ultrasound, however, a later CT and MRI examination confirmed FIGO Stage III ovarian cancer with a normal sized uterus. This case is of vital importance in highlighting how operator dependant ultrasound examination is, particularly as in this case a transvaginal scan was not performed.

3.3.6 CA125 Analysis

A wide variation in CA125 values was found through reviewing each case on the Winpath database at Milton Keynes Hospital with a range of 7U/ml to 5000U/ml. A CA125 of above 35U/ml is normally accepted as elevated in premenopausal women and above 30U/ml in postmenopausal women. Interestingly, six patients diagnosed with ovarian cancer were found to have CA125 values within the normal range:

- Cases 12,47 and 50 were diagnosed with FIGO Stage I disease.
- Case 16 was found to have FIGO Stage II disease with a CA125 value of just 11U/ml and also a family history of mother and sister previously diagnosed with ovarian cancer.
- Cases 29 and 58 are perhaps the most interesting and concerning finding of this retrospective study as advanced FIGO Stage III and IV disease was diagnosed, with normal range CA125 levels

In order to provide an overview of CA125 levels in relation to FIGO stage at diagnosis, a boxplot has been used as shown in Figure 3.5.

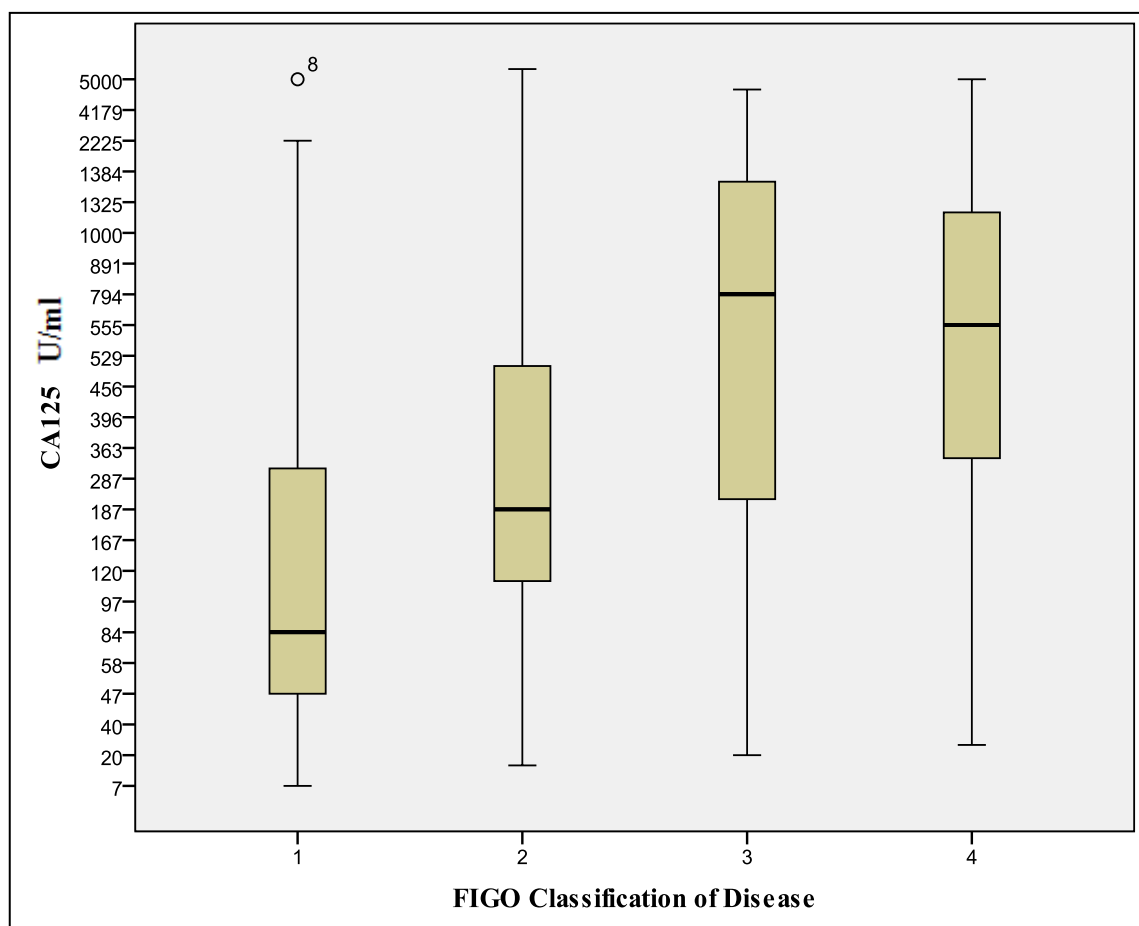


Figure 3.5 Boxplot of FIGO Classification of Disease and CA125

Key findings from Figure 3.5 are as follows:

1. Cases of ovarian cancer with a CA125 within the normal range were found in all four FIGO stages of disease.
2. Several cases had a very high (>4000U/ml) CA125 regardless of FIGO stage at diagnosis.
3. A statistically significant difference was found between each group using the ANOVA test, resulting in a p-value of 0.003542. These findings therefore, indicate that there is a gradual increase in CA125 with advancing FIGO classification of disease.

3.3.7 Documented History of Cancer

A low incidence of cancer history from the 75 cases was found with six cases having a documented history in their medical records.

- Cases 10, 35, 51 and 65 had a documented family history of breast cancer with one patient being a BRCA1 gene carrier. Interestingly, three of these cases had advanced (Stage IV) ovarian cancer at time of diagnosis.
- Case 16 had family history of ovarian cancer with mother and sister already diagnosed with the disease.
- Case 18 had a history of cervical cancer.

This may therefore, suggest an incidence of 6.7% familial ovarian cancer rather than sporadic disease (5 cases from the 75 found).

3.4 Results of Second Retrospective Study

A search performed using the radiology database at Milton Keynes Hospital provided 169 patients with at least one of the search terms, as described in Chapter 3.2, used in their imaging reports. Through examining all of the imaging reports highlighted in this search, 35 cases suspicious of ovarian malignancy or unable to be classified as benign were found, all of which resulted in either further imaging or histology analysis to confirm benign ovarian pathology following surgery.

3.4.1 Age Range

A wide age range was found from 16 to 83 years of age with the majority of patients (89%) being premenopausal.

3.4.2 Imaging Findings

In the 35 cases analysed all patients had a complex pelvic mass that often involved solid components and meant that through initial imaging alone either the Radiologist or Reporting Sonographer were unable to characterise the pathology as benign. The size of abdominal or pelvic masses ranged from 5cm up to 32cm. 89% of the cases found involved ultrasound imaging with the remaining 11% involving CT or MRI being unable to characterise the mass as benign on first examination. Similar imaging findings were documented as follows:

- Ovarian mass with cystic and solid components.
- Complex ovarian cyst with thick internal septations and solid areas.
- Multilocular cystic mass.
- Enlarged ovary with abnormal lesions and wall irregularity.
- Free pelvic fluid.

3.4.3 Outcome of Cases

The outcome of each case was investigated through searching the radiology database reports for follow-up or histology reports following surgical intervention. Each case found either involved further imaging examinations or surgical removal of the mass for histology analysis in order to confirm non-malignancy.

Figure 3.6 provides an overview of how each case reached a diagnosis of benign pathology. Of the 35 cases investigated, four methods were used, histology analysis following surgical intervention, MRI, CT or further ultrasound imaging. The largest number of cases either resulted in histology analysis following surgical removal or MRI imaging to establish a diagnosis. A large percentage of patients (40%) still required surgical intervention when imaging suggested ovarian pathology of unknown nature. 60% of patients required further imaging through a different modality most commonly MRI or a further ultrasound at a later date for reassessment of the ovaries decided by the clinician.

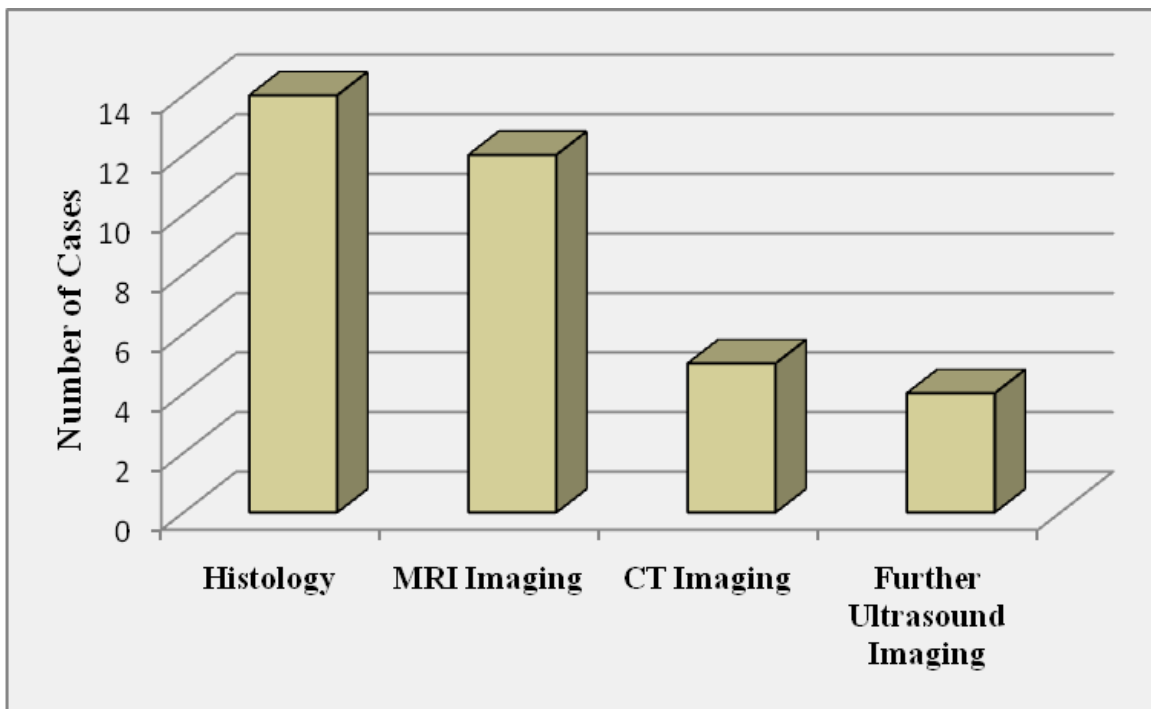


Figure 3.6 How a diagnosis of benign pathology was reached

Non-malignant gynaecologic pathology was diagnosed in 34 of the 35 cases investigated with the outcome of each case recorded in Table 3.2. A single case of suspected ovarian malignancy on imaging resulted in bowel pathology following surgical intervention and histology analysis.

Table 3.2 Outcome of suspected ovarian pathology diagnosis

Outcome	Number of Cases
Benign simple ovarian cyst or further imaging demonstrates normal ovaries	11
Endometrioma	7
Dermoid Cyst	6
Uterine fibroid	4
Haemorrhagic cyst	3
Ovarian fibroma	1
Pelvic abscess	1
Fluid collection	1

As shown in the largest number of cases the outcome was benign simple ovarian cysts or following further imaging the cyst had resolved meaning ultrasound or MRI/CT demonstrated normal ovaries. Other cases involved gynaecological conditions of endometriosis, dermoid cysts, uterine fibroids, haemorrhagic cysts or an ovarian fibroma. Two cases were found to have loculated fluid collections or pelvic abscess following further imaging.

3.5 Discussion of Retrospective Studies

Through the two retrospective studies performed at Milton Keynes Hospital NHS Foundation Trust, an insight has been provided into the clinical problem that ovarian cancer and benign pathology presents at a local level. A total of 75 cases of ovarian cancer were found over a five year period through applying the search methods described with variations in age, menopausal status, symptoms experienced and FIGO stage at diagnosis found.

As five-year survival rates are related to the age at which the disease is diagnosed with women under the age of 50 years likely to be diagnosed with local disease and women over 65 years being more likely to have distant metastases, the stage at diagnosis is vital for treatment management and survival. The first retrospective study found that 81% of women diagnosed with ovarian cancer were above the age of 50 with 77% of women being postmenopausal. This finding agrees with Cancer Research UK (2009) who state that over 80% of ovarian cancer cases are diagnosed in women over 50yrs of age as seen in Figure 1.3. 17 women were found to be premenopausal with the majority referred due to irregular vaginal bleeding and pelvic pain. Figure 1.5 demonstrates the difference from women aged 15-39 having a five-year survival rate of nearly 70% to that of 12% survival if diagnosed between 80-89 years of age. Both FIGO and Menon and Jacobs (2002) find that approximately 25% of patients present with Stage I or Stage II disease. However, this retrospective study found 44% of all cases at Milton Keynes Hospital were diagnosed earlier than progressing to Stage III as shown in Figure 3.4. Reasons for this were not apparent from this retrospective study as the clinical presentation and symptoms experienced were similar across all stages of ovarian cancer. It potentially could be due to the raised awareness of the disease with more women

seeking advice when symptoms initially present and general practitioners referring for more diagnostic examinations when symptoms experienced are vague. The largest group of cases were diagnosed with advanced FIGO Stage IV disease (31%) interestingly followed by Stage I disease (27%). This suggests that many cases will be diagnosed with advanced disease involving distant metastases as suggested by Rufford et al (2007) due to often vague symptoms experienced, however, many cases were found to have tumour concentrated only in the ovaries. The most common symptom found was abdominal or pelvic pain often with distension, with 80% of the cases reviewed having this symptom documented. Cases 17, 39, 42 and 49 highlight the problems of vague symptoms as due to changes in bowel habit with weight loss, bowel pathology was suspected by referring general practitioners rather than ovarian disease. Case 29 is of particular interest as FIGO Stage III disease was detected on surgical laparoscopy, however, just four months prior had a normal CT examination. This case provides a key example of how quickly ovarian cancer can develop and spread.

Based on current literature (Jacobs, 2009) a reduction in the specificity of imaging diagnosis and false-positive rates are higher in premenopausal women due to benign functional cysts, uterine fibroids and cases of endometriosis in this population. This aspect of imaging and implications for screening premenopausal women is highlighted by the second retrospective study with 35 cases found all resulting in further imaging or histology analysis to reach a diagnosis of benign pathology. A single false positive case was found in which an enlarged fibroid uterus was diagnosed by ultrasound and further imaging prior to surgical intervention found FIGO Stage III ovarian cancer. Therefore, in relation to ovarian cancer screening through ultrasound, gynaecologists and those performing ultrasound examinations must be aware of these limitations. However, it is

important to mention that in this case a transvaginal scan was not performed. CA125 is often limited in predicting how advanced ovarian disease is at time of diagnosis and often will not detect the disease at all regardless of FIGO stage based on this retrospective study. Six patients diagnosed with ovarian cancer were found to have a CA125 within the normal range. A statistically significant difference was found between each FIGO stage and CA125 values recorded indicating that older women tend to have more advanced disease at time of diagnosis.

3.5.1 Strengths and Limitations of Retrospective Studies performed

Through deciding on a study design prior to any searches being performed the inclusion criteria was clear with the maximum number of patients found through several routes used. The objectives decided upon were achieved for each of the retrospective studies performed with additional information gathered through access to the radiology and histology database meaning if information was missing from the medical notes this could be accumulated and confirmed through other sources. Statistical advice was requested from a senior research officer meaning any statistically significant differences in information collected could be confirmed and highlighted. The first study was carried out over a five year timescale meaning a large amount of information was analysed. The second study could only be carried out over an 18 month timescale due to a new radiology system being in place, meaning fewer patients were found and included however, still provides an investigation of 35 cases.

3.5.2 Conclusion of Retrospective Studies

This retrospective study shows that ovarian cancer affects a wide age range with many women having no family history of breast or ovarian cancer. Many women were found to have ovarian cancer at FIGO Stage I or II however, the largest group of women were found to have metastatic disease at time of diagnosis. One of the most interesting findings from this audit in terms of symptoms experienced is the 80% of cases found had abdominal or pelvic pains often with distension. However, the often varied symptoms experienced by women with this disease reflect the known difficulty in detecting the cancer in its early stages. The vague abdominal pains or changes in bowel habit can often be similar to irritable bowel symptoms or other non-gynaecological conditions and therefore, the ovarian tumour can potentially go undiagnosed for some time. Key findings relevant to screening for ovarian cancer are firstly, the biomarker CA125 used in both clinical practice and the majority of screening studies analysed in chapter two has limitations. Six patients with the disease were found to have a CA125 level in the normal range, one of which had advanced FIGO Stage IV disease, indicating the sensitivity limitations CA125 has with detecting ovarian cancer even at advanced stages. Secondly, the majority of patients in this study had no family history of breast or ovarian cancer and an age range from 30 to 87 years old, meaning that premenopausal women are at risk of developing ovarian cancer as well as postmenopausal women. This finding agrees with Taylor et al (2003) who found a large proportion of ovarian cancers (15 of the 20) in premenopausal women. Finally, Case 29 provides a key example of how quickly ovarian cancer can develop and spread with FIGO Stage III disease detected on surgical laparoscopy, however, just four months prior had a normal CT examination. This case indicates that annual screening for ovarian cancer is not suitable and either examination of the ovaries through imaging or biomarker analysis within a 12 month time period is vital for early diagnosis.

4 COST ANALYSIS OF OVARIAN CANCER SCREENING

4.1 Cost Analysis Introduction

It is estimated that the treatment of cancer accounts for 5 per cent of all NHS expenditure. £3.4 billion was spent on cancer services in 2003/04, £3.8 billion in 2004/05 and £4.3 billion was spent in 2005/06, demonstrating an increase of 12% per year. In total, approximately £4.35 billion was spent on cancer services in 2006/07 (Cancer Research UK, 2009).

The cost of offering screening is of key importance when proposing or justifying the National Health Service in offering such a programme. As suggested by Lux et al (2005) early cancer detection can prove to be a psychological strain for women at risk and a financial burden to the health system but it is a less invasive option than prophylactic surgery. Through the literature review no study was found investigating the costs associated with ovarian cancer screening alone. Miller et al (2001) investigated the health related quality of life and cost-effectiveness in the prostate, lung, colon and ovary trial (PLCO trial). This study provides an insight into the framework for cost-effectiveness and health related quality of life measurements. Figure 4.1 provides the framework used to facilitate decisions on the measurements and timing that may be required with each numbered node indicating a point in the screening, diagnosis, treatment, follow-up and final endpoint process when health-related quality of life changes and cost expenditures occur.

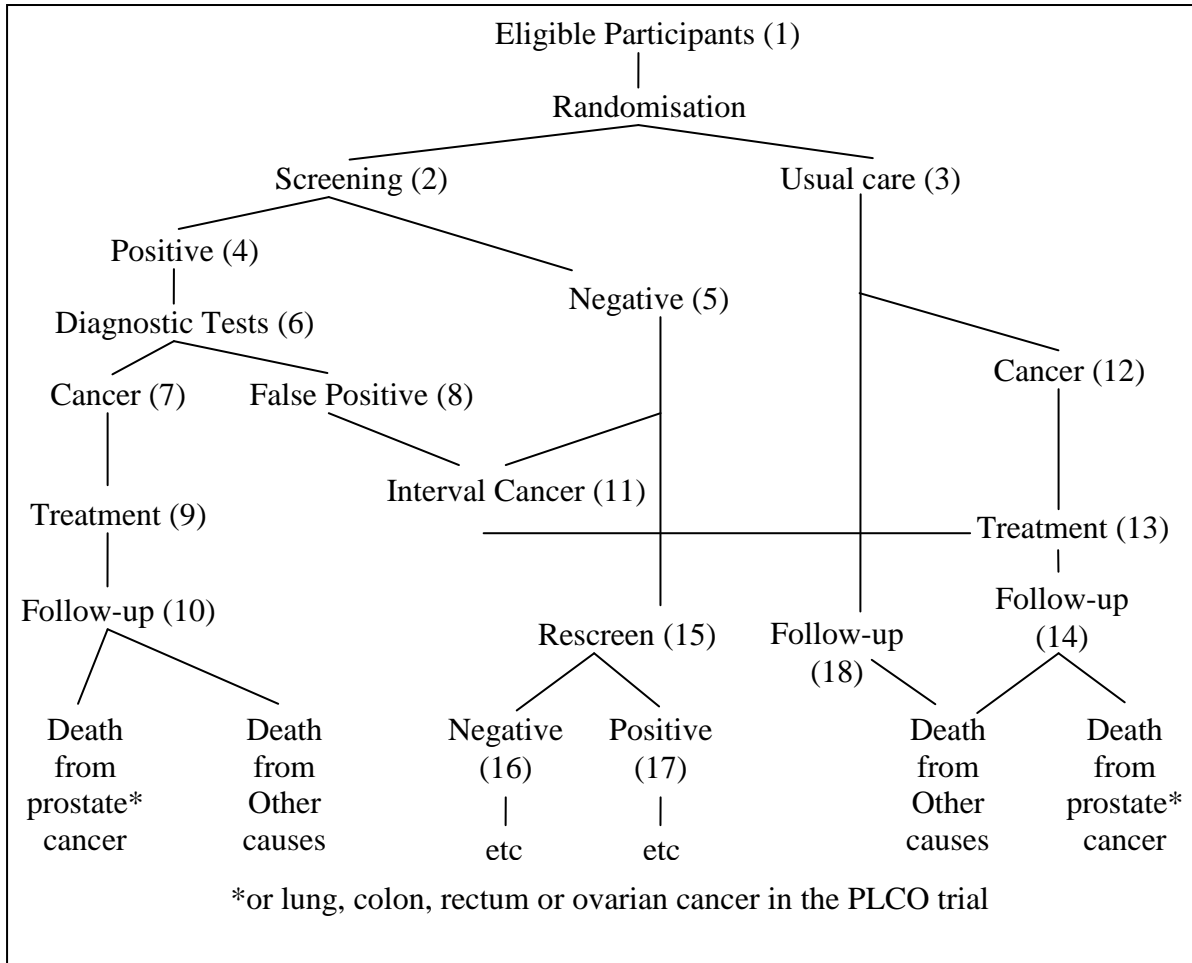


Figure 4.1 Framework for cost-effectiveness and health-related quality of life measurements (Miller et al, 2001)

Currently the PLCO trial is still ongoing and therefore, costs associated with the screening offered are still being determined. However, Figure 4.1 demonstrates that assessing quality of life and costs within a large screening trial is not a simple exercise. Miller et al (2001) provides an explanation of each numbered node and costs associated with screening as found in Table 4.1.

Table 4.1 Explanation of each numbered node (Miller et al, 2001)

1	There is a cost associated with identifying participants eligible for screening.
2	Costs associated with the screening tests are important, as they may be the major cost of the screening process.
3	Costs associated with usual care including physician's visits for symptoms associated with cancer and any diagnostic tests.
4/5	There are costs associated with notifying screen-test results.
6/8	Distinguishing true from false positives and managing false-positives require special study, as these may not be under the control of the screening centre with implications for insurance.
7/9/10	The costs of treating true-positives will vary by stage.
11/12/13/ 14	The costs of identifying, treating and managing interval and non-screen-detected cancers should be the same by stage, age and centre as for the general population.
15/16/17	Re-screening costs will be similar to the initial screening, although they involve costs associated with ensuring compliance.
18	Associated costs of follow-up of the usual care group.
19/20	Associated costs with terminal illness from fatal cancers may be incurred earlier in life in the usual care group than the study group.
21/22	Associated costs for caring for people dying of other causes will also require study.

A later publication by Lafata et al (2004) identified 1,087 participants in the same PLCO screening trial with the aim of determining the medical and non-medical costs associated with false-positive prostate, lung, colorectal and ovarian cancer screens. 43% of the sample incurred at least one false-positive cancer screen with the majority of these patients (83%) receiving follow-up care. Significantly higher medical care expenditures were found in the year following screening among those with a false-positive screen. Transvaginal ultrasound alongside CA125 was used as the screening method in the PLCO trial resulting in a false positive result of 3.2% with transvaginal ultrasound and 0.5% with CA125 in this sample analysed. The most frequently used follow-up tests for women with a false-positive ovarian cancer screen were repeat CA125 (55.6%) and transvaginal ultrasound (44.4%).

4.2 NHS Based Cancer Screening Programmes

There are three cancer screening programmes currently offered in the National Health Service, breast, cervical and bowel.

4.2.1 Breast Cancer Screening

The NHS Breast Screening Programme was setup in 1988 and provides free breast screening every three years to all women in the UK aged 50 to 70 years of age. This age range will be extended to 47 to 73 years of age by 2012. Breast cancer screening was implemented following Forrest recommendations that mammography can lead to prolongation of life for women aged 50 and over with convincing evidence that based on clinical grounds a change in UK policy was required. Key figures at 31st March 2008, most recently available, (The Health and Social Care Information Centre, 2009):

- Among women aged 53-64 over three-quarters (76.6%) had been screened at least once in the previous three years.
- Over 2.2 million women (aged 45 and over) were invited for screening with over 1.7 million women being screened.
- 14,100 cases of cancer were diagnosed in women aged 45 years and over. Of all cancers diagnosed 11,110 (78.7%) were invasive and of these 5,814 (52.3%) were 15mm or less which could have not been detected by hand.
- In England the budget for the breast screening programme is now estimated to be approximately £75 million. This works out at around £37.50 per woman invited or £45.50 per woman screened.
- The breast screening programme is to develop further extending the age range from 47 to 73 years of age over time.

4.2.2 Cervical Cancer Screening

Cervical screening is a method of preventing cancer by detecting and treating early abnormalities which, if left untreated could lead to cancer of the cervix. The study aims to reduce the incidence of invasive cervical cancer and its associated mortality rates. All women aged 25 to 64 are eligible for a free cervical screening test every three to five years depending on their age. Key figures at 31st March 2008, most recently available, (The Information Centre for Health and Social Care, 2008):

- 4.18 million women were invited for screening with 3.4 million women being screened in 2007-08.
- Cervical screening, including the cost of treating cervical abnormalities, has been estimated to cost around £157 million a year in England. Primary Care Trusts commission cervical screening from the overall allocation they receive from the Department of Health.

4.2.3 Bowel Cancer Screening

Bowel cancer screening aims to detect bowel cancer at an early stage in asymptomatic people when treatment is more likely to be effective. The NHS bowel cancer screening programme offers screening to all men and women aged 60-69. Key figures at 31st March 2008, most recently available, (NHS Cancer Screening Programmes, 2008):

- A pilot study was performed with 478,250 residents of pilot areas invited to take part with an uptake of 56.8%. 552 cancers were detected by screening.
- Following the pilot, NHS bowel cancer screening was introduced in July 2006.
- In 2006-07 the cost of the bowel screening programme was £10 million.
- In 2007-08 the cost was £27.5 million.
- In 2008-09 the cost is estimated at £55 million.

4.2.4 Comparison of ovarian cancer screening with currently offered cancer-screening programmes

It is clear from analysing the three currently offered NHS cancer screening programmes that the main aim is to detect disease at an early stage when treatment should be more effective. The UK National Screening Committee (August, 2009) provide criteria for appraising the viability, effectiveness and appropriateness of a screening programme with key points that must be met as follows:

The Condition

- The condition should be an important health problem
- The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage.
- All the cost-effective primary prevention interventions should have been implemented as far as practicable.

The Test

- There should be a simple, safe, precise and validated screening test.
- The test should be acceptable to the population.
- There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.

The Treatment

- There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.

The Screening Programme

- There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public.
- The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).
- The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (ie. value for money).
- Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme.

Each screening programme currently offered has specific age criteria for inclusion and screening intervals justified by clinical evidence and preliminary work prior to introduction into the NHS screening setting. In particular, prior to the bowel screening programme being introduced a large pilot study was performed to determine the feasibility of introducing a national screening programme for colorectal cancer based on faecal occult blood testing into the NHS. The current (2009) policy position of the UK National Screening Committee is that *“ovarian cancer screening should not be offered except in the context of the Medical Research Council randomised control trial”*(UK National Screening Committee, 2009). This policy was reviewed in July 2006 and will be reviewed again in 2009/10. The Medical Research Council (MRC) has funded a randomised control trial of ovarian cancer screening, UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) that is due to report in 2010/11. 200,000

postmenopausal women have been recruited and randomised to screening involving ultrasound and CA125 analysis or randomised to a control group as part of this research.

The same researchers based at University College, London have introduced the United Kingdom Familial Ovarian Cancer Screening Study (UKFOCSS). The UKFOCSS is investigating whether ovarian screening is beneficial for those women who are at an increased risk of developing ovarian cancer. Researchers are aiming to detect ovarian cancer at an early stage when treatment has a higher success rate and prove whether screening is effective at detecting cancer and actually save lives (Jacobs, 2009). The UKFOCSS aims to recruit 5000 women, 35 yrs or above with an increased risk of developing ovarian cancer due to family history of cancer or are a breast cancer gene carrier. As found from the literature review performed, several studies used this approach to screening, however, many others screened only postmenopausal women and others pre and postmenopausal women without increased risk of developing ovarian cancer. It is therefore, difficult to establish what approach is more 'beneficial' in screening for ovarian cancer as the studies analysed vary in their screening techniques and inclusion criteria.

The findings from both the UKCTOCS and UKFOCSS will be vital in determining the cost implications of screening to the NHS, what anxieties and fears are associated with screening and complications that might arise through screening. This information will be used by the UK National Screening Committee to make an informed decision about the introduction of an NHS based national screening programme for ovarian cancer.

4.3 NHS Screening Programme for Ovarian Cancer

Should the findings from both the UKCTOCS and UKFOCSS provide clinical evidence and benefit that ovarian cancer screening is feasible and should be offered in the NHS setting, extensive cost analysis will need to be performed and decisions made into which screening strategy should be implemented and why.

4.3.1 Inclusion Criteria

Through the literature review performed and experience in UK National Screening studies, it is clear that two main screening populations and inclusion criteria exist. Firstly, screening postmenopausal women aged 50 – 74 years of age as used in UKCTOCS (Menon et al., 2005). Secondly, focusing on those women determined to be at high risk of developing ovarian cancer due to family history or a genetic predisposition aged 35 years and above, as used in UKFOCSS (Jacobs, 2009). However, again through evidence from the literature review and performing retrospective studies at Milton Keynes Hospital, a third option may also exist based on this researcher's opinion.

There is a clear benefit in screening premenopausal women as Taylor et al (2003) detected the majority of cancers in this age group and through the retrospective study of ovarian cancer cases diagnosed at Milton Keynes Hospital, 17 of the 75 cases were found in premenopausal women. Around 20% of all ovarian cancer cases in the UK are found in women below 50yrs of age and therefore, offering screening to all premenopausal women would not be justified. Premenopausal women are at lower risk of developing ovarian cancer due to age and known to have benign gynaecological conditions that increase the number of false positive screening rates using CA125 and ultrasound (Jacobs, 2009). Identifying those women at risk of developing ovarian

cancer due to family history of the disease or a genetic predisposition, including premenopausal women, as used in UKFOCSS, is also proposed in scenario three. The most successful screening study of the 17 analysed in the literature review was by Menon et al (2002) that involved postmenopausal women undergoing a transvaginal ultrasound using complex morphological ultrasound criteria following a raised CA125 result. The highest PPV of all studies analysed was achieved at 37.2% with a sensitivity of 100% and specificity of 97%. It is therefore proposed in the third scenario, that pre and postmenopausal women at high risk of developing ovarian cancer and all postmenopausal women with a raised CA125 result are offered screening. This approach was not found in any of the studies included in the literature review and would provide screening to both those at risk of developing ovarian cancer due to age and due to a family history or genetic predisposition.

4.3.2 Scenario One

UKCTOCS focused on postmenopausal women from the general population aged 50 to 74 years of age with 202,638 participants recruited over three years. 13 NHS Hospitals in different regions of the UK were involved in the study, meaning an average annual recruitment of **5,196 participants** per Hospital involved in UKCTOCS.

4.3.3 Scenario Two

UKFOCSS focuses on women aged 35 years and older determined to be at high risk of developing ovarian cancer due to family history of the disease or a genetic predisposition. Currently 4550 participants have been recruited into 36 NHS Hospitals in different regions of the UK, meaning an average annual recruitment of **63 participants** per Hospital involved in UKFOCSS.

4.3.4 Scenario Three

The inclusion criteria used in scenario three will include those women in UKFOCSS and postmenopausal women with a raised CA125 result. Based on Menon et al (2000) 22,000 women volunteered for screening with 714 (3.25%) found to have an elevated CA125 result. Therefore, screening scenario three would expect 63 participants through the UKFOCSS inclusion and 3.25% of the 5,196 recruited through UKCTOCS, meaning an average annual recruitment of **232 participants** per NHS Hospital involved in scenario three. Figure 4.2 provides an overview of the screening population in Scenario Three and a breakdown of expected participants recruited based on experience in the UKFOCSS at Milton Keynes Hospital and literature reviewed.

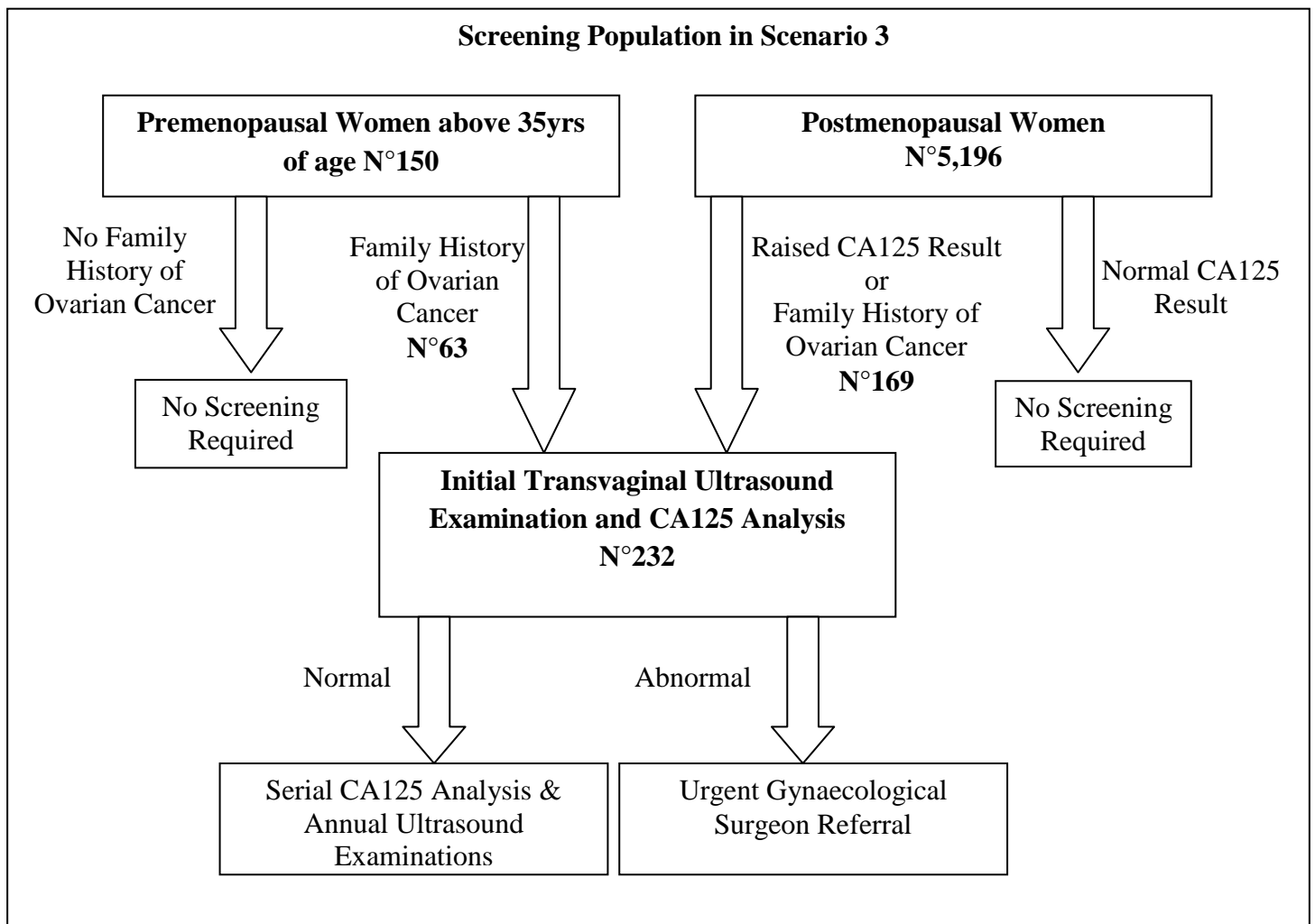


Figure 4.2 Screening Population in Scenario 3

Figure 4.2 provides a flow diagram of scenario three from initial recruitment and initial ultrasound and CA125 analysis. The numerical data is based on the UKCTOCS and UKFOCSS data with approximately 232 participants expected per NHS hospital involved in this suggested screening population and protocol. If numerical data found in the Milton Keynes Hospital audit (Chapter 3) was used to interrogate this scenario, it would mean due to the majority of patients diagnosed with ovarian cancer being postmenopausal (77%) and as the majority of cases regardless of menopausal status had a raised CA125 (92%) the postmenopausal population should have a high sensitivity of screen detected disease. As previously mentioned, false positive screening rates are

higher in premenopausal women due to a host of benign gynaecological conditions (Jacobs, 2009) however, 17 of the 75 cases in the Milton Keynes Hospital Audit were in this population with five cases found to have a family history of breast or ovarian cancer. Therefore, scenario three provides a means of screening those premenopausal women at risk of developing familial ovarian cancer as screening all premenopausal women would not be feasible or ethically justified.

4.3.5 Screening Method

Studies analysed in the literature review varied from those using ultrasound alone for screening and others that incorporated biomarker analysis with ultrasound examination. Ultrasound examination particularly through the use of transvaginal scanning provides a diagnostic, non-ionising, sensitive method of imaging the ovaries and therefore, an ideal screening tool. Ultrasound was found to be of particular diagnostic benefit when incorporated with a complex ultrasound morphological criteria as used by Menon et al (2000), achieving the highest PPV of all studies in the literature review (an example of one used in UKFOCSS can be found in Appendix G). The benefit of incorporating biomarker analysis into screening for ovarian cancer was clearly found by Buys et al (2005) with a positive predictive value of 1% with ultrasound alone, 3.7% with CA125 alone and a combined positive predictive value of 23.5%. The limitations of CA125 are acknowledged and have previously been explained however, at present no other clinically proven biomarker in the NHS setting for ovarian cancer detection is available.

The surveillance of women offered screening was also found to vary in the studies analysed with some reviewing women annually and others screening three to four times per year. Stirling et al (2005) concluded that annual surveillance with ultrasound and CA125 is ineffective in detecting tumours at a sufficiently early stage to influence

prognosis with three cancers (two FIGO Stage III and one FIGO Stage IV) not being detected by screening and presenting in the interim screening period. The retrospective study performed at Milton Keynes Hospital also highlights how unsuitable annual screening for ovarian cancer is, with case 29 diagnosed with FIGO Stage III disease on surgical laparoscopy and a normal CT examination reported just four months prior. Therefore, should NHS based ovarian cancer screening be introduced it is clear that due to the often aggressive nature of ovarian cancer more frequent intervals of screening will be required during a period of 12 months.

The inclusion criteria and screening methods decided upon for NHS implementation will have a direct impact in the cost implications for screening. UKFOCSS aims to screen participants every 3 months with CA125 and perform annual ultrasound examinations, as used in scenario three, based on evidence that annual screening with current tests may not provide adequate sensitivity for early stage disease or impact on mortality rates (Jacobs, 2009).

4.3.6 Quality Control of a Screening Programme

Should the UK National Screening Committee decide to implement ovarian cancer screening this researcher feels similar steps to the UK Fetal Anomaly Screening Programme (FASP) could be used. The FASP aims to set standards and oversee the implementation of a good quality screening programme for all women in England. Guidance and standards that must be met are provided with recently employed regional screening leads to visit hospitals involved in the screening programme to offer advice and assistance at a local level. This approach has already been proven to be effective and provide continual guidance and support for those Hospital Trusts offering

screening. The screening method for ovarian cancer regardless of screening population decided upon by the National Screening Committee will involve ultrasound examination and therefore, Sonographers involved in this screening may require a certain level of gynaecological experience and reporting criteria to adhere to. This researcher feels that given the nature of ultrasound examinations, double checking of images would not be feasible or diagnostically beneficial in every participant however, advice from a senior colleague or referring gynaecologist could be sought in difficult or uncertain cases and would aid in the learning process of staff involved in a screening programme.

4.4 Proposed Cost Analysis for NHS Implementation of Screening

In order to provide a cost analysis of the three screening options, the annual finance required will be estimated based on the expected number of participants recruited and costs associated with diagnosis, surgical intervention and consultant referral for consent and clinical management. It is expected that should NHS based ovarian cancer screening be offered, extra facilities may be required on Hospital sites, additional equipment such as ultrasound machines and costs associated with recruitment of participants. However, these requirements would be individual to the needs of each NHS trust and its surrounding population and therefore, not within the scope of this study to estimate. Therefore, cost analysis will focus on direct costs applicable to all NHS trusts involved in the screening process alone, based on NHS national recommended tariff costs.

The following costs were established through collecting financial data from Milton Keynes Hospital NHS Foundation Trust Finance Department based on national recommended tariff costs:

- Ultrasound - £65 per examination
- CA125 - £31 per analysis
- Laparoscopic surgical procedure – £1,256
- Consultant Gynaecologist referral – £158 for initial consultation
£76 per follow-up attendance

Cost Analysis for Scenario One – Based on UKCTOCS (Menon et al., 2005)

Inclusion Criteria

- Screen women aged 50 – 74 years of age.
- Postmenopausal:
 - 12 months amenorrhoea following natural menopause or hysterectomy
 - 12 months of hormone replacement therapy commenced for menopausal symptoms

Exclusion Criteria

- Bilateral oophorectomy
- Currently active non-ovarian malignancy (excluding skin cancer)
- Women who have had an ovarian malignancy in the past
- Women at high risk of ovarian cancer due to a familial predisposition
- Woman participating in other ovarian cancer screening trials

Table 4.2 Cost Analysis for Scenario One – Based on UKCTOCS

	Ultrasound Examination	CA125	Laparoscopic surgery	Gynaecological Consultation	Estimated Total Costs per regional centre
Annual Cost per participant	£65	£31	£1,256 per laparoscopy required	£158	£257
Annual Cost for 5,196 participants (expected number of participants based on UKCTOCS experience)	£337,740	£161,076	£15,663 (*0.24% of 5,196 participants)	£820,968	£1,335,447
*Based on research by Menon et al (2005) using the UKCTOCS strategy of the 6,532 women who underwent screening, 144 women with an elevated risk from CA125 had a transvaginal ultrasound resulting in 16 women undergoing surgery (0.24% of total number screened).					

Cost Analysis for Scenario Two – Based on UKFOCSS (Jacobs, 2009)

Inclusion Criteria

- Women aged 35 years and over.
- Inclusion in the study will be on the basis of a family history of cancer confirmed by histopathology report or death certification or a documented mutation of an ovarian cancer causing gene.

Exclusion Criteria

- Bilateral oophorectomy
- Women less than 35 years of age
- Woman participating in other ovarian cancer screening trials

Table 4.3 Cost analysis for Scenario Two – Based on UKFOCSS

	Ultrasound Examination	CA125 3 per annum	Laparoscopic surgery	Gynaecological Consultation	Estimated Total Costs per regional centre
Annual Cost per participant	£65	£31 x 3	£1,256 per laparoscopy required	£158	£348
Annual Cost for 63 participants (expected number of participants based on UKFOCSS experience)	£4095	£5859	£2057 (*2.6% of the 63 participants)	£9954	£21,965
*Based on research by Stirling et al (2005) using UKFOCSS strategy of the 1,110 women who underwent screening, 29 women required surgery (2.6% of the total number screened).					

Cost Analysis for Scenario Three – Based on Literature Review and Retrospective Study

Inclusion Criteria

- Women aged 35 years and over at increased risk of developing ovarian cancer due to family history or a genetic predisposition (UKFOCSS).
- Postmenopausal women with a raised CA125 result (>30U/ml).
 - 12 months amenorrhoea following natural menopause or hysterectomy
 - 12 months of hormone replacement therapy commenced for menopausal symptoms

Exclusion Criteria

- Bilateral oophorectomy
- Woman participating in other ovarian cancer screening trials

Table 4.4 Cost Analysis for Scenario Three

	Ultrasound Examination	CA125 3 per annum	Laparoscopic surgery	Gynaecological Consultation	Estimated Total Costs per regional centre
Annual Cost per participant	£65	£31 x 3	£1,256 per laparoscopy required	£158	£348
Annual Cost for expected 232 participants	£15,080	£21,576	£7,576 (*2.6% of the 232 participants)	£36,656	£80,888
*Based on research by Stirling et al (2005) using UKFOCSS strategy of the 1,110 women who underwent screening, 29 women required surgery (2.6% of the total number screened).					

4.5 The Impact on Milton Keynes Hospital in offering an ovarian cancer-screening programme

Milton Keynes Hospital NHS Foundation Trust has been involved in the UKFOCSS for over three years and has recruited in that time 30 eligible participants. Participation in this study currently requires the following:

- A named consultant gynaecological surgeon to be aware of the study design, consent eligible participants and receive referrals if suspicion of cancer exists or medical advice is required.
- A research nurse to co-ordinate the participants and liaise with the main research centre when ultrasound examinations and blood tests are required.
- A reporting sonographer with gynaecology experience to perform annual ultrasound examinations on participants and more frequent examinations or follow-up scans as required.

The main research centre based at the University College, London (UCL) co-ordinates the participant's management from the blood analysis and ultrasound reports. The research nurse is then informed should a participant need a referral to the named gynaecologist or follow-up ultrasound examinations. Therefore, the involvement of Milton Keynes Hospital in this study is relatively small as the main workload is managed by the main research centre. Should the UK National Screening Committee decide that ovarian cancer screening should be offered by a hospital such as Milton Keynes NHS Foundation Trust, the impact would depend on which scenario to implement. However, as the implementation would be a screening programme, rather than research based studies, Milton Keynes Hospital would have a dramatically increased involvement.

4.5.1 Impact of Scenario One

The impact of scenario one (based on UKCTOCS) would be substantial to Milton Keynes Hospital as approximately 5,196 participants would require screening. This scenario would not only cost in the region of £1,335,447 as explained in Table 4.2, but also require additional facilities and staffing associated with a screening programme of this size. This scenario would require several full-time members of staff to be involved in the screening programme including:

- Gynaecological surgeon(s) to refer patients with abnormal screening tests, perform surgical interventions and manage treatment options if malignant disease is diagnosed.
- Several reporting sonographers would be required to perform ultrasound examinations on such a large number of anticipated women recruited with new equipment purchased for the screening. A number of additional ultrasound examinations would also be required in the interim periods due to abnormal CA125 levels.
- Several staff familiar with screening would be needed to co-ordinate consent and eligibility checks on recruited women, manage blood tests and ultrasound examination results.

A separate screening unit on site would be required at Milton Keynes Hospital as current facilities could not manage the number of women offered screening. It is expected that many cases would require discussion in multi-disciplinary team meetings when monitoring of ovarian cysts and CA125 levels are equivocal. Therefore, a large amount of time would be needed to decide on patient management. The costs of scenario one are therefore, high and in excess of those predicted in Table 4.2, as new premises would be required, multiple members of staff involved and ultrasound

equipment purchased. Recruitment of possible eligible women for screening would be substantial as CA125 levels would be required from the outset.

The main benefit of scenario one would be through offering screening to those women at risk of developing ovarian cancer due to age as over 80% of cases are diagnosed in women over 50yrs of age, with a steep increase in incidence in postmenopausal women (aged 55yrs and over), as seen in Figure 1.3 (Cancer Research UK, 2009). No screening would be offered to those women at risk of developing ovarian cancer due to family history of the disease, a genetic predisposition of the disease or premenopausal women. Scenario one uses a biomarker that has been proven to be limited in its sensitivity of detecting ovarian cancer with elevated levels found in 29-75% of cancers diagnosed at the earliest stage (Menon & Jacobs, 2002). Therefore, scenario one differs from several other screening studies reviewed as ultrasound was often used alongside CA125 analysis, however, in scenario one only those women with elevated CA125 levels undergo an ultrasound examination. The only positive aspect of using CA125 in this screening population is the specificity of CA125 is expected to improve as premenopausal women are not included and are known to have elevated CA125 levels due to benign ovarian disease, fibroids, endometriosis and pelvic inflammatory disease, summarised in Table 1.6 (Menon & Jacobs, 2002).

4.5.2 Impact of Scenario Two

The impact of scenario two on Milton Keynes Hospital (based on UKFOCSS) would be far less as approximately 63 (expected number based on UKFOCSS national experience) participants would require screening. Scenario two is expected to cost in the region of £21,965 (Table 4.3) in direct screening costs for this number of participants. This cost and workload would therefore, be manageable in the same or similar manner

at present with patients co-ordinated by a nurse with screening experience who co-ordinates eligibility checks, consent and the screening results, with ultrasound examinations performed in the imaging department. The costs of scenario two would therefore, be significantly less in comparison with scenario one, as fewer staff would be required, no new premises or at the present time, ultrasound equipment required.

Scenario two focuses on familial ovarian cancer and therefore, does not offer screening to those at risk of developing the disease due to age. As scenario two incorporates premenopausal women it is expected that additional ultrasound examinations and gynaecological reviews would be required due to the known elevated CA125 levels associated with benign gynaecological conditions in this screening population. Therefore, costs associated with additional ultrasound examinations and gynaecological referrals must be considered as clinical management of not only CA125 levels will be required but also incidental findings of benign gynaecological disease (Menon et al, 2000). A higher proportion of surgical interventions due to benign gynaecological pathology associated with premenopausal women is expected (Stirling et al, 2005) and as shown in the second retrospective study performed at Milton Keynes Hospital, the majority of false positive imaging cases were in premenopausal women. Therefore, a named gynaecologist that can be referred to directly would be frequently required to coordinate additional ultrasound examinations or further diagnostic imaging to decide when surgical intervention is necessary.

4.5.3 Impact of Scenario Three

The impact of scenario three lies somewhere between scenarios one and two with approximately 232 participants expected to be recruited. This researcher's opinion for screening was based on the literature review performed and retrospective studies at Milton Keynes Hospital. Scenario three would involve both a financial cost in the region of £80,888 (Table 4.4), with several members of staff required and space for clinics to be held for confirmation of eligibility, consent and imaging. It is expected that additional staff dedicated to the screening programme would be required to take blood for initial CA125 screening and eligibility checks, but also to manage CA125 analysis every three - four months and coordinate ultrasound examinations as required.

The main benefit of scenario three is that screening is offered to those women at increased risk of developing ovarian cancer due to age and familial or genetic predisposition and therefore, focusing on women at increased risk of the disease regardless of menopausal status. As annual screening was found to be ineffective in detecting tumours at a sufficiently early stage to influence prognosis (Stirling et al, 2005, Gaarenstroom et al, 2006 and Fishman et al, 2005), monitoring of CA125 levels is proposed every three - four months with ultrasound examination performed annually or when required based on CA125. A single reporting sonographer could perform ultrasound examinations as required on those women recruited with the named gynaecological surgeon receiving referrals for clinical management. Additional facilities would be required for this scenario at Milton Keynes Hospital and the costs of this scenario would be higher than in scenario two, however, more women at risk of developing ovarian cancer would be offered screening.

4.6 Conclusion of Cost Analysis

It is clear from the cost analysis of the three scenarios that due to the different inclusion criteria used there is a large difference in the expected number of participants with UKCTOCS expected to recruit 5,196, UKFOCSS expected to recruit 63 and scenario three expected to recruit 232. This difference obviously has a significant impact on the costs associated with the screening proposed with UKCTOCS costing £1,335,447, UKFOCSS costing £21,965 and scenario three costing £80,888 per annum. The cost analysis performed has provided an overview of direct costs applicable to all NHS trusts involved in the screening process alone, based on NHS national recommended tariff costs. Each NHS trust involved in a screening programme will have individual needs for facilities, staffing and equipment. There will also be significant costs associated with the recruitment of participants, eligibility checks and additional ultrasound examinations / CA125 analysis for surveillance.

The UK National Screening Committee will therefore, have to decide once the findings of UKCTOCS are published in 2010/11 as to the cost benefit of offering ovarian cancer screening in the NHS setting. An annual cost of at least £1,335,447 (if based on UKCTOCS) should be expected per NHS Trust involved, based on this basic cost analysis, in addition to individual NHS trusts needs to offer such screening. The results of UKFOCSS will not be known for some time as the study is still ongoing at the time of this research. Scenario three based on this researcher's opinion offers a novel screening protocol from those analysed in the literature review and a means for those women at risk of developing ovarian cancer due to age or by having familial / genetic predisposition ovarian cancer screening.

5 DISCUSSION

5.1 Ovarian Cancer Screening

The aim of this project was to investigate the feasibility of an NHS based ovarian cancer screening programme with regard to current clinical evidence, resources required, costs involved and implications for a local NHS Foundation Trust. In order to achieve this aim several research methods have been used to provide evidence based conclusions and justified recommendations. As NHS based ovarian cancer screening is not currently recommended by the UK National Screening Committee a research project of this nature is of relevance both at a local level in investigating the requirements of a screening service and at a national level in key points found from the systematic literature review and retrospective studies.

5.1.1 Why offer ovarian cancer screening?

Ovarian cancer accounts for more deaths than all the other gynaecological cancers combined. In 2007, the most recently available statistics, 4,317 UK women died from ovarian cancer, accounting for around 6% of all female deaths from cancer (Cancer Research UK, 2009). The majority of women who develop ovarian cancer have few symptoms until the cancer has spread, by then treatment is more difficult. Symptoms experienced are vague and difficult to recognise particularly in the early stages of the disease (Rufford et al., 2007). Through the retrospective study performed the largest group of cases at Milton Keynes Hospital were diagnosed with advanced FIGO Stage IV disease (31%) meaning distant metastasis and a five-year survival rate of 15%, in comparison to over 85% if diagnosed at Stage I (Menon and Jacobs, 2002). Cases 17, 39, 42 and 49 highlight the problems of vague symptoms as due to changes in bowel habit with weight loss, bowel pathology was suspected by referring general practitioners rather than ovarian disease. Therefore, symptoms cannot be used to screen for this disease. The majority of patients (93%) diagnosed with ovarian cancer in Milton

Keynes Hospital were due to sporadic disease rather than familial and therefore, patients were not known to be at risk of developing ovarian cancer due to a familial or genetic predisposition. All cases in the retrospective study with confirmed ovarian cancer had features of malignancy on imaging prior surgical intervention. Through the second retrospective study 35 cases over an 18 month period highlight the limitations of imaging, as ovarian pathology was suggested of unknown nature. Many of these cases simply required follow-up with ultrasound or MRI/CT, resulting in 40% still requiring surgical intervention to reach a final diagnosis of non-malignancy.

5.1.2 Who should be offered screening?

A systematic literature review was used to provide an insight into recent published studies investigating ovarian cancer screening and each study analysed for inclusion criteria and methods adopted. This review highlighted the range of screening methods used with six different inclusion criteria (Figure 2.3) in the 17 studies analysed with variations found in age, menopausal status and associated risk of developing ovarian cancer due to family history of the disease as follows:

1. Peri and postmenopausal women.
2. Postmenopausal women.
3. Postmenopausal women with raised CA125.
4. Premenopausal and postmenopausal women.
5. Premenopausal and postmenopausal women at high risk of developing ovarian cancer.
6. Women >50yrs of age and women >25 yrs of age at high risk of developing ovarian cancer.

Both findings from the first retrospective study and Cancer Research UK (2009) indicate that around 80% of women diagnosed with ovarian cancer are above the age of 50 which equates to 77% of women being postmenopausal. However, 17 women from

the 75 diagnosed with cancer at Milton Keynes Hospital were premenopausal with three of this group diagnosed with advanced FIGO Stage IV disease. A high incidence of premenopausal cancers was also found by Taylor et al (2003) with 15 of the 20 cancers detected in this group. Literature suggests around 5-10% of all cases of ovarian cancer are the result of an inherited gene or genes (Sekine, 2001). Five cases from the retrospective study were found to have a documented family history of breast or ovarian cancer resulting in a 6.7% incidence of familial ovarian cancer at Milton Keynes Hospital. Therefore, this research implies that should ovarian cancer screening be offered in the NHS setting both pre and postmenopausal women are at risk of developing the disease and whilst some may have a family history or carry a BRCA gene mutation, a large proportion of cancers will result from sporadic disease particularly in postmenopausal women.

5.1.3 How to screen for ovarian cancer

Variations in screening tools used were found through the systematic literature review with six studies using ultrasound examination alone and 11 studies incorporating the use of tumour markers alongside ultrasound. The studies analysed that incorporated serum tumour markers have a large variation in their sensitivity and positive predictive values. The benefit of incorporating biomarker analysis into screening for ovarian cancer was clearly found by Buys et al (2005) with a positive predictive value of 1% with ultrasound alone, 3.7% with CA125 alone and a combined positive predictive value of 23.5%. The most successful screening study of the 17 analysed was by Menon et al (2000) that involved postmenopausal women undergoing a transvaginal ultrasound using complex morphological ultrasound criteria following a raised CA125 result, resulting in the highest positive predictive value of all studies analysed at 37.2%. Through the retrospective study at Milton Keynes Hospital, 73 of the 75 cases had a

pelvic tumour detected through imaging often through the use of ultrasound examination with secondary disease, if present, detected in all cases on CT/MRI. The limitations of both ultrasound and CA125 are well documented and have already been discussed however, as no other clinically proven biomarker other than CA125 is presently available and as 92% of patients with ovarian cancer in the retrospective study had a raised CA125 level, it is clear both imaging and CA125 analysis are required for screening in the NHS setting. Transvaginal ultrasound has been recognised for several years as the ‘gold standard’ of ultrasound clinical practice, offering improved image resolution and visualisation of the female pelvis. However, it is important to address the efficacy of performing invasive examinations on screening patients. Andrykowski et al (2007) and Drescher et al (2004) found that compliance of women to a semi-annual screening protocol diminished rapidly. In comparison Pavlik et al (2000) found high levels of continuation through annual ultrasound screening with 96% of women returning for visits within two years, indicating that women take ovarian cancer disease seriously and it is of consequence to them through continuing with screening.

5.1.4 How often to screen for ovarian cancer

How often to perform ovarian cancer screening is of great importance when investigating the impact to an NHS hospital both in clinical diagnosis and cost implications with variations found as shown in Tables 4.2, 4.3 and 4.4. Stirling et al (2005) found ultrasound and CA125 when performed annually ineffective in detecting tumours at a sufficiently early stage to influence prognosis with three cancers presenting within the 12 month screening period. Similar findings were observed by Gaarenstroom et al (2006) and Fishman et al (2005) with advanced cancers being detected at screening or presenting in the interim screening period with symptoms. Case 29 in the retrospective study also highlights how unsuitable annual screening for ovarian cancer

is and how quickly it can develop and spread. This case had FIGO Stage III disease detected on surgical laparoscopy however, a normal CT examination was reported just four months prior to diagnosis. Therefore, both literature and the retrospective study suggests that monitoring of ovarian appearance and biomarker analysis is required more frequently than every 12 months and as frequent transvaginal scanning may result in poor participant compliance, CA125 analysis every three to four months is proposed alongside annual transvaginal ultrasound as used in the UKFOCSS.

5.1.5 Impact to a local NHS Trust

It is clear from the cost analysis in chapter four, that due to the different inclusion criteria used there is a large difference in the expected number of participants and impact on the costs associated with screening. Scenario three was proposed based on the systematic literature review and retrospective studies performed meaning that women at risk of developing ovarian cancer due to family history or a genetic predisposition and all postmenopausal women with a raised CA125 result are offered screening. This approach was not found in any of the studies included in the literature review and provides a novel method of offering screening to those at risk of developing the disease. It was decided that offering screening to all premenopausal women would not be ethical or justified as they are at lower risk of developing ovarian cancer due to age and not diagnostically beneficial due to increased false positive screening rates caused by benign gynaecological conditions using both ultrasound and CA125 (Jacobs, 2009). Therefore, if this screening method is adopted in a local NHS Hospital such as Milton Keynes a cost in the region of £80,888 per annum would be expected. It is anticipated that these costs would be higher as a number of participants will require more than one ultrasound examination per annum and additional CA125 analysis for surveillance.

Regardless of the method of screening decided upon for NHS introduction, specialist screening staff as currently used in breast and bowel screening at Milton Keynes Hospital will be required in order for the screening to be managed appropriately. A wide variation in the number of participants is predicted depending on who is offered screening by the UK National Screening Committee. As shown in Figure 4.1, Miller et al (2001) provides a breakdown of where costs are associated with screening and also an insight into the time implications involved in following up participants and deciding on management depending on screening results obtained.

5.2 Conclusion

It is apparent from the literature on ovarian cancer screening that internationally extensive research is performed however, there is lack of consensus on who to offer screening to, and the most efficacious way of offering it. A wide variation of screening methods were found all varying in their inclusion criteria and tools for early cancer detection with many using ultrasound examination and CA125 analysis for screening. The majority of ovarian cancer cases diagnosed at Milton Keynes Hospital over a five year period were found to have advanced (FIGO Stage IV) disease at time of diagnosis, meaning a five-year survival in the region of 15% (Menon and Jacobs, 2002). Statistically significant differences were found in the ages of women diagnosed with FIGO classification stages of disease and CA125 levels. A wide age range of women were diagnosed with ovarian cancer with varying symptoms experienced and clinical presentation. The retrospective studies highlight the limitations of imaging and often ultrasound in the characterisation of ovarian lesions.

Key aspects of this research could now be developed further from the retrospective studies, ultrasound reporting and national implementation of ovarian cancer screening. Further analysis of data collected at Milton Keynes Hospital could compare groups of women diagnosed with ovarian cancer to determine if there are any similarities with lifestyle or family history of cancer not documented in the medical notes. The most successful screening study found was performed by Menon et al (2000) that incorporated using complex ovarian morphology classification achieved a positive predictive value of 37.2%. Kurjak et al (2005) also provides a sensitivity of 100% and specificity of 99.4% using three-dimensional ultrasound and power Doppler. Therefore, as provided in Appendix G, it may be useful to incorporate a complex ovarian

morphology classification system into radiological reporting on a routine NHS based ultrasound examination and should screening be introduced, it would provide a consistent method for all practitioners to adhere to. Three dimensional ultrasound is not currently routinely used in the NHS however, based on results published by Kurjak et al (2005) it could provide a means of improving the specificity of lesion characterisation. Further work would also be required based on this research into costs involved in an ovarian cancer screening programme. It is clear the large variations in expenditure based on scenarios discussed in this paper and the NHS alongside NICE would need to ensure adequate funding is in place prior to implementation of a new NHS based programme. This researcher feels that an ovarian cancer screening programme is only feasible with the necessary resources and specialist staff alongside appropriate national guidance and support. The financial impact of such a programme is expected to be large however, as shown from the literature review early ovarian disease can be detected prior to symptoms developing ie: screen detected, and therefore, should provide more effective treatment at an earlier stage. The suggested scenario three that includes both premenopausal and postmenopausal women is aimed at detecting ovarian cancer in groups at risk of the disease due to family history and age. This researcher suggests that based on literature and the local audit performed, an inclusion criterion such as this is vital as although the majority of cases were postmenopausal women, many cases of premenopausal women were also found in studies reviewed. Obviously, CA125 is a biomarker with known limitations in its sensitivity and specificity however, given that the majority (92%) in the local audit performed had a raised level, this screening test is required in scenario three until a more diagnostically useful marker is developed.

Investigating how implementation of screening at a national level could be performed, should the National Screening Committee decide that screening will be offered in the

NHS. As breast screening is based at a hospital or in a mobile screening unit and cervical screening is typically based at a local general practitioner clinic, it would be interesting to see whether ovarian cancer screening could be offered by one NHS Trust providing screening services for a region or if every Trust would need to offer a screening service. It is clear through both the literature reviewed and the retrospective studies that annual screening is inadequate for early detection of disease however, performing transvaginal scans every three to four months would not be feasible in the NHS setting. Research is ongoing into the development of a biomarker that proves more sensitive to early disease and specific to ovarian malignancy, as clearly this is urgently required in clinical practice (Gogoi et al, 2006). Knowledge about the characteristics of ovarian cancer, stages, grades, histologies, inheritance factors and aetiology is required to define criteria for searches of possible useful markers. Should a new more sensitive biomarker be found the application and translation from the laboratory to clinical use is vital. With the additional requirement that all marker analysis must be undertaken in a manner, which is suitable for use within an NHS Hospital where equipment, which is able to undertake detailed molecular analyses, may not be available.

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APPENDICES

APPENDIX A
Studies Included from Cochrane Library Database Search

Author and Year of Publication	Study Objectives and Study Design	SIGN Grading	Key Findings
Study No° 1 (Andersen et al., 2007)	Investigate the effects of participation in an ovarian cancer screening programme on worry about cancer risk and quality of life. Randomised controlled clinical trial with two groups – one group assigned to screening and risk counselling and one group randomised to usual care alone.	1+	Ovarian cancer screening does not have significant negative effects on participants, at least when they do not receive abnormal results. For those who receive abnormal results, screening may have long-term effects and increase worry about cancer risk.
Study N° 2 (Bell et al., 1998)	Systematic review to provide the NHS Health Technology Assessment programme with an overview of the results of research evaluating screening for ovarian cancer.	2++	Wide variations in inclusion criteria and modalities used for screening study participants. Uncontrolled screening studies cannot provide reliable evidence concerning the effect of ovarian cancer screening on health outcomes such as mortality and quality of life.
Study N° 3 (Buys et al., 2005)	Ovarian cancer screening with transvaginal ultrasound (TVS) and CA125 evaluated in the Prostate, Lung, Colorectal and Ovarian (PLCO) trial.	1++	Positive predictive value with CA125 was 3.7%, 1.0% for an abnormal TVS and 23.5% if both testes were abnormal. Effect of screening on ovarian cancer mortality in the PLCO cohort has yet to be evaluated. Screening identified early and late stage neoplasms with relatively low predictive value.
Study N° 4 (Drescher et al., 2004)	Report on rates of compliance with an ovarian cancer screening protocol using CA125 and transvaginal ultrasound. 292 women at average to intermediate risk for developing ovarian cancer were randomly assigned to arms of a controlled clinical trial.	1+	Despite extensive follow-up, compliance of average and intermediate risk women to an ovarian cancer screening protocol requiring semi-annual screening diminishes rapidly. Semi-annual screening incorporating TVS may be too intensive for use in this population.
Study N° 5 (Jacobs et al., 1999)	Pilot randomised control trial to assess multimodal screening with sequential CA125 and ultrasound. Postmenopausal women randomised to a control group and screened group.	1+	A positive predictive value was 20.7%. Median survival of women with index cancers in the screened group was 72.9 months and in the control group was 41.8 months. Results show a multimodal approach to ovarian cancer screening in a randomised trial is feasible and justify a larger randomised trial to see whether screening affects mortality.

Study N° 6 (Jeyarajah et al., 1999)	Randomised control trial to assess correlation between CA125 elevation, a past history of cancer and future risk of non-gynaecological cancer among asymptomatic postmenopausal women. 22,000 women included in study.	1+	Asymptomatic postmenopausal women who have elevated CA125 are at substantially increased risk of gynaecologic cancer. No increased risk of breast carcinoma or other non-gynaecological cancer. Previous history of breast carcinoma is associated with CA125 elevation it is not a predictor of recurrence.
Study N° 7 (Lacey et al., 2006)	Evaluation of positive predictive values of CA125 or transvaginal ultrasound screening for ovarian cancer according to family history or breast or ovarian cancer. Randomised control trial with 28,460 women receiving baseline and annual CA125 and transvaginal ultrasound examinations. Women classified as average, moderate and high risk based on family history or due to a personal history of breast cancer.	1+	Probabilities of abnormal annual CA125 and transvaginal ultrasound screens were similar across groups. Ovarian cancer was more likely to be diagnosed after an abnormal screening result among women at higher family history-based risk than among women at lower risk.
Study N° 8 (Lafata et al., 2004)	Evaluation of medical and non-medical costs associated with false-positive prostate, lung, colorectal and ovarian cancer screens. 1,087 trial participants were identified enrolled in a large managed care organisation. Medical care use and costs were compiled from automated resources and trial data.	2	43% of the study sample incurred at least one false-positive cancer screen with the majority (83%) receiving follow-up care. Significantly higher medical care expenditures in the year following screening were found among those with false-positive screen. The adjusted mean difference was \$1,024 for women and \$1,171 for men.
Study N° 9 (Menon et al., 2005)	To evaluate prevalence screening in the first prospective trial of a new ovarian cancer screening strategy (risk of ovarian cancer (ROC) algorithm) on the basis of age and CA125 profile. Postmenopausal women randomly assigned to a control group and screened group. Those with elevated values underwent transvaginal ultrasound and those with persistently equivocal ultrasound were referred to a gynaecologist.	1++	13,282 were recruited. 6,682 were randomly assigned to screening. 16 women underwent surgery – 11 had benign pathology, one woman had ovarian recurrence of breast cancer, one woman had borderline and three women had primary invasive epithelial ovarian cancer. Specificity and positive predictive value for primary invasive epithelial ovarian cancer were 99.8% and 19% respectively. An ovarian cancer screening strategy using the ROC algorithm is feasible and can achieve high specificity and positive predictive values in postmenopausal women.
Study N° 10 (Rufford et al., 2007)	Randomised control trial to determine the feasibility of screening for ovarian cancer using symptoms as selection criteria. 390 General Practitioner surgeries were included with rapid access to ultrasound and CA125 for women suffering from symptoms that may be caused by ovarian cancer.	1+	23 women had abnormal findings on ultrasound. 20 managed conservatively and 3 surgically. No ovarian cancer cases were detected in this pilot study, possibly due to the size of the cohort.

APPENDIX B
Studies Included from SCOPUS Database Search

Author and Year of Publication	Study Objectives and Study Design	SIGN Grading	Key Findings
Study N° 1 (Andersen et al., 2002)	Reports of perceived risk of ovarian cancer, worry, and screening use in a large sample of women. Well designed cohort study. 3257 women participated by completing a survey on ovarian cancer risk.	2++	Family history did predict perceived risk, difficulties due to worry and use of ovarian cancer screening. Most women over-estimated their risk of developing ovarian cancer. Some average-risk women get screening although it is not recommended outside of randomised control trials and a significant percentage of women at high risk fail to get recommended screening.
Study N° 2 (Andrykowski et al., 2007)	Identification of clinical, demographic, dispositional and attitudinal variables associated with return for routine, annual TVS screening for ovarian cancer. Well-designed cohort study. 585 asymptomatic, average to high risk women participating in a university-based ovarian cancer-screening programme.	2++	Despite recommendations to return in 12 months for screening, over 25% of the sample did not return for repeat TVS screening within 24 months of their baseline TVS. Possessing more than 12 years of education was associated with a greater likelihood of returning for screening. Assuming the effectiveness of cancer screening is predicted on timely repeat screening, the results in this study are worrisome and suggest the need to develop effective means of increasing the proportion of women returning for repeat screening.
Study N° 3 (Bosse et al., 2006)	Evaluation of the accuracy of TVS in combination with CA125 to detect ovarian cancer in women at hereditary risk for ovarian cancer. A prospective cohort study of 676 women including 85 BRCA mutation carriers. Surgical intervention was performed if TVS revealed a suspicious cyst or elevated CA125 levels.	2++	10 women underwent histological verification that revealed one serious cystadenocarcinoma stage 1c. No interval ovarian cancer occurred. Specificity of surgical intervention reached 98.7% and a positive predictive value of 10%. The low positive predictive value is due to the unexpectedly low incidence of ovarian cancer. Large scale investigations are needed to further evaluate accuracy and effectiveness of ovarian cancer screening for women at high risk.
Study N° 4 (Crayford et al., 2000)	Whether some benign ovarian cysts can develop into cancerous cysts is not known. Cohort follow-up of 5479 asymptomatic women participating in ultrasound based screening was assessed to determine whether the removal of persistent ovarian cysts from these women was associated with a reduction in the number of deaths from ovarian cancer.	2++	Removal of persistent ovarian cysts was not associated with a decrease in the proportion of expected deaths from ovarian cancer. For population-based screening of healthy women without a family history of ovarian cancer, a screening test is required that is specific and sensitive to early malignant disease.

Study N° 5 (DePriest and DeSimone, 2003)	Study reports on two cohort ultrasound based screening studies using simplistic abnormality criteria. Kentucky trial screened 14,469 women. Hirosaki trial screened 51,550 women.	2++	180 women underwent surgery in the Kentucky trial with 17 ovarian cancers detected, 11 of which were invasive epithelial lesions. 344 women underwent surgery in the Hirosaki trial with 22 ovarian cancers detected. Both studies showed the low positive predictive value of ultrasound screening.
Study N° 6 (Fishman et al., 2005)	Investigation into the usefulness of ultrasound in the detection of early-stage epithelial ovarian cancer in asymptomatic high-risk women who participated in the National Ovarian Cancer Early Detection Programme. Cohort study of 4526 women – both pre and postmenopausal.	2++	A total of 98 women with persistent adnexal masses were identified, with 49 invasive surgical procedures performed diagnosing 37 benign tumours and 12 gynaecologic malignancies. Two women had stage 3 ovarian cancer. All cancers were detected in asymptomatic women who had normal ultrasound and physical examinations 12 and 6 months before the cancer diagnosis. Study demonstrated the limited value of diagnostic ultrasound examination as an independent modality for the detection of early stage epithelial ovarian cancer.
Study N° 7 (Gaarenstroom et al., 2006)	Cohort screening study of 269 women at high risk of hereditary ovarian cancer is reported in this paper. Screening was performed using TVS and CA125 testing. 113 of the 269 women had a breast cancer gene (BRCA) mutation. 127 of the 269 women underwent a salpingo-oophorectomy.	2++	In eight women having both elevated CA125 levels and abnormal ultrasound findings a malignancy was found- one borderline, one stage 1a, one stage IIIb and one stage IIIc were detected at first screening visit. One stage IIIb and one stage IIIc were detected at the second screening visit after 12 months. Two stage IIIc and one stage IV were detected 8 and 10 months after the first screening visit. Conclude that the efficacy of screening women at high risk of ovarian cancer seems poor because the majority of cancers were detected at an advanced stage.
Study N° 8 (Goff et al., 2007)	Case control study of 149 women with ovarian cancer, including 255 women who were in a screening programme and 233 women who were referred to pelvic ultrasound. Symptom types, frequency, severity and duration were compared between cases and controls.	2+	Symptoms that were associated significantly with ovarian cancer were pelvic/abdominal pain, urinary urgency/frequency, increased abdominal size, difficulty eating/feeling full when they were present for <1yr and occurred >12 days per month. Symptoms in conjunction with their frequency and duration were useful in identifying women with ovarian cancer.
Study N° 9 (Hensley et al., 2003)	Recommendations for women at high risk of ovarian cancer include prophylactic salpingo-oophorectomy (PSO) or screening with ultrasound and CA125. The best strategy for improving survival and maintaining quality of life is not known. High-risk women >30yrs enrolling in a screening study completed quality of life perception measurement.	2++	Premenopausal women perceive their ovarian cancer risk to be higher, report greater ovarian cancer risk-related anxiety and are more likely to have false-positive screening results than postmenopausal women. Few high-risk women elect PSO in the short term. Knowledge of the frequency of false-positive screening results and psychosocial outcomes is important for high-risk women choosing strategies for managing ovarian cancer risk.

<p>Study N° 10 (Kurjak et al., 2005)</p>	<p>Cohort study to determine whether introducing three-dimensional (3D) ultrasonography with power Doppler as a primary screening test for ovarian cancer improves the accuracy of ovarian cancer screening.</p> <p>Cohort study of 3,201 peri and postmenopausal asymptomatic women aged >50yrs.</p>	<p>2++</p>	<p>25 patients (0.8%) with persisting ultrasound abnormalities after primary and secondary ultrasound screening underwent surgery to remove the tumour.</p> <p>3D ultrasound combined with power Doppler had a sensitivity of 100%, specificity of 99.4%, positive predictive value of 20% and negative predictive value of 100%.</p>
<p>Study N° 11 (Lux et al., 2005)</p>	<p>Prospective follow-up study to evaluate the influence of risk and genetic counselling on use of early cancer detection. 556 BRCA 1/2 gene carriers attended primary consultation in the interdisciplinary cancer clinic. Semi-annular transvaginal ultrasound and pelvic examination was used.</p>	<p>2+</p>	<p>At present it is not known if there is an individual benefit of an intensified early cancer detection programme for women at risk. No studies present a decrease of mortality through early detection especially for women with a family history of breast / ovarian cancer.</p> <p>Early cancer detection can prove to be a psychological strain for women at risk and a financial burden to the health system but it is a less invasive option than prophylactic surgery.</p>
<p>Study N° 12 (Marchetti et al., 2002)</p>	<p>Aim of study to verify if ultrasound as a first level test can be trusted as a screening test for ovarian cancer. 4,350 women with an average age of 49 years underwent ultrasound examination.</p>	<p>2++</p>	<p>29 patients had ultrasound findings indicative of malignant lesions and 147 findings of benign lesions. 2 patients were found to have malignant lesions, both of which were detected by ultrasound.</p> <p>Sensitivity of 100%, Specificity of 99.81% and positive predictive value of 20%. Ultrasound offers an inexpensive, safe and imaging modality capable of picking out possible or malignant ovarian lesions.</p>
<p>Study N° 13 (Menon et al., 2000)</p>	<p>To assess the performance of ultrasonography in a multimodal ovarian cancer screening strategy.</p> <p>741 Postmenopausal women, >45 years with a raised CA125 underwent a pelvic ultrasound. Scans classified as normal, abnormal or equivocal based on ovarian morphology and size.</p>	<p>2++</p>	<p>The sensitivity for detection of ovarian cancer of different ultrasound criteria was 100% for abnormal morphology, 89.5% for abnormal volume and 84% for complex morphology.</p> <p>The highest specificity (97%) and positive predictive value (37.2%) was achieved using complex morphology. A variety of ultrasound criteria can achieve high sensitivity, specificity and positive predictive value for index cancers.</p>
<p>Study N° 14 (Miller et al., 2001)</p>	<p>Decisions on policies for screening for ovarian cancer require that information upon health-related quality of life (HRQL) and cost-effectiveness (CE) be available. A framework within which both HRQL and cost-effectiveness of ovarian cancer screening can be assessed is presented in this study.</p>	<p>1+</p>	<p>Assessment of quality of life and costs within a large screening trial is not a simple exercise. There is potential for significant respondent burden, which could adversely affect the main trial processes. Costs are still being collected from the US Prostate, Lung, Colon and Ovary Trial.</p>

<p>Study N° 15 (Van Nagell Jr. et al., 2007)</p>	<p>To determine the efficacy of annual transvaginal sonography (TVS) as a screening method for ovarian cancer.</p> <p>Annual screening was performed on 25,327 asymptomatic women above 50yrs of age or above 25yrs of age with a family history of ovarian cancer. Persisting abnormal TVS had a serum CA125, tumour morphology indexing and Doppler flow ultrasound.</p>	<p>2++</p>	<p>364 patients with persisting TVS abnormalities underwent surgical intervention with 35 primary invasive ovarian cancers detected. 28 Stage I, 8 Stage II and 8 Stage III. TVS screening was associated with a sensitivity of 85%, specificity of 98.7%, positive predictive value of 14.01% and negative predictive value of 99.9%.</p> <p>TVS screening when performed annually is associated with a decrease in stage at detection and a decrease in case-specific ovarian cancer mortality. TVS screening does not appear to be effective in detecting ovarian cancer in which ovarian volume is normal.</p>
<p>Study N° 16 (Pavlik et al., 2000)</p>	<p>The effect of ovarian cancer screening on survival is enabled by women who continue to actively participate in screening. This study examines factors that affect participation.</p> <p>Background, health history and reasons for participating in transvaginal ultrasound screening were collected from 13,963 women above 50yrs old by means of a questionnaire.</p>	<p>2++</p>	<p>The probabilities of a return screen at 1,2,5 and 7.5 years were 77.8%, 72%, 58.7% and 50.6% respectively. A total of 96% of return visits occurred within 2yrs. Perceived family history was not observed to affect continuation. However, abnormal findings were associated with a shortened participation.</p> <p>High levels of continuation in ultrasound screening indicate that women take this disease seriously and demonstrate that this disease is of consequence to them.</p>
<p>Study N° 17 (Roupa et al., 2004)</p>	<p>The aim of this study was to evaluate the combination of serum CA125 and TVS as a screening procedure for ovarian cancer in pre and postmenopausal women.</p>	<p>2+</p>	<p>TVS and increased CA125 levels detected 120 women with ovarian cancer. A sensitivity of 81.7%, specificity of 100% was achieved in predicting ovarian cancer. By combining TVS and CA125 an accurate prediction for the presence of ovarian cancer may be achieved.</p>
<p>Study N° 18 (Saito et al., 2005)</p>	<p>A new efficient screening for ovarian cancer based on a combination of two tumour markers, CA602 and CA546 is reported in this study. When the level of one or both tumour markers exceeded the cut-off, the individual was referred for secondary tests including TVS and CA125.</p>	<p>2+</p>	<p>A combination of CA602 and CA546 increased the detection rate of ovarian cancer from 77.8% to 85.8%, compared with CA602 alone, demonstrating that the combination assay was effective at detecting ovarian cancers.</p>
<p>Study N° 19 (Salsman et al., 2004)</p>	<p>Clinical, demographic and psychological characteristics of new, asymptomatic participants in a transvaginal ultrasound-screening programme for ovarian cancer. A cohort of 312 women were assessed immediately before undergoing a TVS for ovarian cancer.</p>	<p>2++</p>	<p>Analysis revealed that the ovarian cancer screening group characterised not only by more ovarian cancer specific distress and a more extensive family history of ovarian cancer but also by less optimism and less knowledge of ovarian cancer risk factors.</p> <p>88.3% of women invited to undergo ovarian cancer screening provided informed consent. Those who declined screening cited reasons as too busy or too stressed.</p>

<p>Study N° 20 (Sato et al., 2000)</p>	<p>Cohort study of 183,034 women participating in ovarian cancer screening programme. Purpose of study to summarise and evaluate screening results for the last 10yrs with respect to ovarian carcinoma diagnosis and risk factors. TVS was limited to a 30 second examination for identification of a pelvic mass above 30mm in size.</p>	<p>2+</p>	<p>Surgery was performed on 324 participants with 22 primary tumours and 2 metastatic tumours detected.</p> <p>Of the 22 tumours, 17 (77.3%) were classified as Stage 1. These results are significant in that 77.3% of the primary ovarian carcinomas found during the screening were of curable Stage 1.</p>
<p>Study N° 21 (Stirling et al., 2005)</p>	<p>To assess the effectiveness of annual ovarian cancer screening using TVS and CA125 in detecting presymptomatic ovarian cancer in women at increased genetic risk.</p> <p>A cohort of 1,110 women at increased risk were screened. 553 were moderate-risk individuals and 557 were high-risk individuals.</p>	<p>2+</p>	<p>13 epithelial ovarian malignancies developed in the cohort. 10 tumours were detected at screening – three at Stage I, two at Stage II, four at Stage III and one at Stage IV.</p> <p>Of the three cancers not detected by screening two were stage III and one was stage IV.</p> <p>Annual surveillance by TVS and CA125 is ineffective in detecting tumours at a sufficiently early stage to influence prognosis. With a positive predictive value of 17% and a sensitivity of less than 50%.</p>
<p>Study N° 22 (Tailor et al., 2003)</p>	<p>To assess the use of TVS as a screening test for familial ovarian cancer and secondarily, to determine the potential role of CA125 levels in the screening procedure. 2500 asymptomatic women with at least one close relative who had developed ovarian cancer were studied.</p>	<p>2+</p>	<p>Women were aged 17 to 78 with 65% premenopausal and 26% postmenopausal. 104 screens gave a positive result with 11 cancers detected. One additional cancer was reported within 12 months of the last scan and classified as a false-negative screen result. Eight cancers were reported at follow-up (1-9 years after last scan).</p> <p>15 of the 20 cancers occurred in premenopausal women. Ultrasound sensitivity was 92% with a specificity of 97.8%. TVS can effectively detect ovarian cancer and tumours of borderline malignancy in women with a family history of the disease.</p>
<p>Study N° 23 (Zhang et al., 2007)</p>	<p>Artificial neural network (ANN) as a modelling tool has demonstrated its ability to assimilate information from multiple sources and to detect subtle and complex patterns. ANN has been evaluated in this study for its performance in detecting early stage ovarian cancer using multiple serum markers.</p> <p>100 apparently healthy women, 45 with benign conditions arising from the ovary and 55 invasive epithelial ovarian cancer patients.</p>	<p>2+</p>	<p>The combined use of multiple tumour markers through an ANN improves the overall accuracy to discern healthy women from patients with early stage ovarian cancer.</p> <p>At a fixed specificity of 98%, the sensitivities for ANN and CA125 alone were 71% and 46% respectively.</p>

APPENDIX C
**Ethical Approval Document from Milton Keynes Local Research Ethics
Committee for Retrospective Studies Performed**



National Research Ethics Service

Milton Keynes Local Research Ethics Committee

Room 7B, PGEC
Milton Keynes Hospital Site
Standing Way
Eaglestone
Milton Keynes
MK6 5LD

01908 243750 (tele/fax)

14 July 2008

Professor Christopher B-Lynch
Consultant Obstetrician and Gynaecological Surgeon
Milton Keynes Hospital NHS Foundation Trust
Standing Way
Milton Keynes
MK6 5LD

Dear Professor B-Lynch

Study title: Ovarian Cancer Screening Biomarker Pilot Study
REC reference: 08/H0603/14
Amendment number: 1 01.07.08
Amendment date: 01 July 2008

The above amendment was reviewed at the meeting of the Sub-Committee of the REC held on 09 July 2008.

Ethical opinion

On the 14th July 2008 S Nicholson confirmed that he and Professor Lynch would be the only two people accessing the medical records for the retrospective study.

The members of the Committee present gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Protocol	1.4	01 June 2008
MSc in Clinical Research Proposal	1	01 January 2008
Notice of Substantial Amendment (non-CTIMPs)	1 01.07.08	01 July 2008

Membership of the Committee

The members of the Committee who were present at the meeting are listed on the attached sheet.

This Research Ethics Committee is an advisory committee to South Central Strategic Health Authority
*The National Research Ethics Service (NRES) represents the NRES Directorate within
the National Patient Safety Agency and Research Ethics Committees in England*

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

08/H0603/14:

Please quote this number on all correspondence

Yours sincerely



Mrs Nicky Searle
Committee Co-ordinator

E-mail: scsha.MiltonKeynesREC@nhs.net

Enclosures

List of names and professions of members who were in attendance at the meeting

Copy to:

Professor Clifford Friend
Deputy Vice-Chancellor
Cranfield University
Cranfield
Beds MK43 0AL

Mr S Nicholson
14 Balsam Close
Walnut Tree
Milton Keynes
MK7 7NB

K Hunter
R&D Manager
Milton Keynes Hospital

Milton Keynes Local Research Ethics Committee

Attendance at Sub-Committee of the REC meeting on 09 July 2008

Name	Position (or reason for attending)
Mr Zvi Friedman	Lay Member
Dr J Zachariah	General Practitioner

APPENDIX D

Table of Ovarian Cancer Cases diagnosed at Milton Keynes Hospital NHS Foundation Trust

Case No	Menopausal Status	Age at Diagnosis	Presenting Symptoms	Diagnostic Findings	CA125	History of Cancer	FIGO
1	Postmenopausal	65	Adenocarcinoma in right pleural effusion	Pelvic mass. Omentum replaced with tumour. Ascites.	541		4
2	Postmenopausal	50	Weight loss. Pelvic pains. Abdominal swelling.	Bilateral pelvic masses. Ascites.	4403		2
3	Postmenopausal	58	Abdominal distension and epigastric pain.	Large ovarian mass. Inguinal lymph node. Omental spread.	1564		3
4	Postmenopausal	62	Intermittent right sided pain.	Bilateral ovarian and tubal malignancies. Omental spread. Involvement of sigmoid. Peritoneal spread.	1136		3
5	Postmenopausal	60	Pelvic pain / swelling. Previous hysterectomy.	Complex irregular mass in right adnexa 8cmx7cm.	90		3
6	Postmenopausal	60	Abdominal swelling.	Pelvic mass.	41		2
7	Postmenopausal	60	Abdominal pains.	Pelvic mass. No spread.	43		1
8	Postmenopausal	60	Abdominal swelling.	Localised pelvic mass. No spread.	90		1
9	Postmenopausal	57	Pleural effusion. Abdominal swelling.	Cystic / solid pelvic mass on ultrasound. Ascites. Pleural effusion.	599		4
10	Postmenopausal	63	Abdominal pain. Change in bowel habit.	Ascites. Peritoneal metastatic disease. Omental thickening.	2500	Mother and 1st cousin breast ca.	4
11	Postmenopausal	60	Pelvic discomfort. Change in bowel habit.	Enlarged ovary containing a simple cyst on ultrasound. Ascites. Bilateral disease on CT.	547		3
12	Premenopausal	50	Abdominal discomfort	Large complex ovarian cyst. No spread.	31		1
13	Postmenopausal	58	Pain and swelling in abdomen.	Large pelvic mass. Bowel involvement.	1000		3
14	Postmenopausal	59	Abdominal discomfort.	Large pelvic mass.	40		1
15	Postmenopausal	77	Change in bowel habit. Weight loss.	11cmx8cm solid mass infiltrating the rectum on CT. Ascites and liver metastasis.	1054		4
16	Premenopausal	43	Pelvic pains.	Complex pelvic mass.	11	Mother and sister have had ovarian cancer.	2
17	Postmenopausal	53	Pelvic pains. Palpable mass.	Solid / Cystic pelvic mass in pelvis on U/S and CT. No distal spread.	97		1
18	Postmenopausal	57	Abdominal distension. Pelvic pain.	Ascites. Pelvic mass.	187	History of Cervical cancer.	2
19	Postmenopausal	63	Mass felt in pelvis. ? Ovarian cyst.	Pelvic tumour. Omental thickening.	120		3
20	Postmenopausal	55	Abdominal discomfort. Right leg pains.	Pelvic mass. Malignant cells in peritoneum.	47		3

21	Postmenopausal	78	Abdominal pain. Change in bowel habit.	Pelvic mass. Peritoneal spread. Ascites. Pleural effusion.	290		4
22	Postmenopausal	78	Shortness of breath. Abdominal distension.	Loculated cystic area 11cmx6cm on CT. Pleural effusion. Omental thickening.	1325		4
23	Postmenopausal	87	Postmenopausal bleeding.	Pelvic mass. Ascites. Liver metastases disease. Bowel metastases.	396		4
24	Postmenopausal	65	Abdominal pains.	Pelvic mass on CT and U/S. Ascites and Omental thickening. Liver metastasis.	84		4
25	Postmenopausal	74	Change in bowel habit.	Complex pelvic mass. Ascites.	115		2
26	Postmenopausal	60	Abdominal bloating	Complex pelvic mass. No spread.	153		1
27	Postmenopausal	70	Pelvic pain.	Pelvic mass. Omental thickening.	92		2
28	Postmenopausal	63	Postmenopausal bleeding.	Complex pelvic mass. Omental spread.	98		3
29	Postmenopausal	52	Right iliac fossa / pelvic pain.	Bilaterally enlarged ovaries on CT. Peritoneal spread.	20		3
30	Postmenopausal	58	Abdominal pain / discomfort. Urinary symptoms.	Complex pelvic cyst.	363		1
31	Postmenopausal	65	Abdominal distension.	Complex pelvic mass. Periaortic lymph node.	286		1
32	Postmenopausal	67	Abdominal distension and pelvic mass felt.	Multi-cystic mass arising from pelvis and solid components. Enlarged nodes. Liver mets.	529		4
33	Postmenopausal	83	Abdominal distension and urinary frequency.	US shows 12cmx8cm cystic lesion with irregular wall thickening, ascites and liver mets.	1379		4
34	Postmenopausal	75	Postmenopausal bleeding.	Complex pelvic mass. Spread to small bowel.	4924		3
35	Postmenopausal	72	Urinary symptoms and frequency.	Abdominal mass. Localised 16cm tumour.	51	Family history of breast cancer.	1
36	Postmenopausal	75	Lower abdominal pains.	6cm Pelvic mass.	471		1
37	Postmenopausal	74	Abdominal pain and anaemia.	Cystic / solid pelvic mass on US and CT. Possible liver mets.	2355		3
38	Premenopausal	47	Pelvic discomfort. Change in bowel habit.	Cystic / solid pelvic mass 12cm x 14cm. One mass open.	176	Breast cancer	2
39	Premenopausal	30	Abdominal distension and shortness of breath.	Large mass filling abdomen with cystic and solid components. Ascites / pleural effusion.	268		4
40	Postmenopausal	53	Abdominal pain	Complex pelvic mass 6-8cm in size. Omental spread.	287		2
41	Postmenopausal	71	Abdominal swelling. Weight loss.	Pelvic tumour. Ascites and bowel involvement. Deposits under the diaphragm.	4179		3
42	Postmenopausal	73	Pelvic pain. Irregular bleeding.	15cm Complex cystic / solid pelvic mass on US and CT. Lymphadenopathy.	5036		2
43	Postmenopausal	79	Abdominal swelling.	Ovarian tumour with extensive ascites.	431		3
44	Postmenopausal	59	Lower abdominal pains.	Complex ovarian mass 12cmx8cm. No distal spread.	2225		1
45	Postmenopausal	78	Lymphoedema.	Pelvic mass on CT and US. Lymphadenopathy.	378		3

46	Premenopausal	44	Pelvic pain. H/O endometriosis.	Localised pelvic mass. No spread.	5000		1
47	Postmenopausal	59	Postmenopausal bleeding.	Complex pelvic cyst. No other spread.	7		1
48	Postmenopausal	63	Weight loss. Pelvic discomfort.	Ascites, peritoneal mets, lung mets. No ovarian mass detected.	1384		4
49	Premenopausal	39	Abdominal pain. Urinary symptoms.	Large pelvic mass. Cervical lesion.	413		2
50	Premenopausal	52	Irregular vaginal bleeding. Pelvic pain.	Localised pelvic mass. No spread.	9		1
51	Postmenopausal	57	Abdominal distension.	Pelvic mass. Ascites. Adhered to bowel and liver. Omentum replaced with tumour.	910	Mother breast and bowel Ca. Cousin breast Ca.	4
52	Premenopausal	53	Postmenopausal bleeding.	Complex pelvic mass. Cancer of ovary with spread to uterus and cervix.	500		2
53	Postmenopausal	68	Change in bowel habit. Weight loss.	Ascites. Omental thickening. Pelvic mass. Pleural effusions. Liver metastases.	182		4
54	Postmenopausal	51	Postmenopausal bleeding.	Bilateral ovarian masses. Extensive peritoneal seedlings.	866		3
55	Premenopausal	40	Abdominal distension.	Bilateral ovarian masses. Ascites and omental thickening.	794		3
56	Postmenopausal	71	Abdominal bloating.	Complex abdominal mass. Omental spread.	456		3
57	Postmenopausal	60	Lower limb swelling. Abdominal mass felt.	Complex solid mass on CT 9cmx8cm. Peritoneal seedlings.	1370		4
58	Premenopausal	54	Abdominal distension. Pain.	Large abdominal mass. Ascites. Pleural effusion.	21		4
59	Premenopausal	39	Right iliac fossa / pelvic pain.	Bilateral ovarian masses. One mass opened - one closed.	891		2
60	Premenopausal	44	Pelvic pain.	Bilateral ovarian tumours. Omental spread	155		4
61	Postmenopausal	61	Abdominal discomfort. Vaginal bleeding.	Abdominal mass. Omental nodular disease spread.	800		4
62	Postmenopausal	55	Abdominal distension. Change in bowel habit.	Complex abdominal mass. Omental spread.	5000		4
63	Premenopausal	52	Irregular vaginal bleeding. Pelvic pain.	Fibroid uterus misdiagnosed on US. CT demonstrates complex ovarian mass. Ascites.	978		3
64	Premenopausal	49	Abdominal pain / distension	Solid / necrotic pelvic mass. No spread.	58		1
65	Postmenopausal	57	Abdominal distension and pain.	15cm Pelvic tumour involving the rectum and sigmoid colon. Lung metastatic disease.	325	Bilateral breast cancer. BRCA1 Carrier.	4
66	Postmenopausal	71	Abdominal distension. Change in bowel habit.	Pelvic mass. Ascites. Pleural effusion.	1596		3
67	Postmenopausal	75	Abdominal discomfort and distension.	Pelvic Mass. Ascites. Mesenteric nodularity. Pleural effusion.	364		4
68	Postmenopausal	56	Weight loss/change in bowel habit.	Complex pelvic mass. Liver Metastatic disease.	555		4

69	Postmenopausal	57	Abdominal swelling. Change in bowel habit.	10cm Pelvic mass.	500	1
70	Premenopausal	37	Pelvic pains. Irregular vaginal bleeding.	13cm complex pelvic mass. Ascites. No distal spread.	167	2
71	Postmenopausal	71	Shortness of breath. Abdominal distension.	Liver mets, pleural effusion. Cystic / solid pelvic mass on US.	629	4
72	Postmenopausal	53	Pelvic pain. Palpable mass.	Complex pelvic mass 10cmx14cm. No spread.	60	1
73	Postmenopausal	59	Mass felt in pelvis by GP.	Complicated pelvic mass / cystic lesion.	48	1
74	Premenopausal	41	Altered bowel habit. LIF fullness.	Localised pelvic mass. No spread.	78	1
75	Premenopausal	48	Left iliac fossa tenderness. Unwell.	Complex multilocular cystic lesion on US. No spread.	120	1

APPENDIX E

Table of Suspected Ovarian Cancer Cases diagnosed at Milton Keynes Hospital NHS Foundation Trust

Case No	Menopausal Status	Age	Imaging Modality	Diagnostic Findings / Suspected Pathology	Outcome
1	Premenopausal	43	US	Complex adnexal mass 10cm x 9cm x 6cm with solid areas within.	MRI - confirms dermoid / haemorrhagic cyst.
2	Premenopausal	40	US	Large multiseptated pelvic mass	HISTOLOGY - Benign ovarian cyst with haemorrhagic component
3	Premenopausal	39	MRI	Large ovarian mass with cystic and solid components. Suspected ovarian neoplasm.	HISTOLOGY confirms bowel neoplasm.
4	Premenopausal	37	US	Complex right ovarian mass 7cm x 5cm x 4cm with internal echoes and thickened septae.	HISTOLOGY -endometriotic cyst.
5	Premenopausal	47	CT	Complex adnexal mass on CT ? Fibroid ? Ovarian Ca	MRI - Confirms fibroid.
6	Premenopausal	49	US	Complex multilocular cyst on US	CT - 1 month later no abnormality detected.
7	Premenopausal	29	CT	9cm multilocular cystic lesion with solid components and small volume of free fluid on CT	US - Benign cyst - decreased in size 2 weeks later
8	Premenopausal	53	US	Complex heterogenous mass 8cm x 7cm x 5cm. Unable to exclude malignancy.	HISTOLOGY -mucinous cystadenoma. No malignancy.
9	Postmenopausal	72	US	Large complex cystic ovarian lesion on US	CT - dermoid cyst
10	Premenopausal	48	US & CT	19cm complex mass in pelvis on US and CT. ? Fibroid ? Ovarian Ca	MRI - fibroid.
11	Premenopausal	49	US & CT	Complex solid masses bilaterally on US and CT.	MRI - enlarged ovaries with benign functional cysts.
12	Postmenopausal	71	US & CT	Complex multilocular solid mass on US 9cmx 6cm confirmed by CT as ?Ca.	HISTOLOGY - benign cyst.
13	Premenopausal	45	US & CT	Complex solid pelvic mass. No distal spread. Malignancy suspected.	HISTOLOGY -benign ovarian cyst with haemorrhagic component
14	Postmenopausal	83	US	Large 25cm cyst with septations and wall irregularity on US.	HISTOLOGY - Benign cyst
15	Premenopausal	30	US & CT	Bilateral complex ovarian cysts on US and CT.	MRI - endometriotic cysts.
16	Premenopausal	30	US	Complex cyst with internal septae and solid areas.	HISTOLOGY - Haemorrhagic cyst following laparoscopy.
17	Premenopausal	32	US & CT	Complex solid pelvic mass on US and CT.	HISTOLOGY - Benign endometriotic cyst
18	Premenopausal	38	CT	Multilocular cystic mass in pelvis with solid components. Possible bowel involvement.	HISTOLOGY - confirms benign ovarian fibroma - 25cm in diameter.
19	Premenopausal	16	US & MRI	Bilateral complex ovarian masses with cystic and solid areas within on US and MRI.	US - 3 months time no longer present.
20	Premenopausal	32	US	Irregular complex cystic area in pelvis with solid areas - US.	CT - dermoid cyst
21	Premenopausal	33	US & CT	Enlarged ovary with heterogenous and cystic lesions on US. CT confirms solid / cystic mass.	HISTOLOGY - Endometrioma.

22	Premenopausal	26	ALL	18cmx15cm Pelvic mass with multiple septations and solid components on US / CT and MRI.	HISTOLOGY - Mucinous cystadenoma.
23	Premenopausal	44	US	Solid complex mass on US 7cmx6cm.	CT and MRI required to confirm haemorrhagic / endometrioma.
24	Premenopausal	31	US	Complex ovarian cyst on US with raised CA125. ?Ca	MRI - dermoid cyst
25	Premenopausal	46	US	Solid ovarian mass on US.	MRI - large uterine fibroid.
26	Premenopausal	36	US	Large pelvic mass measuring 32cmx16cmx27cm. ? Fibroid on US. Unable to exclude Ca.	MRI - confirms large uterine fibroid.
27	Postmenopausal	56	US	Solid / cystic mass on US 7cmx3cm.	MRI and CT - confirm dermoid cyst.
28	Premenopausal	27	US	Enlarged complex appearing right ovary measuring 7cmx6cm.	CT confirms pelvic abscess
29	Premenopausal	22	US	Complex ovarian mass on US.	US in 3 months now simple cyst.
30	Premenopausal	44	US	Complex mass in right adnexa 10cmx9cm.	HISTOLOGY - Endometrioma.
31	Premenopausal	36	US	Irregular adnexal mass with solid components.	US in 3 months functional cysts.
32	Premenopausal	41	US	Complex adnexal mass on US 7cmx4cmx9cm. Unable to characterise.	MRI - Endometrioma
33	Premenopausal	27	US	Complex midline pelvic mass on US with solid components measuring 7cmx8cm.	MRI confirms fluid collection.
34	Premenopausal	29	US	Complex ovarian mass on US measuring 6cm x 5cm. Unable to characterise.	MRI - Dermoid cyst
35	Premenopausal	38	US	Abdominal cystic mass filling cavity. ?Endometrioma ?Malignancy	HISTOLOGY - Benign cyst.

APPENDIX F
Email Contact with Cost Accountant at Milton Keynes Hospital
NHS Foundation Trust

From: Catharell Caroline (RD8) Milton Keynes Hospital
Sent: Tue 14/07/2009 11:29
To: Nicholson Simon (RD8) Milton Keynes Hospital
Subject: RE: NHS Costings

Simon,

The 2008/9 cost for an Elective Q49.1 (which links to HRG4 code MA10Z - Upper Genital Tract Laparoscopic / Endoscopic Minor Procedures) is £1,235 which inflated by 1.7% to get to 2009/10 cost would be £1,256.

Hope this helps,

Caroline Catharell
Cost Accountant
Milton Keynes Hospital NHS Foundation Trust
Tel: 01908 826565

-----Original Message-----

From: James Anne-marie (RD8) Milton Keynes Hospital
Sent: 02 July 2009 11:47
To: Nicholson Simon (RD8) Milton Keynes Hospital
Cc: Catharell Caroline (RD8) Milton Keynes Hospital
Subject: RE: NHS Costings

Simon

The OPCS4 code for excision of an ovarian cyst is as follows:

Q49.1 - Endoscopic extirpation of lesion of ovary

Anne-Marie
Anne-Marie James | Clinical Coding Manager | ☎ 01908 660033 (ext 2630) or 01908 (24)3930

-----Original Message-----

From: Nicholson Simon (RD8) Milton Keynes Hospital
Sent: 02 July 2009 10:57
To: James Anne-marie (RD8) Milton Keynes Hospital
Subject: FW: NHS Costings

Dear Ann-marie

Could you provide me with a OPCS code for a laparoscopy performed by a gynaecologist for removal of a cyst/lesion please. I imagine an overnight stay would also be required.

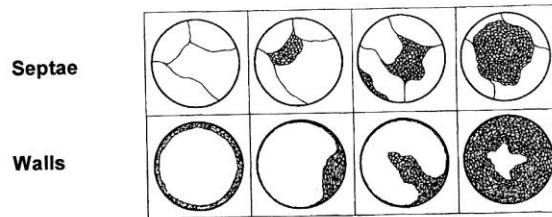
Many thanks.
Simon Nicholson
Reporting Sonographer / Research Fellow

APPENDIX G

UK Familial Ovarian Cancer Screening Study Complex Ovarian Morphology Classification

UK FOCSS UK Familial Ovarian Cancer Screening Study

Figure 2. Examples of Complex Ovarian Morphology



The overall scan result is classified as *Normal (N)*, *Unsatisfactory (U)* or *Abnormal (A)*, depending upon the following Table 2:

Table 2. Transvaginal Scan Classification Algorithm

Ovary 1	Ovary 2	Result
Not visualised, poor view	Not visualised, poor view	U
Not visualised, poor view	Normal morphology	U
Not visualised, poor view	Simple cyst of $\leq 60\text{cc}$ or mean diameter $\leq 5\text{cms}$	U
Not visualised, poor view	Not visualised, good view of iliac vessels	U
Abnormal morphology	Normal morphology	A
Abnormal morphology	Not visualised, good view of iliac vessels	A
Abnormal morphology	Not visualised, poor view	A
Abnormal morphology	Simple cyst of any size	A
Simple cyst $>60\text{cc}$ or mean diameter $>5\text{cms}$	Normal morphology	A
Simple cyst $>60\text{cc}$ or mean diameter $>5\text{cms}$	Not visualised, poor view	A
Simple cyst $>60\text{cc}$ or mean diameter $>5\text{cms}$	Simple cyst $>60\text{cc}$ or mean diameter $>5\text{cms}$	A
Simple cyst $>60\text{cc}$ or mean diameter $>5\text{cms}$	Not visualised, good view of iliac vessels	A
Ascites or fluid in POD $>10\text{mms}$, irrespective of ovarian findings		A
Normal morphology	Normal morphology	N
Normal morphology	Simple cyst of $\leq 60\text{cc}$ or mean diameter $\leq 5\text{cms}$	N
Normal morphology	Not visualised, good view of iliac vessels	N
Not visualised, good view of iliac vessels	Not visualised, good view of iliac vessels	N

POD = Pouch of Douglas, N = Normal, U = Unsatisfactory, A = Abnormal.

Blood flow: Colour Doppler measurements (presence of a signal, site) are recorded in cases where a simple cyst or complex ovarian morphology is detected.

Fallopian Tube Morphology: This will be recorded as Normal or Abnormal for each tube. Abnormal morphology will result in the volunteer being placed on "Clinical Decision" (see Table 3, page 17), unless the overall classification of the scan (using the ovarian morphology criteria in Table 2 above) is Abnormal, in which case the volunteer will be referred to her named rapid access gynaecologist for assessment.