GENETIC EPIDEMIOLOGY OF COLORECTAL, BREAST AND OVARIAN CANCER: USE IN CLINICAL PRACTICE

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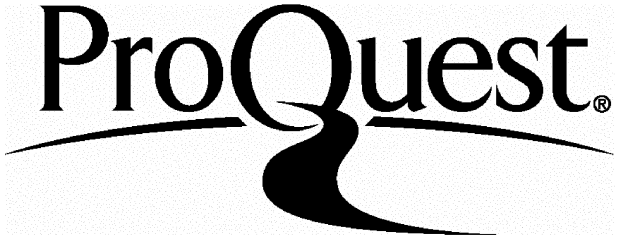

ABSTRACT

The genetic epidemiology of colorectal, breast and ovarian cancer was investigated and used to provide risk estimates for use in clinical practice.

The risk of colorectal, breast and ovarian cancer in first degree relatives of patients with these cancers was determined empirically from extensive sets of pedigrees taken from patients with these cancers or from consultands. For each of these cancers, risks were highest for those relatives of patients diagnosed at a young age.

Complex segregation analysis showed that the familial aggregation of colorectal, breast and ovarian cancer is most compatible with the inheritance of dominant genes. The frequencies of these deleterious genes account for a significant proportion of colorectal, breast and ovarian cancer in young individuals, however, in older age groups the majority of those affected are phenocopies. Using estimates of the probability of inheriting the deleterious gene and the age specific penetrance enables the genetic component of risk at different ages for relatives to be calculated. With an early age of diagnosis the genetic risk to offspring is high, but with increasing age at diagnosis this diminishes. This information can be used to identify more precisely those family members at high risk of colorectal, breast or ovarian cancer and estimate the chance that a dominant gene is responsible for any family aggregation.

The estimates of risk, gene frequency and penetrance were used in two family cancer clinics to determine the screening requirements of relatives of patients with colorectal and breast cancer. Screening was targeted to the relatives at a high risk of cancer. Detection rates for adenomas of the colon and colorectal cancer using colonoscopy, and breast cancers using mammography and ultrasound were high.

In conclusion, family history can be used to identify individuals at a high risk of colorectal and breast cancer who may benefit from screening at an earlier age than members of the general population.

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DECLARATION OF AUTHORSHIP

I worked on these studies as an Imperial Cancer Fund Clinical Research Fellow whilst at the Royal Free Hospital School of Medicine, London, St. Mark's Hospital, London and the Cancer Research Fund Group in Genetic Epidemiology, Southampton University Hospital.

The collection of the clinical data on colorectal cancer and breast cancer was made by myself and other clinicians in the course of our work in genetic clinics at the Royal Free and St. Mark's Hospitals. Pedigrees of ovarian cancer were collected by a worker from the Department of Obstetrics and Gynaecology at King's College Hospital under the direction of Professor W.P. Collins. This was a collaborative study between King's and the Imperial Cancer Research Fund and the pedigrees were kindly made available to me for study. The pedigree worker who collected the data for the King's study was trained in the Department of Clinical Genetics at the Royal Free Hospital.

I am indebted to Professor Newton Morton for his tuition and in allowing me access to the computer facilities in his department at Southampton University.

As indicated by the references to my own publications I was the first author on 10 of the 12 publications resulting from these studies and was primarily responsible for the calculations and drafting of these papers (refer section 7).

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ABBREVIATIONS

AIC	Akaike Information Criterion.
APC	adenomatous polyposis coli.
B_j	risk in the i th liability class for relatives of affected individuals.
BRCA1	putative breast cancer gene on chromosome 17q.
CA	intergenerational variance differences.
ci	multifactorial transmissible component of an individual's phenotype.
C	variance component due to multifactorial transmissible effects.
CFS	cancer family syndrome (Lynch syndrome type II).
COMDS	COMbined segregation and linkage with Diathesis and Severity
X^2	Chi-square(d).
ci	multifactorial transmissible component.
d	dominance.
DCC	(gene) deleted in colorectal cancer.
d.f.	degrees of freedom.
E	random environmental variance.
Ej	expected number of deaths in the j th decade.
ei	environmental contribution to phenotype.
FIGO	International Federation of Gynaecology and Obstetrics, staging of ovarian cancer.
gi	major gene effect.
G	allele G.
G'	deleterious form of allele G.
H	childhood heritability.
HNPCC	hereditary non-polyposis colon cancer.
HSSCC	hereditary site-specific colon cancer (Lynch syndrome type II).
HZ	adult heritability.
I	incidence.
ICD	International Classification of Diseases.
ln (L)+c	log likelihood incorporating a constant value, c.
M	mortality.
MCC	(gene) mutated in colorectal cancer.
μ	mean phenotypic value.
n or N	number.
O	observed number.
OPCS	Office of Population Census and Surveys.
PAP	Pedigree Analysis Package.
P (aff I G)	probability of affection given genotype.

P (G I aff)	probability of genotype given affection.
π	ascertainment probability.
q	gene frequency.
R_j	population risk in j th liability class.
RR	relative risk.
SBLA	sarcoma, breast cancer, lung and laryngeal cancer, leukaemia, and adrenocortical carcinoma syndrome (Li-Fraumeni syndrome).
t	displacement.
TNM	tumour, node, metastasis: UICC Classification of malignant tumours.
V	total phenotypic variance.
xi	an individual's phenotype measurement.
z	mean.
Z	ratio of adulthood to childhood heritability.

SECTION 1: BACKGROUND AND OBJECTIVES

1.1 INTRODUCTION

The majority of cancers are thought to arise as a result of tissue-specific somatic alterations induced by environmental exposure. It is therefore not surprising that cancer epidemiologists have traditionally focused on identifiable factors that increase the risk of cancer in those exposed. Dietary factors have been shown to be important in the development of colorectal and breast cancer [Rogers and Longnecker, 1988; Vecchia, 1989], and the risk of ovarian and breast cancers appears to be influenced by hormonal factors [Van Leeuwen and Rookus, 1989; Adami et al., 1990].

There then might initially appear to be conflict with the suggestion that a large proportion of cancers, including colorectal, breast and ovarian are attributable to genetic factors. However, the genetic basis of cancer has lately evolved into a virtually undisputed concept [Weinberg, 1989]. This view is based on four lines of evidence: (1) The recognition of rare syndromes inherited in a Mendelian fashion associated with cancer such as adenomatous polyposis coli [Bishop and Thomas, 1990], (2) population studies which show that subsets of common cancers such as breast cancer are due to inherited susceptibility [Porter and Steel, 1992], (3) the recognition that sensitivity to the environment is genetically determined and that some individuals are at a higher risk than others for common cancers, such as lung cancer [Levine et al., 1989]; and (4) that inherited and environmental cancer may be genetically the same [Knudson, 1989], that is, the same genes may be responsible for cancers caused by somatic alterations as for cancers caused by inherited germ-line mutations.

This section outlines the evidence for genetic factors in the aetiology of colorectal, breast and ovarian cancer.

1.2 FAMILIAL PATTERNS OF COLORECTAL, BREAST AND OVARIAN CANCER

1.2.1 Familial Patterns of Colorectal Cancer

A number of Mendelian syndromes predisposing to colorectal cancer are recognised (Table 1). They can be divided into two groups; those with multiple adenomas of the bowel and those associated principally with hamartomas, although adenomas do occur. Each can be further subdivided by the presence of either polyposis or extracolonic features [reviewed in Haggitt and Reid, 1986; Murday and Slack, 1989; Bishop and Thomas, 1990].

Of all the inherited syndromes predisposing to colorectal cancer adenomatous polyposis coli (APC) is the most well known and is recognised as the condition associated with the highest risk of bowel cancer. The prevalence of APC is at most 1 in 7000 [Neel 1954; Alma and Licznerski, 1973; DeCoffe et al., 1977; Lipkin et al., 1980], therefore its impact on the overall burden of colorectal cancer risk is very small (less than 0.1%). Still rarer syndromes predisposing to colorectal cancer include Turcot's, Muir-Torre, Peutz-Jeghers, juvenile polyposis and Ruvalcaba-Myrhe; described in Table 1.

The dominantly inherited non-polyposes colorectal cancer syndromes may, however, be responsible for 5% of all colorectal cancers [Lynch et al., 1988], accounting for between 8.6% and 39% of cases diagnosed before age 50 [Mecklin, 1987; Westlake et al., 1990].

Hereditary non-polyposis colorectal cancer syndromes (HNPCC) are usually divided into two groups: Hereditary site-specific colon cancer (HSSCC or Lynch syndrome type I), which predisposes specifically to colonic cancer, and cancer family syndrome (CFS or Lynch syndrome type II), in which there is a predisposition to colorectal cancer and other adenocarcinomas including breast, ovary, uterine and stomach [Lynch et al.,

Table 1. Inherited syndromes associated with colorectal cancer:
Adenomatous Polyposis Syndromes

Adenomatous Polyposis Coli

Multiple colorectal adenomas (typically greater than 100) develop during childhood to early adulthood and progress to adenocarcinomas mainly in the third and forth decades [Bussey, 1975]. Inherited as an autosomal dominant, the gene has been mapped to 5q21-22 [Bodmer et al., 1987; Kinzler et al., 1991a]. The population frequency is between 1 in 7000 and 1 in 30 000 [Neel 1954; Alma and Licznerski, 1973; De Coffe et al., 1977; Lipkin et al., 1980] with 10% to 47% of cases due to new mutations [Jagelman, 1988; Bussey, 1975; Bulow, 1987]. Extracolonic features include; multiple osteomas, epidermoid cysts, desmoid tumours and congenital hypertrophy of retinal pigment epithelium [Gardner, 1951; Smith, 1958; Gardner, 1962; Bulow, 1987; Traboulsi et al., 1988; Chapman et al., 1989; Heyen et al., 1990]. An increased incidence of upper gastrointestinal malignancies [Domizio et al., 1990], papillary carcinoma of the thyroid [Plail et al., 1987] and hepatoblastoma [Kingston et al., 1983; Li et al., 1987] is now recognised in gene carriers.

Turcot's Syndrome

Characterised by adenomas of the colon (fewer than in APC), central nervous system tumours (mainly astrocytomas), focal nodular hyperplasia of the liver [Turcot et al. , 1959; Braughman et al., 1969] and multiple cutaneous features including cafe au-lait patches [Everson and Fraumeni ,1976; Itoh et al., 1979]. Some authors have postulated an autosomal recessive mode of inheritance [McKusick, 1962; Rothman et al., 1975; Erbe, 1976], however, the condition seems more likely to be a variant of APC, at least in those patients with more than 100 adenomas [Lewis et al., 1983].

Table 1. Inherited syndromes associated with colorectal cancer:
Adenomatous Non-Polyposes Syndromes

Muir Torre Syndrome

Autosomal dominant inheritance of carcinomas of the colon, duodenum and larynx in association with kerato-acanthomas and sebaceous adenomas; originally described by Muir et al. [1967]. The cutaneous lesions such as sebaceous cysts have also been reported in association with cancers of the oesophagus, uterus, ovary, bladder and breast [Anderson, 1980a], suggesting an expanding phenotype and possible overlap with the Lynch syndrome type II [Lynch et al., 1988].

Hereditary Non-Polyposis Colorectal Cancer Syndromes

Hereditary non-polyposis colorectal cancer (HNPCC) syndromes are divided into hereditary site-specific colon cancer (HSSCC or Lynch syndrome type I) which predisposes specifically to colorectal cancer and cancer family syndrome (CFS or Lynch syndrome type II) which predisposes to colorectal cancer and other adenocarcinomas, including breast, ovary, stomach and uterine [Lynch et al., 1988]. Both are dominantly inherited, the lifetime penetrance of the deleterious gene has been estimated to be between 0.5 and 0.9 [Mecklin et al., 1986a; Lynch et al., 1988]. In both Lynch syndromes types I and II the peak age of onset of colorectal cancer in affected individuals is in the fifth decade. Furthermore, cancers tend to be right-sided and are more likely to be synchronous or metachronous than in sporadic cases [Mecklin and Jarvinen, 1986; Mecklin et al., 1986b; Lynch et al., 1988]. In one large kindred HNPCC has been shown to be linked to a region close to a gene altered in colorectal cancer, the DCC gene (deleted in colorectal cancer) on chromosome 18q [Lynch et al., 1985; Boman et al., 1988; Fearon et al., 1990]. However, other workers have been unable to confirm this assignment [Peltomaki et al., 1991; Dunlop, 1992].

Table 1. Inherited syndromes associated with colorectal cancer:
Hamartomatous Polyposes

Peutz- Jeghers Syndrome

Autosomal dominant disorder characterised by multiple gastrointestinal hamartomas and mucocutaneous pigmentation. Melanin flecks occur on the face, especially periorally, but may also be present on the fingers, toes and perianally [Utsunomiya et al., 1975] . An increased risk of malignancy, of the gastrointestinal tract and other sites including breast and ovary has been shown in those affected [Utisunomiya et al., 1975; Foley et al., 1988; Giardiello et al., 1988; Spiegelman et al., 1989].

Juvenile Polyposis

Familial juvenile polyposis appears to be inherited as a autosomal dominant. It is characterised by hamartomatous polyposis (more than 10) and an increased prevalence of adenomas of the colon [Veale et al. 1966]. It is not entirely clear whether the hamartomas or the associated adenomatous polyps confer the increased risk of colorectal cancer [Stempler et al., 1975; Grotsky et al., 1982; Mils and Fechner, 1982: Jarvinen and Franssila ,1984; Grosfeld and West ,1986; Jones et al., 1987; Jass et al. ,1988]. Dysmorphic features reported in association with familial juvenile polyposis include, macrocephaly, congenital heart disease and gastrointestinal malformations [Veale et al., 1966; Bussey et al., 1978].

Ruvalcaba-Myhre Syndrome

A probable variant of juvenile polyposis associated with macrocephaly, mental retardation, perianal freckling, diabetes mellitus and seizures [Erbe ,1976; Ruvalcaba et al., 1980; DiLiberti et al., 1983].

1988]. In both syndromes the peak incidence of colorectal cancer is in the fifth decade, and two thirds of cancers are proximal as compared with one third in the general population. Furthermore, cancers are more likely to be synchronous or metachronous than in sporadic cases [Mecklin and Jarvinen, 1986; Mecklin et al., 1986a; 1986b; Lynch et al., 1988].

1.2.2 Familial Patterns of Breast Cancer

The major familial syndromes predisposing to breast cancer are detailed in Table 2.

Families with the classical features of the Li-Fraumeni syndrome are readily identifiable [Li and Fraumeni, 1969; 1982; Li et al., 1988]. However, the occurrence of high grade astrocytomas and soft tissue sarcomas in adult members of families that in other respects fit the description of the Lynch syndrome type II suggests a possible overlap between these two syndromes [Birch, 1990; Steel et al., 1991; Buckley et al., 1992]. This may be clarified with the identification of constitutional mutations of the p53 gene in classical Li-Fraumeni [Malkin et al., 1990; Srivastava et al., 1990; Santibaez-Koref et al., 1991].

The Cowden and Gorlin syndromes also may not be entirely distinct. Both have a variable phenotype and share a number of similar features, such as palmer pits and abnormalities of the neurological and skeletal systems. The relationship between the two syndromes is likely to be better understood following the finding of linkage between chromosome 9q(22.3) and Gorlin's syndrome [Farndon et al., 1992].

Ataxia-telangectasia is an autosomal recessive syndrome in which cancers develop in affected homozygotes at a rate approximately 100 times higher than in unaffected individuals. It is now recognised that individuals heterozygous for the ataxia-telangectasia gene, who may make up approximately 1 per cent of the general population, also have an excess risk of cancer, particularly breast cancer in women [Swift et al., 1987; 1991].

Table 2. Inherited syndromes associated with breast cancer.

'Cancer Family' Syndromes

[Lynch et al., 1988; Lynch et al., 1989; Deville and Cornelisse, 1990].

1. Site-specific breast cancer

   Dominant inheritance of breast cancer only, males occasionally affected .

2. Breast-ovarian cancer

   Dominant inheritance of breast and ovarian cancer only, probable effects of single gene with pleiotropic effects.

3. Lynch syndrome type II

   Autosomal dominant inheritance of colon and other adenocarcinomas including breast, ovary, uterus and stomach. Presumed to be due to the inheritance of a single deleterious gene.

Linkage of early onset breast cancer and breast-ovarian cancer to 17q22 reported [Hall et al., 1990; Narod et al., 1991; Easton et al., 1992].

Li-Fraumeni Syndrome (SBLA)

Classically soft tissue sarcomas in children and young adults, and early onset breast cancer in close relatives, also an excess of adrenocortical tumours, brain tumours, osteosarcoma and leukaemia. High incidence of multiple primary malignancies. Autosomal dominant pattern of inheritance [Li and Fraumeni ,1969; Lynch et al., 1978; Duncan et al., 1983; Pearson et al., 1982; Hartley et al., 1986; Strong et al., 1987; Li et al., 1988]. Germ line mutations in p53 (on chromosome 17p) underlie a proportion of cases [Malkin et al., 1990; Srivastava et al., 1990; Satibanez et al., 1991]. The overall contribution of mutations in p53 to early onset breast cancer is probably small [Prosser et al .,1991. Sidransky et al., 1992].

Table 2. Inherited syndromes associated with breast cancer.

Ataxia Telangectasia

An autosomal recessive syndrome of progressive cerebellar ataxia and occulocutaneous telangectasias with immunological defects [Boder ,1985]. The main defective gene localised to 11q [Gatti et al., 1988]. Affected individuals demonstrate an exquisite sensitivity to ionising radiation and have an approximately 100 fold greater risk of developing cancer, especially lymphomas and lymphocytic leukaemias [Spector et al. ,1982]. Cancer rates also higher in obligate heterozygotes (1% of the white population) [Swift et al., 1987; 1991]; specifically carcinomas of the lung, pancreas, gallbladder, stomach and breast, but not colorectal cancer. The increased risk of breast cancer (5.1 fold) may be related to a history of exposure to ionising radiation [Swift et al., 1991].

Cowden's Syndrome

Adenomas and fibromas of the thyroid, gastrointestinal tract, skeletal system and central nervous system are found in association with mucocutaneous lesions (lipomas, sebaceous cysts and angiomas) in the dominantly inherited multiple hamartoma syndrome (Cowdens disease) [Gentry et al., 1974; Burnett et al., 1975; Brownstein et al. ,1979]. Whilst 35% of patients have polyps in the gastrointestinal tract [Salem and Steck ,1983] the polyps in Cowden's disease are not neoplasms and do not have malignant potential. However, up to 50 per cent of affected women develop breast cancer and 10 per cent of both sexes develop cancer of the thyroid [Brownstein et al., 1978; Walton et al., 1986].

Gorlin's Syndrome

Gorlin (naevoid-basal-cell-carcinoma) syndrome is a fully penetrant, autosomal dominantly inherited disorder characterised by multiple basal-cell naevi of varying degrees of malignancy. Other features include recurrent odontogenic keratocysts, intracranial calcification and agenesis of the corpus callosum, palmer pits and skeletal malformations [Berlin ,1966; Gorlin, 1987]. The minimum prevalence is 1 per 57 000 [Evans et al., 1991]. An increased risk of medulloblastomas, astrocytomas and breast cancer also seen in gene carriers [Gorlin, 1987; Evans et al. ,1991]. Defective gene located within 9q22.3-31 [Farndon et al., 1992].

Homozygotes show an unusual sensitivity to ionising radiation, but whether diagnostic or occupational exposure to ionising radiation increases the risk of breast cancer in women heterozygous for ataxia-telangectasia, remains unclear [Swift et al., 1991; Kuller and Modan, 1992; Boice, 1992; Borie and Miller, 1992; Wager, 1992.

Even collectively, the Cowden, Li-Fraumeni and Gorlin syndromes are rare. There are however, several presumptive dominantly inherited cancer family syndromes (site-specific breast cancer, breast-ovarian cancer and the Lynch syndrome type II) which are likely to have a greater impact on the risk of breast cancer in the general population [Lynch and Lynch, 1985]. They appear to have a later onset of breast cancer than in the Li-Fraumeni and Cowden syndromes and so can be expected to reach higher frequencies at mutation selection. Whether site-specific breast cancer represents a distinct entity has been questioned, since the pedigrees of many of these types of families, when extended, invariably show an excess of other cancers [Steel et al., 1991]. The finding of linkage between the long arm of chromosome 17q22 to both early onset breast cancer [Hall et al., 1990; Easton et al., 1992], and the dominant inheritance of breast and ovarian cancer [Narod et al., 1991; Easton et al., 1992], suggests the inheritance a single gene with pleiotropic effects.

1.2.3 Familial Patterns of Ovarian Cancer

Syndromes predisposing to ovarian cancer are less well defined than the syndromes conferring a high risk of either colorectal or breast cancer. From studies of extended pedigrees, Lynch and co-workers have, however, distinguished three types of family clusters involving ovarian cancer : (1) Site -specific ovarian cancer, (2) breast-ovarian cancer syndrome and (3) the Lynch syndrome type II, with ovarian cancer in association with cancers of the colon, uterus, breast and other adenocarcinomas [Lynch et al., 1990; Lynch et al., 1991]. The pattern of inheritance in these families is consistent

with a dominant mode of inheritance. However, in the families reported the possibility of familial aggregation of ovarian cancer with other cancers by chance cannot be entirely ruled out.

Support for the existence of a breast-ovarian cancer syndrome comes from epidemiological studies that have shown an association between breast and ovarian cancer and vice-versa [Schildkraut et al., 1989], and from recent linkage studies [Narod et al., 1991; Easton et al., 1992]. Furthermore, greater than chance occurrences have been reported for multiple primary cancers of the breast and ovary [Prior and Waterhouse, 1981; Ewertz and Storm, 1989].

1.3 FAMILIAL CLUSTERING OF COLORECTAL, BREAST AND OVARIAN CANCER : EPIDEMIOLOGICAL ASPECTS

Epidemiological studies have shown that colorectal, breast and ovarian cancers show a tendency to aggregate in families. For first degree relatives (mothers, fathers, daughters and sons) of patients with colorectal, breast and ovarian cancers, in the absence of sex limitation, the risk of developing cancer at the same site is increased by 2 to 4 fold; Table 3.

Such moderate increases in risk may initially appear unlikely to have a substantial genetic basis and have in the past been thought to suggest a common environmental exposure due to a shared lifestyle rather than genetic factors. Paradoxically, however, these moderate increases in relative risks can result from very substantial genetic effects [Peto, 1980]. For example, a dominant gene with a frequency of 0.001 conferring a relative increase in risk of 25 fold is only associated with a one and half fold increase in risk in a sibling [Easton and Peto, 1990]. Furthermore, empiric data supporting the role of genetic factors in the aetiology of colorectal, breast and ovarian cancer comes from observing the age distribution of cancer incidence in susceptible individuals. A gene conferring a high lifetime risk of

developing cancer will produce an unusual age distribution, since the proportion of surviving susceptible individuals will fall progressively with increasing age. A direct consequence of this is that the relative risk will be highest in young relatives of young patients.

Table 3. Summary estimates of relative risks to first degree relatives of affected individuals with colorectal, breast and ovarian cancer.
Ranges of relative risk given in parentheses

Site	Cases affected	**Relative risk of cancer at same site**	References
Breast	768	**2.2** (2.2-2.3)	Claus et al 1990 Tulinius et al 1992a
Colorectum	239	**2.0** (1.6-3.3)	Woolf 1958 Macklin 1960 Lovett 1976 Songergaard et al1991
Ovary	80	**4.4** (2.3-18.2)	Casagrande et al 1979 Hildreth et al 1981 Cramer et al 1983 Tzonou et al 1984 Schildkraut and Thompson 1988 Ponder et al 1990

There are a number of genetic syndromes associated with a predisposition to develop colorectal, breast and ovarian cancer. Some, such as adenomatous polyposis coli and the Li-Fraumeni syndrome, are clearly Mendelian diseases in the classical sense, but they are rare. Of potentially greater importance are those syndromes that are defined not by clinical features, but which show high densities of early onset cases of colorectal,

breast and ovarian cancer which cannot be accounted for by chance alone. The cardinal feature of this second group of families is not their epidemiological distinctiveness but their apparent biological similarity with colorectal, breast and ovarian cancer in the general population.

How much of the increased risk of colorectal, breast and ovarian cancer in relatives reflects Mendelian patterns of inheritance is not established. The most rigorous method for examination of this question and developing a model of susceptibility to these cancers is by use of complex segregation analysis. This is ideally carried out on a population based series of families ascertained through sequential probands [Morton, 1984].

1.4. OBJECTIVES AND SCOPE OF ENQUIRY

The recognition that some individuals are placed at a high risk of colorectal, breast or ovarian cancer because of their genes makes taking a family history a powerful method for identifying individuals at whom tumour prevention strategies can be targeted.

The principle objective of this thesis was to quantify the role of family history in the aetiology of colorectal, breast and ovarian cancer and to use this information in clinical practice to identify those placed at a high risk who may benefit from selective screening.

To pursue these aims a number of specific studies were undertaken:

1. Extensive sets of pedigrees taken from patients or consultands with colorectal, breast and ovarian cancer were used to estimate the risk of these and other cancers in first degree relatives of patients diagnosed at different ages.

2. These pedigrees were analysed by complex segregation analysis to determine the underlying genetic basis of the observed familial clustering of colorectal, breast and ovarian cancer. Estimates of the most likely mode of inheritance, gene frequency and penetrance should permit the genetic risk associated with family history to be better defined than by empiric methods.

3. The estimates of risk of colorectal, breast and ovarian cancer associated with a family history were used in clinical practice in two cancer clinics for counselling and determining the screening requirements of first degree relatives of patients with these cancers.

SECTION 2: STUDIES OF THE GENETIC EPIDEMIOLOGY OF COLORECTAL, BREAST AND OVARIAN CANCER.

2.1 METHODS

2.1.1 Life Table Analysis

Standard life table methods [Bradford Hill, 1961] were used to estimate the years at risk by decades, contributed by first degree relatives of patients with the cancers studied. Index patients were excluded from lifetables. Tables from the Office of Population Censuses and Surveys, England and Wales [OPCS] were used to calculate the expected number of deaths among first degree relatives in 10-year age groups. Each first degree relative contributes years at risk only to those decades through which they have lived. Individuals dying within the jth decade were awarded 5 years towards the total years at risk for that decade; similarly those alive in that decade, but not contributing to subsequent decades were also awarded 5 years. The expected incidence of cancer is low in early life and high later. Only those relatives living through the later decades provide years at risk during which there is a significant incidence of a cancer. This type of analysis eliminates the problem of individuals having differing numbers of relatives and controls for their ages.

The expected number of deaths (E_j) in the j th decade in first degree relatives is calculated by:

$$E_j = \frac{\text{no. dying in j th decade*}}{\text{estimated population in j th decade*}} \times \text{years at risk in j th decade}$$

where (*) are derived from the OPCS mortality statistics.

The ICD numbers [International Classification of Diseases 1978] for the disease states studied are listed in Appendix A; Section 5.

The relative risk (RR) in the $_j$ th decade is defined by the ratio of observed (O_j) to expected numbers of deaths (E_j).

The Poisson distribution was used to estimate the significance of any difference between the observed and expected number of deaths [Pearson and Hartley, 1966]. Ninety-five per cent confidence limits were obtained from the table in Breslow and Day [1987].

Manipulations were carried out using the computer software package EXCEL [Excel; Version 3: Microsoft Corporation, Redmond, U.S.A.] run on a Macintosh LC computer [Apple Computer, Inc. Cupertino, California, U.S.A.].

2.1.2 Complex Segregation Analysis

2.1.2.1 Introductory remarks

The purpose of complex segregation analysis is to define the most probable genetic mechanism (if any) involved in the aetiology of a disease [reviewed in Elston, 1980; Morton, 1982a; 1984]. In essence this involves comparing the observed pattern of disease incidence in pedigrees, given that certain individuals are known a-priori to be affected, with that predicted by a number of different models, i.e. dominant, recessive, polygenic, multifactorial or sporadic. The best fitting model is generally determined by maximum likelihood.

Complex segregation analysis of colorectal, breast and ovarian cancer pedigrees was carried out under the mixed model using the computer program POINTER [Morton et al., 1983a].

2.1.2.2 The mixed model of inheritance [Morton and MacLean, 1974].

The mixed model of inheritance is shown in Figure 1. An individual's phenotype measurement (x_i) is considered to result from a major gene effect (g_i), a multifactorial transmissible component (c_i) and a residual environmental contribution (e_i), each acting independently. The major gene locus is biallelic, giving three major genotypes, GG, GG' and G'G', with corresponding means, z, z + td, and z + t, located from left to right across the phenotype-liability axis. The frequency of the G' allele (deleterious form of allele G) is denoted by q, and 1-q denotes the sum of the frequencies of all other alleles at the major locus. The relative size of each major genotype class, is $(1- q)^2$, 2q (1 - q), and q^2. The distance between the two homozygote means on the liability scale is represented by t, the displacement. The position of the heterozygote genotype mean relative to the means of the two homozygous genotype means is represented by d, the degree of dominance. When the heterozygote mean is near the mean of the lower homozygote, d = 0, the abnormal gene is recessive; when it is near the mean of the higher homozygote, d = 1, the abnormal gene is dominant; and when it is in the middle, d = 0.5, the effect of the abnormal allele is additive. The mean genotypic value, $(1 - q)^2 (z) + (1 - q) (z + td) + q^2 (z + t)$, is equivalent to the mean phenotypic value, μ, under the assumption that both the multifactorial transmissible contribution and the residual environmental contribution have expected values of zero.

It is assumed that variation around each of the genotype means is normally distributed, with common variance C + E, where C is the variance component due to multifactorial transmissible effects and E is the random environmental variance component.

A second multifactorial component, CA, accounts for inter-generational differences; C is restricted to shared determinants of young children and CA denotes the corresponding variance component for adult children and their parents. Multifactorial transmission is defined by parameters, H and HZ,

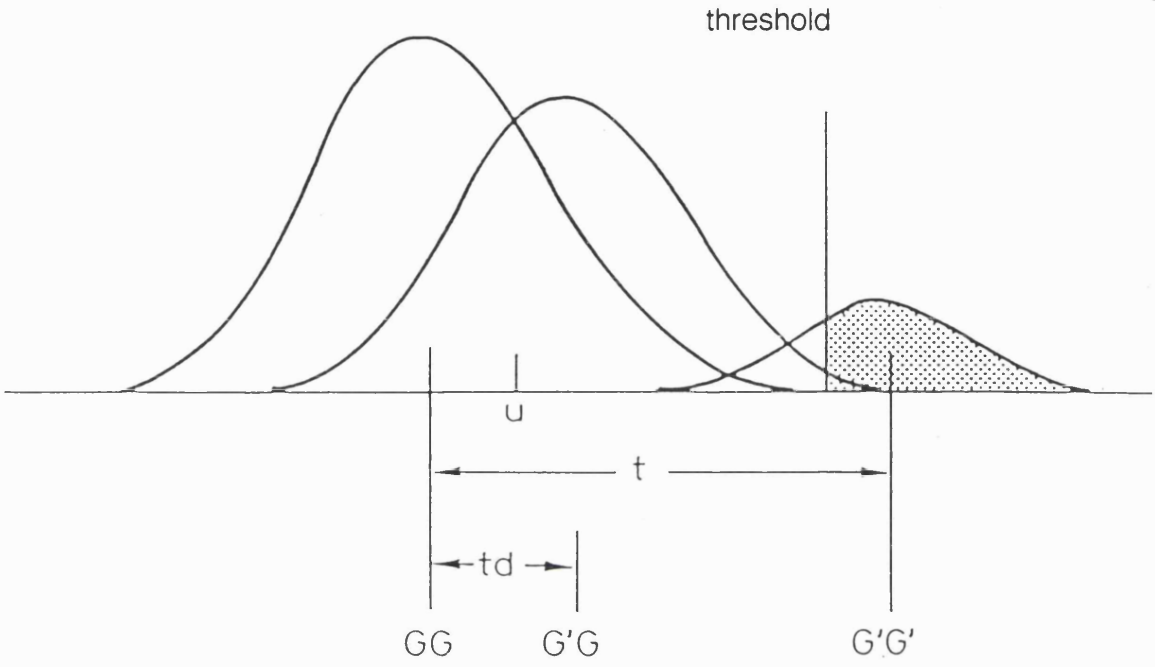


Figure 1. The mixed model for an autosomal major locus.

referred to as childhood heritability and adult heritability respectively. These represent the proportion of the total phenotypic variance (V) explained by multifactorial transmissible effects in young children and adults. In terms of total phenotypic variance:

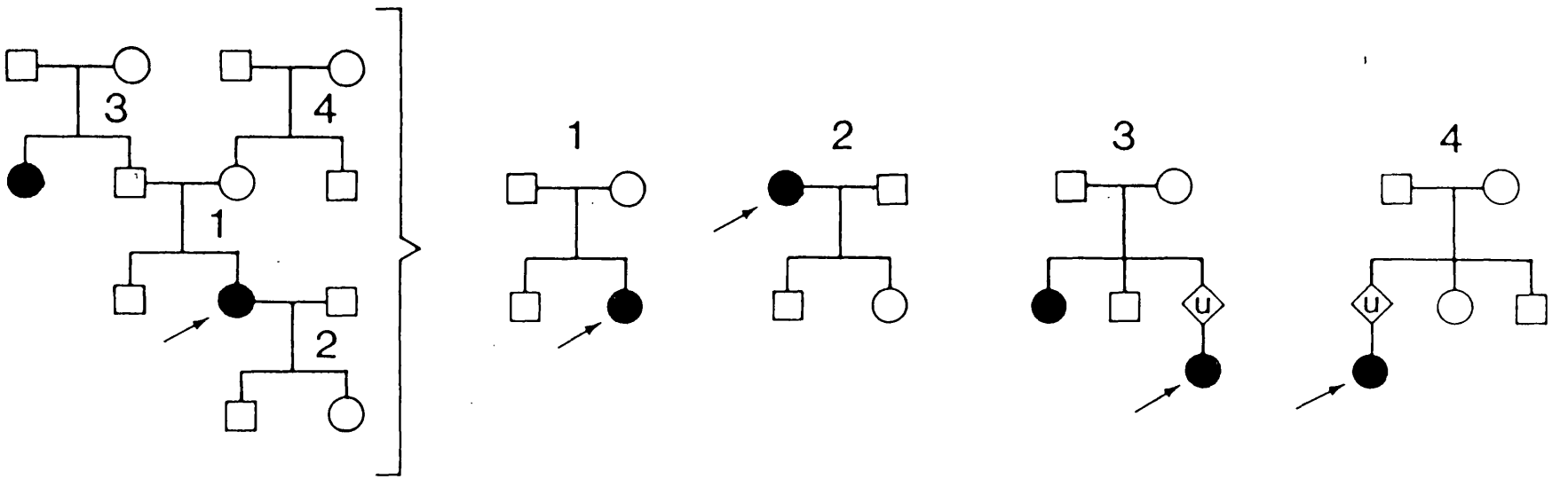
$$H = C / V \text{, and } HZ = CA / V$$

Implicit within the liability scale is a threshold, to the right of which individuals are classified as being affected and to the left as being normal. The location of the threshold is dependant upon the prevalence of the disease and the parameters of the major locus. The prevalence of many diseases such as cancer vary within a population according to age and sex of the individual. To incorporate this information, the population which is being analysed can be polychotomised into risk classes. These classes are referred to as liability classes; within each there is a threshold defined on the liability scale beyond which an individual is classified as affected. Shifting the threshold corresponds to changing the incidence or the risk of the disease and is synonymous with changing the probability of affection. Furthermore, by assigning the proper liability classes to each individual in a pedigree, nonheritable risk factors can be accounted for in the model. The liability classes are defined by a liability indicator. The use of multiple thresholds on a single liability scale is equivalent to considering each risk class to be associated with a different mean liability to affection.

2.1.2.3 The Pointer strategy

The pointer strategy was developed by Lalouel and Morton [1981] as an approach to segregation analysis of multigenerational pedigrees under the mixed model, providing for the mode of ascertainment and the manner in which the pedigrees were extended. In this approach, pedigrees are partitioned for analysis into their component nuclear families and, possibly,

Figure 2. Partition of a pedigree for analysis by the POINTER method.
(u refers to an individual of unknown phenotype).
[Williams and Anderson 1984].



an outside relative who led to ascertainment of the family. The outside relative who points to the family is referred to as a "pointer". Figure 2 shows the process of partitioning a single pedigree into nuclear families.

The pedigree can be partitioned into four different sibships, distinguished by their relationship to the proband and, consequently the type of ascertainment correction necessary. Nuclear families 1 and 2 represent examples of incomplete and complete selection respectively [Cavalli-Sforza and Bodmer, 1971; Morton and MacLean, 1974]. Nuclear families 3 and 4 are derived from two stages of sampling. They are not derived directly through the proband (as a parent or child), but indirectly through a descendant of the proband who is considered to be a pointer to these families.

Knowledge of the ascertainment probability, π, representing the probability that an affected person is a proband, is required to correct for families ascertained under incomplete selection, group 1.

2.1.2.4 POINTER

The computer program POINTER written by Lalouel and Yee [Morton et al., 1983a] analyses families with or without pointers under the mixed model.

There are 3 basic assumptions implicit in POINTER; inclusion of specific mortality in morbid risk, that liability classes of affected individuals are determined by age of last observation, not age of onset; and that probands are drawn at random from those affected.

Support for a particular hypothesis (e.g. dominant, recessive, polygenic, sporadic) requires maximisation of the probability density of the observations with respect to the free parameters of the mixed model. This is carried out in POINTER by minimising the logarithm of this density with a negative sign using the computer program GEMINI [Lalouel, 1979].

Using -2ln (L) + c as a measure, where ln (L) is the log-likelihood and c, is a constant, the unrestricted model will have the smallest value. Each null (restricted) hypothesis can then be tested by means of a likelihood-ratio criterion, with the difference in -2ln (L) + c between two competing hypotheses being distributed asymptotically as a X^2 with the numbers of degrees of freedom (d.f.) equal to the difference in the number of free (iterated) parameters under the two models.

Alternatively, the likelihood of each model can be directly compared using the Akaike Information Criterion (AIC) [Akaike, 1974]. The log likelihood of each model is multiplied by -2 and twice the number of free parameters in each model is added. The lowest value is considered to be the best model.

Ascertainment bias towards affected parents or pointers can be controlled by conditioning the likelihood's on the phenotypes of parents and pointers (conditional likelihood approach). Alternatively, the joint likelihood approach can be used which conditions on the phenotypes of pointers but not on parents. The joint likelihood approach is more informative, but requires that phenotypes of parents do not influence the probability of sampling the family, either through reproductive performance or by being probands [Morton et al., 1991].

2.1.2.5 Implementation of the computer program POINTER

Pedigrees used in this thesis were analysed using the pointer strategy. For those pedigrees ascertained through a consultand, the consultand was discarded and the closest affected relative was taken to be the proband or pointer. If a parent and sib qualified as affected, the parent was taken as the proband for odd-numbered pedigrees and the sib as proband for even-numbered pedigrees.

Sibships were of three types:

1. index sibships including the proband as a child (incomplete single selection) ;
2. children of proband (complete selection);
3. children of collateral and ancestral cases (truncate selection with closest affected relative as a pointer; pedigrees only extended when they include at least one affected relative).

In view of the restrictive sampling frames of the pedigrees analysed and the relatively high frequency of the cancers studied, π must be small, and π was set at 0.001; corresponding to single selection.

In segregation analysis, assuming that cumulative incidence corresponds to morbid risk is incorrect if the disease causes premature death. Taking into account specific mortality, the risk (R) of a particular cancer in the j th liability class can be defined by [Morton, 1991; Iselius et al., 1992] :

$$R_j = \frac{I_j - M_{j-1}}{1 - M_{j-1}}$$

where I_j is the cumulative incidence to the mid-point and M_{j-1} is the cumulative specific mortality to the end of the preceding class. In all the studies presented in this thesis the incidence (I) and mortality (M) of cancers were derived from the Registrar General's Statistical Reviews of England and Wales [Office of Population Census and Surveys, Cancer Statistics and Mortality Statistics].

Age was taken to be age at death or, if alive, at the time of ascertainment. Individuals younger than 20 years were omitted. In the

segregation analysis of the ovarian cancer pedigrees all male relatives were assigned to a single arbitrary liability class with the risk set at a tenth of that in the smallest female liability class.

The transformations used in this thesis to construct the liability classes in order to run the program POINTER are given in Appendix B; Section 5.

Current methods of determining penetrance are generally conditional on the assumption that gene frequency is constant over liability classes. Estimation of penetrance is therefore complicated when specific mortality is taken into account. As an approximation, penetrance (*P*) can be defined as the cumulative incidence for gene carriers in the jth liability class, given by [Iselius et al., 1992]:

$$P_j = P(\text{aff} \mid G', j) + [1 - P(\text{aff} \mid G', j)]\, M'_{j-1},$$

where the genotype specific mortality is defined by:

$$M'_{j-1} = \left\{ \sum_{i=1}^{j-1} P(G' \mid \text{aff}, i)\,(M_i - M_{i-1}) \right\} / \sum P(G' \mid \text{aff}, i)\,(l_i - l_{i-1}).$$

and, *P* (aff I G') denotes the probability of affection given genotype, and *P* (G' I aff) denotes the probability of genotype given affection.

Segregation analysis of nuclear families was carried out using the computer program POINTER. This software was run on a SUN 4/30 work-station computer [Sun Micro Systems, Inc., Mountain View, CA 94043, U.S.A].

Analysis of both colorectal and breast cancer pedigrees which were ascertained through index cases were carried out using the joint likelihood

approach. The ovarian cancer pedigrees ascertained through consultands were analysed using both joint and conditional likelihood approaches.

Transmission probabilities [Elston and Stewart, 1971] were not used in any of the segregation analyses since they are only valid in POINTER if families are drawn under complete selection, without pointers and with no allowance for sporadic cases [Iselius and Morton, 1991].

2.1.2.6 Calculation of risk from estimates of gene penetrance and frequency

Estimates of penetrance and frequency of putative predisposing genes to cancer in different age groups allows the risk in relatives of patients affected at different ages to be calculated. The risk (B_L) in class i for an individual normal in class j is given by [Morton, 1982b]:

$$B_L = \frac{B_i - B_j}{1 - B_j} \qquad (i = j+1 \text{ to } \infty)$$

where, as an approximation when G' is rare,

$$B_j = (P_j)(r)\ P\ (G' \mid \text{aff, proband age}) + P\ (\text{aff} \mid GG, j)\left[1 - (r)\ P\ (G' \mid \text{aff, proband age})\right]$$

and

$$B_i = (P_i)(r)\ P\ (G' \mid \text{aff, proband age}) + P\ (\text{aff} \mid GG, i)\left[1 - (r)\ P\ (G' \mid \text{aff, proband age})\right]$$

and

r = coefficient of relationship
(0.5 for first degree and 0.25 for second degree relatives)

2.2 GENETIC EPIDEMIOLOGY OF COLORECTAL CANCER

2.2.1 Colorectal Cancer Pedigrees

Pedigrees from Lovett's published series [Lovett, 1976] were analysed. These pedigrees were ascertained from 209 consecutive patients undergoing treatment for histologically proven colorectal cancer at St. Mark's Hospital, London. Particular care had been taken to avoid bias and no patient was selected on the basis of family history. Pedigrees were taken to include only first degree relatives and half sibs. Those patients with clinical evidence of adenomatous polyposis coli were excluded. Death certificates had been obtained for all deceased parents and sibs.

2.2.2 Life Table Analysis: Results

These index patients provided a total of 56615 years at risk in first degree relatives. Table 4 shows the years at risk for both male and female first degree relatives of patients diagnosed with colorectal cancer at different ages.

Table 5 shows the observed number of deaths from colorectal cancer and relative risks for first degree relatives of patients diagnosed at different ages. Relative risks were greatest for relatives aged less than 65 who were relatives of patients diagnosed before age 45.

Table 6 shows the risk of colorectal cancer in first degree relatives before age 65 based on the estimates of relative risk, incidence and mortality rates. The risk is similar to the risk of colorectal cancer for members of the general population over 65.

The risk of other cancers was not calculated since this has previously been reported by Lovett [1976] who showed an increased risk of stomach and breast cancer in first degree relatives (2.0 and 1.7 fold respectively).

Table 4. Years at risk contributed by first degree relatives of index patients with colorectal cancer by age groups.

Sex of relative		**Females**			**Males**	
Age of index patient	< 45	45-64	65+	< 45	45-64	65+
Age group of relatives (years)						
15-24	230	3510	2720	255	3890	2800
25-34	185	3105	2515	235	3395	2635
35-44	165	2785	2420	180	2880	2345
45-54	125	2250	2105	125	2370	1790
55-64	80	1575	1715	90	1465	1475
65-74	35	900	1000	50	705	810
75-84	5	435	415	15	300	265
85+	-	110	60	-	55	40

Table 5. Deaths from colorectal cancer observed (O) and relative risk (RR) in first degree relatives of patients with colorectal cancer.

	Age of Index Patient					
	< 45		45-64		≥ 65	
	O	RR	O	RR	O	RR
Age of relative						
< 65	2*	12.5 (1.5-45.1)	16**	5.8 (3.3-9.4)	7 *	2.7 (1.5-3.5)
≥ 65	0	-	7	1.7 (0.7-3.5)	9	1.6 (0.7-3.0)

Significance of difference from expected * $p < 0.05$, ** $p < 0.001$.

95% confidence limits given in parentheses.

Table 6. Risk of colorectal cancer in first degree relatives before age 65. (derived from table 5 and OPCS 1974).

Age of proband	**Increase in risk**	**Incidence**	**Mortality**
Any	5 fold	1 in 17	1 in 29
< 45	12 fold	1 in 7	1 in 12
45-64	6 fold	1 in 14	1 in 24
65 +	3 fold	1 in 28	1 in 48
Dominant pedigree *		1 in 3 lifetime risk	
Population risk: < 65		1 in 84	1 in 144
65+		1 in 20	1 in 25

* assuming a lifetime penetrance of the deleterious gene of 64%.

2.2.3 Segregation Analysis: Results

Table 7 shows the liability classes (4 for men and 4 for women) defined by age groups, each with the calculated risk of having colorectal cancer. A total of 353 nuclear families were derived from these pedigrees. Table 8 shows the results of complex segregation analysis under the joint likelihood approach. A model not providing for family resemblance, in which the familial occurrence of colorectal cancer can be attributed to chance, i. e. sporadic, can be rigorously rejected (X^2 3 d.f. = 72.7, $p < 0.001$). Of the polygenic, multifactorial, recessive and dominant models, the dominant model was significantly favoured, providing an identical likelihood to the general model. The frequency of the deleterious allele (G') was 0.006. Comparison of the likelihood of the dominant model for the total sample with families partitioned according to the mode of ascertainment showed no significant difference (Table 9). This internal consistency provides a measure of the confidence in the result of the dominant model, since evidence of heterogeneity resulting from such a partition would reflect incomplete sampling or an inappropriate model.

Penetrance was estimated taking specific mortality into account; the lifetime penetrance of the deleterious allele is 0.6 (Table 10). Penetrance of the abnormal gene increases with age. An affected individual belonging to a low-risk liability class is more likely to have the putative colorectal cancer gene than an affected individual in a high-risk liability class. This is reflected in Table 10 where the probability of an individual aged between 20 and 34 having the deleterious allele (denoted by *P* (G'I affection)) is 81%, compared with 35% for an affected individual aged between 50 and 64, and about 15% after age 65.

The genetic and sporadic components to risk for first degree relatives and their relationship to age of onset of colorectal cancer in index patients can be determined from the estimates of gene penetrance and frequency in the different age groups (refer section 2.1.2.6). Figure 3 shows the probability

Table 7. Liability classes and risks of colorectal cancer in England and Wales 1970-1974 [OPCS].

Age		Cumulative incidence*	Cumulative mortality**	Risk of having colorectal cancer dead or alive
Male	Female	I	M	R
20-34	-	0.00016	0.00014	0.00016
35-49	-	0.00135	0.00143	0.00121
50-64	-	0.00772	0.00845	0.00630
65+	-	0.04954	0.07875	0.04140
-	20-34	0.00017	0.00012	0.00017
-	35-49	0.00128	0.00132	0.00169
-	50-64	0.00675	0.00736	0.00540
-	65+	0.03745	0.05804	0.03020

* To mid point of interval

** To end of interval

Table 8. Results of segregation analysis for total sample of colorectal cancer pedigrees under joint likelihood.

Model	d	t	q	H	Z	-2lnL+c	AIC
Sporadic	-	-	(0)	(0)	(0)	-281.7	-281.7
Polygenic	-	-	(0)	0.45	(0)	-347.3	-345.3
Multifactorial	-	-	(0)	0.24	3.91	-350.8	-346.8
Major locus							
Recessive	(0)	1.89	0.15	(0)	(0)	-340.7	-336.7
Dominant	(1)	1.69	0.006	(0)	(0)	-354.4	-350.4
Generalised single locus	0.52	3.18	0.006	(0)	(0)	-354.5	-348.5

d = dominance

t = displacement

q = gene frequency

H = childhood heritabliity

Z = ratio of adulthood to childhood heritability

AIC = Akaike Information Criterion

Table 9. Heterogeneity test for the dominant model of colorectal cancer according to type of family

	t	q	-2lnL+c
Complete ascertainment (203 families)	1.76	0.005	-1812.2
Incomplete ascertainment (150 families)	2.02	0.017	+1455.9
All			-354.4
Heterogeneity			1.8
d.f.			2

Table 10. Characteristics of the major locus for colorectal cancer for each liability class when analysed under joint likelihood (d=1.0, q=0.006).

Age range		*P* (affection I genotype)		*P* (G' I affection)*	Penetrance, P_j
Male	Female	GG	GG' or G'G'		
20-34	-	0.00003	0.01093	0.816	0.01
35-49	-	0.00050	0.05844	0.588	0.07
50-64	-	0.00416	0.17937	0.346	0.26
65+	-	0.03611	0.46939	0.138	0.63
-	20-34	0.00003	0.01136	0.813	0.01
-	35-49	0.00048	0.05693	0.593	0.07
-	50-64	0.00345	0.16333	0.368	0.25
-	65+	0.02552	0.40895	0.165	0.64

* The probability of a G' carrier (GG' or G'G') among afffected individuals at this age.

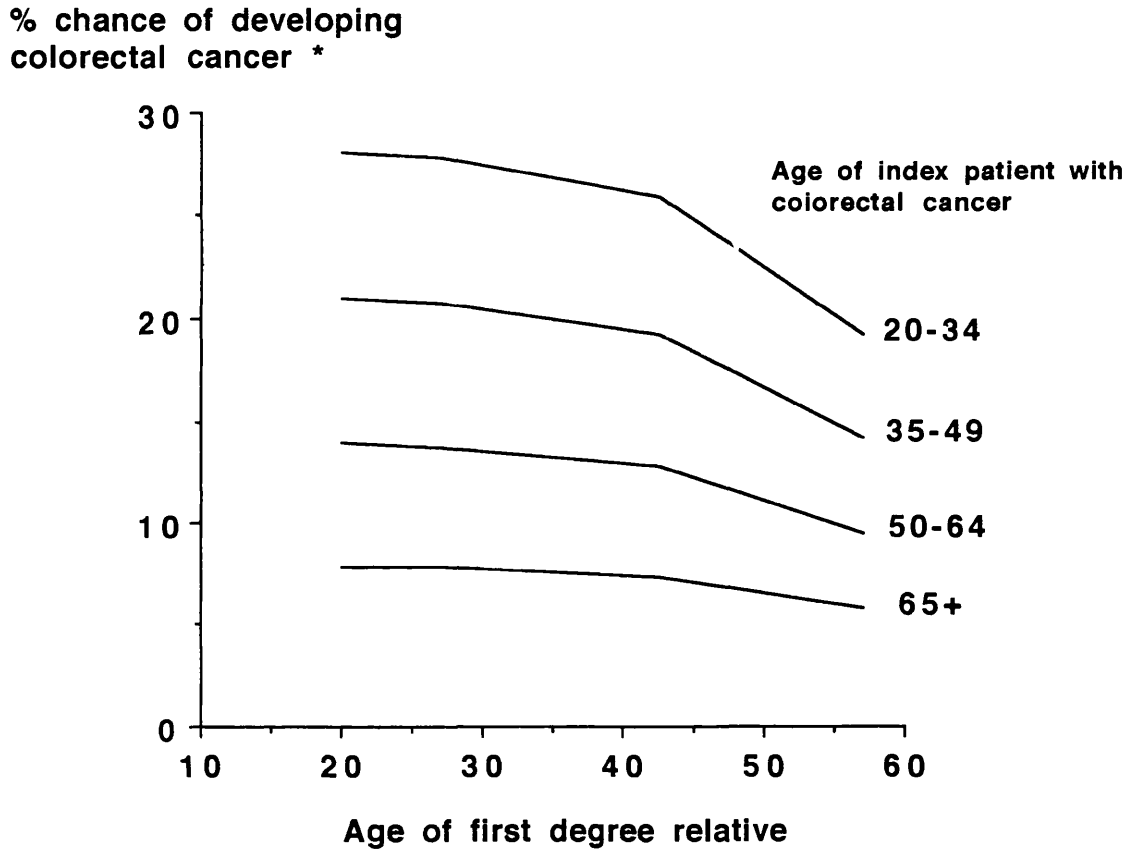


Figure 3. Chance of developing colorectal cancer with increasing age in first degree relatives of patients with colorectal cancer. (* defined as B_i-B_j / 1- B_j ; refer section 2.1.2.6).

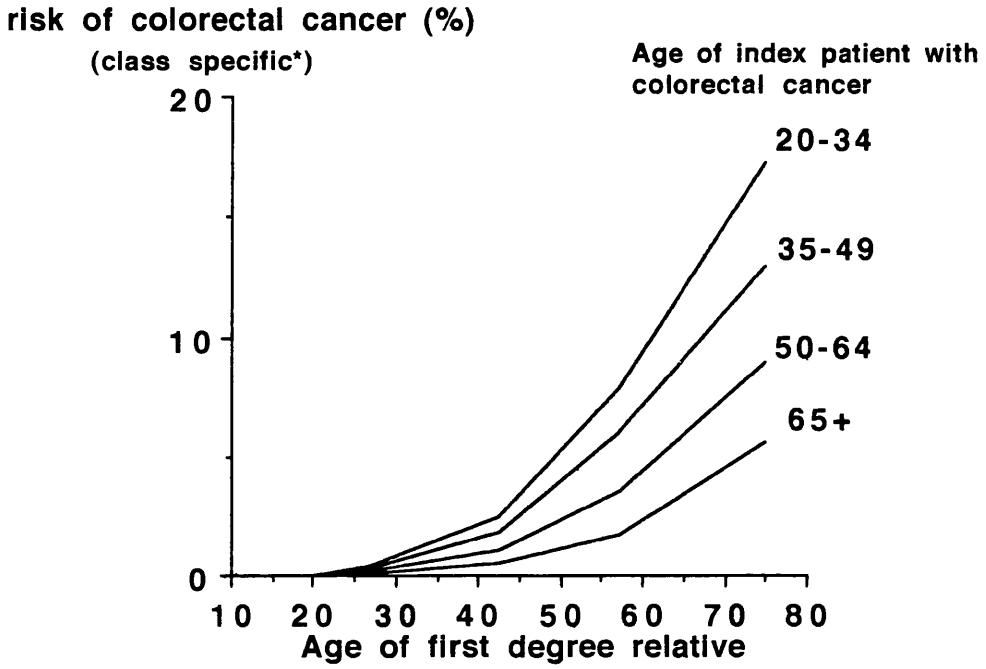


Figure 4. Actual risk of colorectal cancer with increasing age in first degree relatives of patients with colorectal cancer.
(* defined as B_i- B_j ; refer section 2.1.2.6).

of developing colorectal cancer with increasing age in first degree relatives of patients affected at different ages. The genetic risk is greatest for those relatives of patients who develop colorectal cancer at a young age. Figure 4 shows the actual risk (class specific) of colorectal cancer with increasing age in relation to age of affection in index patients.

2.2.4 Discussion

Evidence from both mortality [Woolf, 1958; Macklin, 1960; Lovett, 1976] and incidence studies [Kune et al., 1987; Ponz de Leon et al., 1987; Bonneli et al., 1988; St. John et al., 1989] has shown a 2 to 4-fold increase in risk of colorectal cancer in first degree relatives of patients with colorectal cancer. This analysis of a published series of pedigrees [Lovett ,1976] permitted age-specific risks of colorectal cancer in relatives of patients diagnosed at different ages to be estimated. The risk of colorectal cancer in first degree relatives was greatest for those relatives of patients diagnosed at a young age. This pattern of age-specific risk is entirely compatible with an inherited predisposition to colorectal cancer.

A number of segregation analyses have found support for a major gene predisposing to colorectal cancer, inherited in an autosomal dominant fashion, other than that responsible for adenomatous polyposis coli [Bailey-Wilson et al., 1986; Cannon-Albright et al., 1988]. However, these studies have been performed on small numbers of selected pedigrees and therefore do not necessarily reflect the familial aggregation of colorectal cancer seen in the general population. An attempt has been made in this study to minimise ascertainment bias by analysing a series of pedigrees taken from consecutive patients being treated for colorectal cancer.

In this study it was possible to demonstrate that the familial aggregation of colorectal cancer was most compatible with the inheritance of a major gene. A dominant model was favoured with an estimated gene frequency of

0.006 and lifetime penetrance of 63%, making it responsible for at least 13% of the total burden of colorectal cancer in the general population. The putative colorectal cancer genes identified in the segregation analysis may account for the familial aggregations of colorectal cancer in hereditary non-polyposis colorectal cancer (HNPCC). The likelihood of an affected individual having the deleterious gene at age 50 concords with Mecklin's observation that over 80% of those affected with HNPCC were aged below 50 [Mecklin and Jarvinen, 1986].

A number of lines of evidence suggest that the inherited liability to colorectal cancer may in part be mediated through a predisposition to develop adenomatous polyps. The risk of adenomatous polyps in first degree relatives of patients with colorectal cancer is between 2 and 3-fold higher than in control families [Rozen et al., 1987; Guillem et al. 1989]. This is in keeping with the estimates of colorectal cancer risk derived from mortality [Woolf, 1958; Macklin, 1960; Lovett, 1976] and incidence studies [Ponz de Leon et al., 1987; Bonnelli et al., 1988; St. John et al., 1989].

A study by Cannon-Albright and co-workers [Cannon-Albright et al., 1988] of 34 extended kindreds found twice as many polyps in first degree relatives of probands as in controls. Segregation analysis of these same pedigrees suggested that the observed pattern of inherited susceptibility to develop adenomas was best accounted for by the inheritance of a dominant gene with frequency of 0.19 and lifetime penetrance of 0.4. Furthermore, all adenomas were inferred to arise through an inherited susceptibility.

Alternatively, the influence of family history may be mediated through a more aggressive adenoma-carcinoma sequence. The degree of dysplasia in adenomas [Morson et al., 1983] and the fractional allele loss in colorectal cancers [Kern et al., 1989] have both been correlated with family history.

The gene for adenomatous polyposis coli (APC), and a number of mutations causing the APC syndrome, have been identified [Groden et al., 1991; Kinzler et al., 1991a]. Somatic mutations in the APC gene and the

MCC gene (mutated in colorectal cancer and adjacent to APC on chromosome 5q) have both been shown to be involved in the development of colorectal cancer [Nishisho et al., 1991; Kinzler et al., 1991b]. Chromosome 5q21 markers, known to be linked to APC and MCC, have been linked to a syndrome predisposing to colorectal cancer but which is not associated with such florid polyp formation as seen in adenomatous polyposis coli [Leppert et al., 1990; Lynch et al., 1990b; Spirio et al., 1992]. It is therefore likely that although there will be heterogeneity in the genetic predisposition to colorectal cancer, variation in the APC gene will underlie some inherited syndromes other than adenomatous polyposis coli.

2.3 GENETIC EPIDEMIOLOGY OF BREAST CANCER

2.3.1 Breast Cancer Pedigrees

Two hundred and fifty four consecutive pedigrees were ascertained through women diagnosed with histologically proven breast cancer attending follow up clinics at the Royal Free and University College Hospitals, London. The first 204 were unselected cases but the last 50 were selected for premenopausal onset. No pedigree was selected for family history. Pedigrees were taken to include all first degree relatives and half sibs of patients. One pedigree was excluded from analysis because of insufficient information on family members.

Of the 166 deaths in first degree relatives from all types of cancer, 130 (78%) were verified by death certificates or hospital records, and of 26 first degree relatives alive with cancer the diagnoses were verified from hospital records in 14 (56%).

Of the 20 patients who developed breast cancer between ages 50 and 54, 11 were reported to be premenopausal at diagnosis.

2.3.2 Life Table Analysis: Results

These index patients provided a total of 32085 years at risk in female first degree relatives and 28475 in males. The distribution of years at risk for both female and male first degree relatives of patients diagnosed with breast cancer at different ages is shown in Table 11. Lifetables were constructed using mortality data for the period 1979-1982 [OPCS].

Table 12 shows the observed number of deaths from breast cancer and relative risks. Overall, the relative risk of breast cancer in first degree relatives of all index patients was 1.85, but was most marked for those relatives of index patients less than 45 years old. Furthermore, relative risks were greatest in young women relatives.

Table 11. Years at risk contributed by first degree relatives of index patients with breast cancer by age groups.

	Daughters			Sisters			Mothers					
Age of index patient	**< 45**	**45-54**	**55+**	**< 45**	**45-54**	**55+**	**< 45**	**45-54**	**55+**	**< 45**	**54-54**	**55+**
Age group of relatives (years)												
15-24	290	420	760	835	850	1750	750	640	1135	1365	1660	3760
25-34	85	165	595	705	825	1710	745	640	1120	1145	1445	3510
35-44	25	50	360	435	720	1675	725	620	1100	995	1205	3090
45-54	5	20	165	170	550	1545	675	560	1060	750	930	2610
55-64	-	10	40	60	335	1230	575	480	980	675	655	2010
65-74	-	-	10	10	190	710	280	390	825	360	410	1145
75-84	-	-	-	-	70	210	115	210	560	95	165	405
85+	-	-	-	-	10	30	25	45	205	-	15	75

Table 12. Deaths from breast cancer observed (O) and relative risk (RR) in first degree relatives of patients with breast cancer

Age of first degree relative	Age of Index Case: < 45 O	< 45 RR	45-54 O	45-54 RR	≥ 55 O	≥ 55 RR	All index patients O	All index patients RR
< 50	2	3.45 a	3*	3.95 b	3	1.71 c	8*	2.59 d
< 55	3	3.22 e	3	2.54 f	3	1.08 g	9	1.84 h
≥ 55	5**	4.36 i	1	0.51j	10*	1.83 k	16*	1.86 l
All	8**	3.85 m	4	1.26 n	13	1.57 o	25**	1.85 p

95% confidence limits of RR

a (0.42-12.45)	b (0.81-11.69)	c (0.35-5.06)	d (1.12-5.10)
e (0.66 -9.40)	f (0.52-7.42)	g (0.22 -3.15)	h (0.84 -3.50)
i (1.41 - 10.16)	j (0.01-1.81)	k (0.87 -3.37)	l (1.06 -3.01)
m (1.66 - 7.58)	n (0.34-3.23)	o (0.83 -2.68)	p (1.20 -2.74)

significance of difference from expected * $p < 0.05$, ** $p < 0.01$.

Table 13 shows the deaths from breast cancer and relative risks for mothers, sisters and daughters. There were no breast cancer deaths in sisters or daughters of patients diagnosed with breast cancer below age 55. It should, however, be noted that the number of years at risk for sisters and daughters was only 5765 and 1070 respectively with correspondingly low expected number of deaths from breast cancer of 1.56 and 0.06. Overall, an increased risk for sisters was seen (relative risk 1.31), but this was not significant. Daughters showed a 5.88 -fold increase in risk overall which was statistically significant, but was dependant on only two observed deaths in daughters under 55, the confidence limits of the relative risks are therefore wide.

The observed number of deaths from all causes was no different from the expected for either males or females (n=238, relative risk 0.91 for females and n=327, relative risk 1.07 for males; 95% confidence limits 0.71-1.02 and 0.95-1.19 respectively). Relative risks for all female and male first degree relatives for all cancers and cancers of the ovary, uterus, colorectum, lung and prostate were investigated (Tables 14 and 15).

The pattern of increased risk of breast cancer was reflected in the relative risk for all cancers in women. The relative risk for those relatives of patients diagnosed before 55 was 1.43 and 1.13 if diagnosed with breast cancer at or older than 55. From the complete pedigree analysis no other significant increase in any other cancers was seen in female first degree relatives.

There was an increase in relative risk for male first degree relatives for prostatic cancer with a 2.36- fold increase in risk seen overall. Paradoxically, lung cancer showed a significant reduction in relative risk in men. No other significant difference in risk of other cancers was found.

In this study 15 index patients developed bilateral breast cancer. Three of these were from pedigrees showing apparent dominant inheritance of breast cancer. In 10 patients, the first breast cancer had developed

Table 13. Deaths from breast cancer observed (O) and relative risk (RR) in mothers, sisters and daughters.

Age of first degree relative		Age of index patient: < 55 O	< 55 RR	≥ 55 O	≥ 55 RR	All index patients O	All index patients RR
Mothers	< 55	6**	4.91 (1.80-10.70)	0	-	6*	2.67 (0.98-5.82)
	≥ 55	6	2.50 (0.92-5.45)	4	1.36 (0.37-3.48)	10*	1.84 (0.88-3.38)
	All	12***	3.32 (1.72-5.81)	4	0.98 (0.27-2.50)	16**	2.08 (1.19-2.37)
Sisters	< 55	0	-	1	0.65 (0.16-3.62)	1	0.42 (0.01-2.34)
	≥ 55	0	-	6*	2.53 (0.93-5.51)	6	1.94 (0.71-4.22)
	All	0	-	7	1.79 (0.72-3.69)	7	1.31 (0.52-2.70)
Daughters	< 55	0	-	2*	8.85 (1.07-31.95)	2*	7.14 (0.96-25.77)
	≥ 55	0	-	0	-	0	-
	All	0	-	2*	7.14 (0.86-25.77)	2*	5.88 (0.71-21.22)

significance of difference from expected; * $p<0.05$, ** $p<0.01$, *** $p<0.001$.
95% confidence limits shown in parentheses.

Table 14. Deaths from all cancers, ovarian, uterine, colorectal, stomach and lung cancer observed (O) and relative risks (RR) in female first degree relatives of patients with breast cancer.

	Age of index patient	O	RR	95% confidence limits
All cancers	< 55	33 *	1.43	0.98-2.02
	≥ 55	44	1.13	0.84-1.55
	All	77 *	1.25	0.99-1.56
Ovarian cancer	< 55	3*	1.81	0.37-5.29
	≥ 55	1	0.38	0.01-2.12
	All	4	0.94	0.26-2.41
Uterine cancer	< 55	1	0.62	0.01-3.45
	≥ 55	2	0.86	0.10-3.10
	All	3	0.77	0.16-2.28
Colorectal cancer	< 55	3	0.97	0.20-2.83
	≥ 55	5	0.92	0.30-2.14
	All	8	0.94	0.41-1.85
Stomach cancer	< 55	2	1.21	0.15-4.37
	≥ 55	2	0.68	0.08-2.45
	All	4	0.87	0.24-2.23
Lung cancer	< 55	3	1.14	0.24-3.33
	≥ 55	4	0.83	0.23-2.12
	All	7	0.94	0.38-1.94

Significance of difference from expected * $p < 0.05$.

Table 15. Deaths from all cancers, colorectal, stomach, prostatic and lung cancer observed (O) and relative risk (RR) in male first degree relatives of patients with breast cancer.

	Age of index patient	O	RR	95% confidence limits
All cancers	< 55	32	1.10	0.75-1.56
	≥ 55	38	0.87	0.62-1.19
	All	70	0.96	0.75-1.22
Colorectal cancer	< 55	4	1.29	0.35-3.30
	≥ 55	5	1.06	0.34-2.50
	All	9	1.16	0.53-2.20
Stomach cancer	< 55	5	1.66	0.54-3.87
	≥ 55	6	1.31	0.48-2.86
	All	11	1.28	0.64-2.29
Prostatic cancer	< 55	6 **	3.67	1.35-8.00
	≥ 55	4	1.54	0.42-3.94
	All	10 *	2.36	1.13-4.34
Lung cancer	< 55	7	0.59	0.24-1.21
	≥ 55	7**	0.40	0.16-0.82
	All	14***	0.48	0.26-0.81

Significance of difference from expected. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

premenopausally and in 5, postmenopausally. For first degree female relatives of premenopausal patients there were 865 years at risk, 2 deaths from breast cancer and the relative risk was 7.78 ($p < 0.05$, 95% confidence limits 0.94-28.08). For those first degree relatives of postmenopausal patients, there were 500 years at risk, 1 breast cancer death, which was not significantly different from expected, and the relative risk was 4.78 (95% confidence limits 0.12-26.62). For all first degree relatives of all 15 patients, the relative risk of breast cancer was 6.43 ($p < 0.05$, 95% confidence limits 1.32-18.77).

2.3.3 Segregation Analysis: Results

Table 16 shows the liability classes for women and men defined by age groups, each with the calculated risk of having breast cancer. A total of 431 nuclear families were derived from the 253 pedigrees. Table 17 shows the results of complex segregation analysis using the joint likelihood approach. A model not providing for family resemblance, in which the familial occurrence of breast cancer can be attributed to chance, can be rejected (X^2 3 d.f. = 58.6, $p < 0.001$). Of the polygenic, multifactorial, recessive, and dominant models, the dominant model was favoured, providing an identical likelihood to the general model. The frequency of the deleterious allele (G') was 0.009. In fitting the full model, the polygenic component (H) always went to zero. Support for a major gene was greater using joint likelihood than an analysis of these pedigrees using the conditional likelihood approach by Iselius et al., [1991]. It was however, weaker than a number of other studies [Williams and Anderson, 1984; Newman et al., 1988; Claus et al., 1991]. Exaggeration of support for a major gene may have resulted from neglecting specific mortality when calculating morbid risk in these studies [Iselius et al., 1992].

Comparison of the likelihood of the dominant model for the total sample with families partitioned according to the mode of ascertainment showed no

Table 16. Liability classes and risks of breast cancer in England and Wales 1979-1982 [OPCS].

Age		Cumulative incidence*	Cumulative mortality**	Risk of breast cancer dead or alive
Male	Female	I	M	R
20-54	20-24	0.00005	0.00004	0.00005
55-69	-	0.00024	0.00022	0.00020
70-84	25-29	0.00034	0.00026	0.00012
85+	30-39	0.00025	0.00195	0.00228
-	40-49	0.01179	0.00736	0.00986
-	50-59	0.02625	0.01673	0.01903
-	60-69	0.04418	0.02870	0.02792
-	70-79	0.06130	0.04447	0.03356
-	80+	0.08994	0.06276	0.04759

* To midpoint of interval

** To end of interval

Table 17. Results of segregation analysis for total sample of breast cancer pedigrees under joint likelihood.

Model	d	t	q	H	Z	-2lnL+c	AIC
Sporadic	-	-	(0)	(0)	(0)	-1073.2	-1073.2
Polygenic	-	-	(0)	0.56	(1)	-1128.8	-1126.8
Multifactorial	-	-	(0)	0.43	1.66	-1129.9	-1125.9
Major locus							
Recessive	(0)	0.0	0.22	(0)	(0)	-1121.2	-1117.2
Dominant	(1)	1.79	0.009	(0)	(0)	-1131.8	-1127.8
Generalised single locus	1.0	1.79	0.009	(0)	(0)	-1131.8	-1125.8

d = dominance

t = displacement

q = gene frequency

H = childhood heritability

Z = ratio of adulthood to childhood heritability

AIC = Akaike Information Criterion

Table 18. Heterogeneity test for the dominant model of breast cancer according to type of family.

	t	q	-2lnL+c
Complete ascertainment (248 families)	2.14	0.026	1164.4
Incomplete ascertainment (183 families)	1.86	0.007	+29.6
All			1130.8
Heterogeneity			3.0
d.f.			2

Table 19. Characteristics of the major locus for breast cancer for each liability class when analysed under joint likelihood (d = 1.0, q = 0.009).

Age range (female)	***P*** **(affection I genotype)**		***P*** **(G' I affection) ***	**Penetrance,** P_j
	GG	**GG' or G'G'**		
20-24	0.00000	0.00267	0.959	0.002
male	0.00002	0.01023	0.919	-
25-29	0.00001	0.00627	0.938	0.007
30-39	0.00070	0.08841	0.696	0.097
40-49	0.00556	0.24389	0.444	0.286
50-59	0.12930	0.35081	0.331	0.448
60-69	0.02067	0.42266	0.272	0.579
70-79	0.02574	0.45921	0.246	0.674
80+	0.03870	0.53151	0.201	0.789

* The probability of a G' carrier (GG' or G'G') among affected individuals at this age.

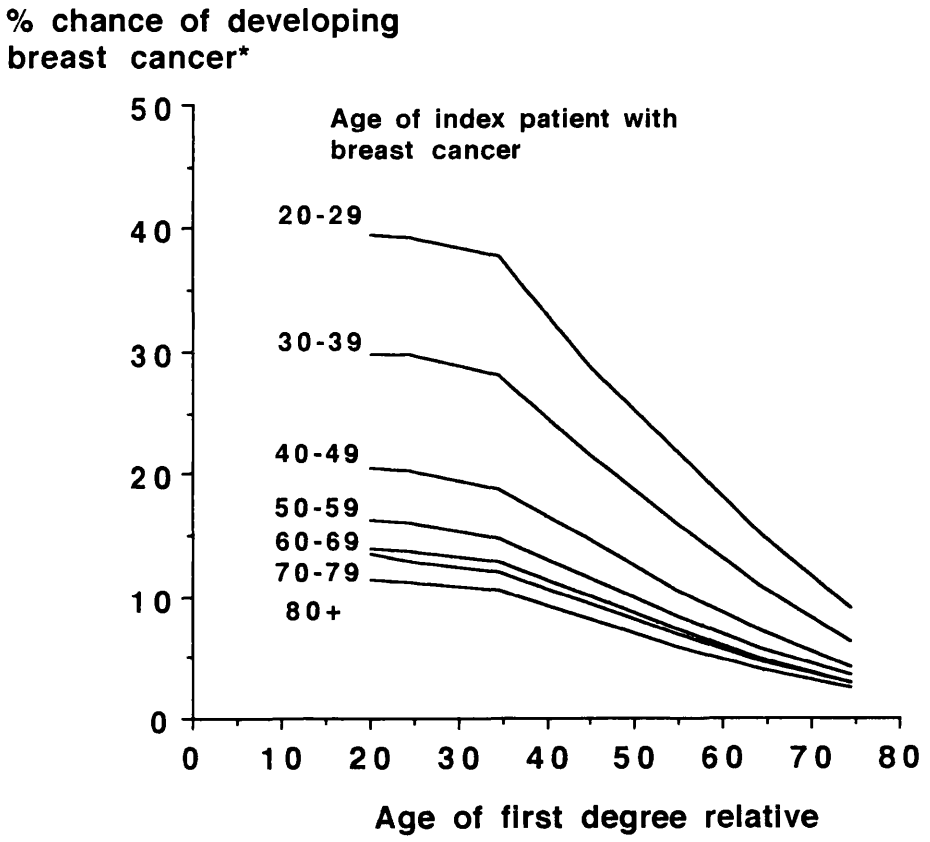


Figure 5. Chance of developing breast cancer with increasing age in first degree relatives of patients with breast cancer.
(* defined as B_i-B_j / 1-B_j ; refer section 2.1.2.6)

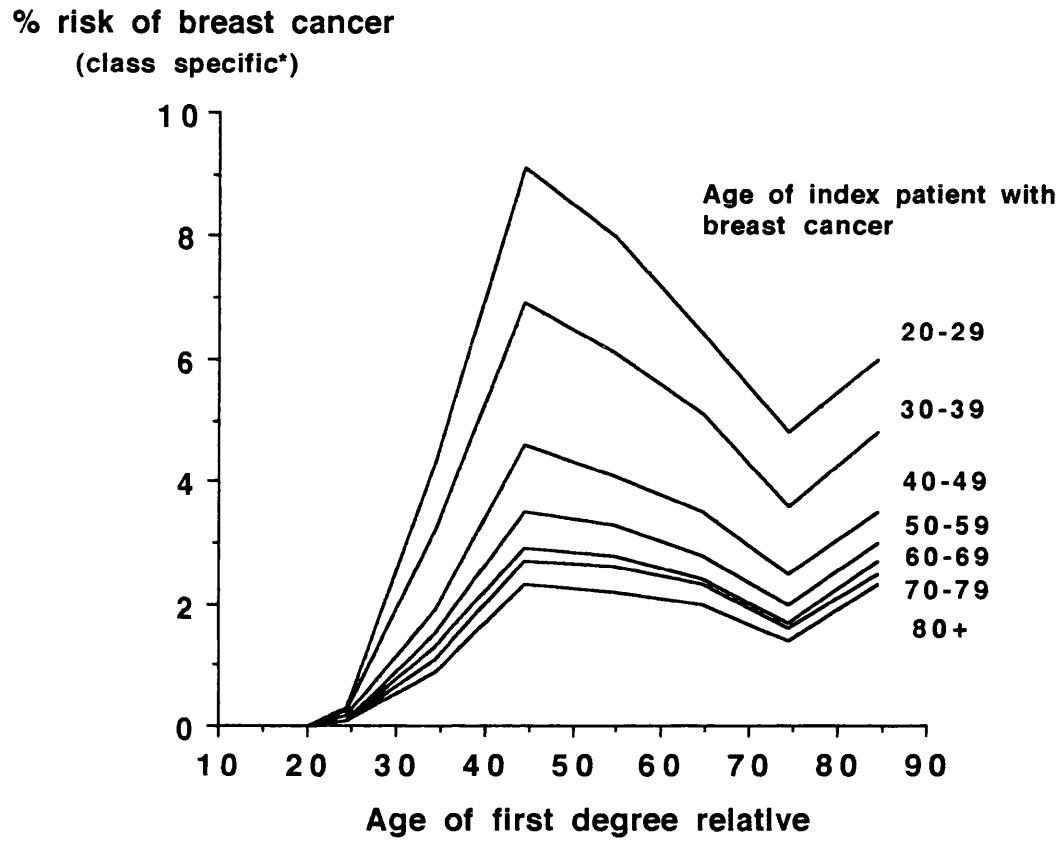


Figure 6. Actual risk of breast cancer with increasing age in first degree relatives of patients with breast cancer.
(* defined as B_i- B_j ; refer section 2.1.2.6).

significant difference (Table 18). Taking specific mortality into account, Table 19 shows the penetrance of the dominant gene. The lifetime penetrance is 0.79. Penetrance of the abnormal gene increases with age. An affected individual in a low risk liability class is more likely to carry the putative breast cancer gene than an individual in a high risk liability class. This is reflected in Table 19.

Using the estimates of gene penetrance and frequency at different ages, Figure 5 shows the chance of developing breast cancer with increasing age in first degree relatives of patients affected at different ages. Figure 6 shows the actual risk (class specific) over 10 years of developing breast cancer with increasing age in relation to age of affection in index patients. There are two components to risk. The risk from the genetic component is only of significance after age 30 for those who are relatives of patients diagnosed young. Later in life the greater part of risk is sporadic.

2.3.4 Discussion

The results from this analysis of pedigrees are in general agreement with a number of previous studies which have demonstrated an increased risk of breast cancer in first degree relatives of patients with breast cancer [Ottman et al., 1983; Sattin et al., 1985; Ottman et al., 1986; Dupont and Page, 1987; Negri et al., 1988; Bouchardy et al., 1990; Claus et al., 1990; Tulinius et al., 1992a]. In this study relative risks were dependent upon the age at diagnosis of breast cancer in the index patient, being greater for those relatives of index patients less than 45, approximating to premenopausal status. This is in keeping with the original pattern described by Anderson [1973] and is confirmed by some workers [Ottman et al., 1986; Claus et al., 1990], but not by others [Sattin et al., 1985].

An increased risk to first degree relatives of patients with bilateral breast cancer has been reported [Anderson et al., 1973; Ottman et al., 1983], although other workers have been unable to demonstrate this effect [Sattin

et al., 1985]. This study supports the view that the presence of bilateral breast cancer indicates a considerable increase in risk to first degree relatives and may suggest a high genetic predisposition.

Previous studies have reported a higher risk for sisters than for mothers of breast cancer patients [Ottman et al., 1983]. Whilst this study is admittedly small, there was no support for this observation. However, it is likely that any genetic inferences from such empiric data comparing relative risks are inappropriate since relative risks for sisters and daughters are likely to be distorted by the very low expected values.

Clustering of prostatic cancer with breast cancer has been reported by a number of independent workers [Thissen, 1974; Cannon et al., 1982; Tulinius et al., 1992b]. In two Icelandic families, prostatic cancer and early onset breast cancer were reported to show linkage to chromosome 17q suggesting that variation at the 17q locus may contribute to the development of prostatic as well as breast and ovarian cancer [Arason et al., unpublished data reported by Tulinius et al., 1992b].

Benign breast disease has been shown to be significantly more common in familial cases of breast cancer than in the general population [Lynch et al., 1989]. The data collected in this study did not permit this to be examined. Skolnick and co-workers [Skolnick et al., 1990], using the computer program PAP (Pedigree Analysis Package) [Hasstedt and Cartwright, 1981], have suggested that proliferative breast disease may be a precursor for breast cancer in high risk families. This inference has however, been questioned by others [Rich, 1990; Morton et al., 1991].

A number of segregation analyses of breast cancer pedigrees have been reported. All studies have applied the POINTER program or a similar model. Despite the fact that most of these studies have in one way or another violated some of the basic assumptions of POINTER (refer section 2.1.2.4), the majority have favoured a dominant gene as being responsible for the familial aggregation of breast cancer, Table 20. Estimates of gene

Table 20. Published segregation analyses of breast cancer pedigrees.
(adapted from Morton ,[1991]; Iselius et al., [1991]).

Reference	Dominant model d=1 gene frequency	penetrance	Potential bias
Bishop and Gardner [1980]	0.0056	0.84	Single selected pedigree, ascertainment and prevalence ignored.
Go et al. [1983]	-	>0.9	At least 3 affected cases in each pedigree, ascertainment and prevalence ignored.
Cannon et al. [1986]	0.0134	0.8	At least 3 affected cases in each pedigree.
Goldstein et al. [1987]	0.0014		Bilateral probands, age of onset substituted for current age.
Newman et al. [1988]	0.0006	0.82	All index cases aged less than 55. Onset substituted for current age.
Bishop et al. [1988]	0.0002	0.84	High risk pedigrees, correction for ascertainment.
Jacobsen [1946] analysed by:			
Williams and Anderson [1984]	0.0076	0.57	Possible enrichment of premenopausal onset.
Iselius et al. [1992]*	0.0092	0.78	
Claus et al. [1991]	0.003	0.92	Probands aged less than 55.

All analyses except Iselius et al. [1992] (*) have neglected specific mortality.

frequencies vary less for the population-based samples (0.003-0.0092) [Claus et al., 1991; Iselius et al., 1992] than those studies of selected families, i.e. pedigrees ascertained through high-risk families (0.0002-0.0134) [Bishop et al., 1988; Cannon et al., 1986]. The segregation analysis of 253 consecutive pedigrees reported here provides further evidence for a dominant gene predisposing to breast cancer. Estimates of gene frequency and penetrance of 0.009 and 0.79 are not dissimilar to those derived from analyses of population data sets carried out by Claus et al., [1991] and Iselius et al., [1992]. Using the estimates of gene frequency and penetrance enabled calculation by age of the likely genetic and sporadic components of breast cancer risk in first degree relatives of patients diagnosed with breast cancer. With an early age of onset, the genetic risk to offspring is high, but with increasing age of onset this component of overall risk rapidly diminishes; furthermore, with the relative remaining disease free the risk of any inherited liability is reduced. In clinical practice this information can be used to identify more precisely those family members who are at high risk and to estimate the probability that a dominant gene is responsible for any familial aggregation of breast cancer.

2.4 GENETIC EPIDEMIOLOGY OF OVARIAN CANCER

2.4.1 Ovarian Cancer Pedigrees

Five hundred and eighteen pedigrees were ascertained through normal consultands who were invited via the media to attend the Ovarian Cancer Screening Clinic at King's College Hospital, London [Bourne et al., 1991]. All had a close relative affected with ovarian cancer. The consultand was questioned about all first and second degree relatives and the pedigree extended where possible regardless of whether any individual was affected. Ovarian cancer was verified from death certificates or from hospital records in 60% of cases. One hundred and twenty seven pedigrees were excluded from the lifetable analysis; 80 pedigrees ascertained through second degree relatives and 47 pedigrees from first degree relatives where insufficient information was available (principally on male relatives). Fifty six of the 518 pedigrees were excluded from the segregation analysis where there was insufficient information on family members.

2.4.2 Life Table Analysis: Results

Three hundred and ninety one pedigrees taken from a consultand with a first degree relative affected with ovarian cancer were analysed by standard life table methods to determine the risk of cancer in male and female first degree relatives of patients with ovarian cancer. This subset was analysed in an attempt to remove the problem of correcting for ascertainment through a second degree relative.

The method of analysis provided a total of 77860 years at risk in female first degree relatives and 61865 for males; the distribution of years at risk contributed by female and male first degree relatives in age groups is shown in Table 21. Tables from the OPCS for 1975 (the median year for deaths of index patients) were used to calculate the expected number of deaths among first degree relatives.

Table 21. Years at risk contributed by first degree relatives of index patients with ovarian cancer by age groups.

Sex of relative		**Female**			**Male**	
Age of index patient	< 45	45-54	55+	< 45	45-54	55+
Age group of relatives (years)						
15-24	1365	3435	12445	885	2555	9800
25-34	1270	3205	12065	840	2320	9390
35-44	1035	2785	11155	750	2060	8535
45-54	705	2315	8990	690	1720	7360
55-64	495	1515	6530	520	1320	5910
65-74	290	865	4235	275	855	3780
75-84	115	415	1995	85	370	1530
85+	30	105	500	10	65	240

Table 22. Deaths from ovarian cancer observed (O) and relative risk (RR) in first degree relatives of patients with ovarian cancer.

	Age of index patient							
	< 45		45-54		≥ 55		All index patients	
Age of relative	O	RR	O	RR	O	RR	O	RR
< 55	7***	29.9 a	6***	9.0 b	9**	3.1 c	22**	5.8 d
≤ 55	1	3.0 e	3	2.9 f	22***	4.1 g	26***	3.8 h
All	8***	14.2 i	9***	5.2 j	31***	3.7 k	48***	4.5 l

95% confidence limits of RR

a (12.0-61.6)	b (3.3-19.6)	c (1.4-5.9)	d (3.6-8.8)
e (0.1-16.7)	f (0.6-8.4)	g (2.6-6.2)	h (2.5-5.6)
i (6.1-28.0)	j (2.4-10.0)	k (2.5-5.3)	l (3.3-6.0)

Significance of difference from expected * p< 0.05, ** p< 0.01, *** p< 0.001.

Table 23. Deaths from breast cancer observed (O) and relative risk (RR) in first degree relatives of patients with ovarian cancer.

	Age of index patient					
	< 55		≥ 55		All index patients	
	O	RR	O	RR	O	RR
Age of relative						
< 55	4*	1.4 a	7	0.8 b	11	0.9
≥ 55	12**	2.8 d	18	1.2 e	30**	1.6 f
All	16**	2.2 g	25	0.9 h	41*	1.3 i

95% confidence limits of RR

a (0.4-3.5)	b (0.3-1.6)	c (0.4-1.6)
d (1.4-4.9)	e (0.7-1.9)	f (1.1-2.2)
g (1.2-3.6)	h (0.6-1.3)	i (0.9-1.8)

Table 24. Deaths from uterine cancer observed (O) and relative risk (RR) in first degree relatives of patients with ovarian cancer.

	Age of index patient					
	< 55		≥ 55		All index patients	
	O	RR	O	RR	O	RR
Age of relative						
< 55	3*	3.7 a	3	1.2 b	6	1.8 c
≥ 55	0	-	4	0.8 d	4	0.6e
All	3	1.4 f	7	1.0 g	10	1.1 h

95% confidence limits of RR

a (0.8-10.8)	b (0.2-3.5)	c (0.7-4.1)
d(0.2-2.1)	e (0.2-1.5)	
f (0.3-4.1)	g (0.4-2.1)	h (0.5-2.0)

Significance of difference from expected * p< 0.05, ** p< 0.01, *** p< 0.001

Table 25. Deaths from colorectal cancer observed (O) and relative risk (RR) in first degree relatives of patients with ovarian cancer.

	Age of index patient					
	< 55		≥ 55		All index patients	
	O	RR	O	RR	O	RR
Age of relative						
< 55	0	-	4	0.9 a	4	0.7 b
≥ 55	5	0.7 c	34**	1.3 d	39	1.2 e
All	5	0.6 f	38*	1.3 g	43	1.1 h

95% confidence limits of RR

	a (0.2-2.3)		b (0.2-1.8)
c (0.2-1.6)	d (0.9-1.8)		e (0.9-1.6)
f (0.2-1.4)	g (0.9-1.8)		h (0.8-1.5)

Table 26. Deaths from lung cancer observed (O) and relative risk (RR) in first degree relatives of patients with ovarian cancer.

	Age of index patient					
	< 55		≥ 55		All index patients	
	O	RR	O	RR	O	RR
Age of relative						
< 55	3	0.9 a	5*	0.5 b	8	0.6 c
≥ 55	6*	0.3 d	32***	0.5 e	38	0.5 f
All	9***	0.4 g	37***	0.5 h	46	0.5 i

95% confidence limits of RR

a (0.2-2.6)	b (0.2-1.2)	c (0.3-1.2)
d (0.1-0.6)	e (0.3-0.7)	f (0.4-0.7)
g (0.2-0.8)	h (0.4-0.7)	i (0.4-0.7)

Significance of difference from expected * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 27. Deaths from prostatic cancer observed (O) and relative risk (RR) in first degree relatives of patents with ovarian cancer.

	Age of index patient					
	< 55		≥ 55		All index patients	
	O	RR	O	RR	O	RR
Age of relative						
< 55	0	-	0	-	0	-
≥ 55	4	1.5 a	5	0.6 b	9	0.8 c
All	4	1.5 d	5	0.6 e	9	0.8 f

95% confidence limits of RR

a (0.4-3.8) b (0.2-1.4) c (0.4-1.5)

d (0.4-3.8) e (0.2-1.4) f (0.4-1.5)

Table 28. Deaths from stomach cancer observed (O) and relative risk (RR) in first degree relatives of patients with ovarian cancer.

	Age of index patient					
	< 55		≥ 55		All index patients	
	O	RR	O	RR	O	RR
Age of relative						
< 55	2	1.7 a	5	1.6 b	7	1.6 c
≥ 55	9	1.6 d	17	0.9 e	26	1.1 f
All	11*	1.6 g	22	1.0 h	33	1.1 i

95% confidence limits of RR

a (0.2-6.1) b (0.5-3.7) c (0.6-3.3)

d (0.7-3.0) e (0.5-1.4) f (0.7-1.6)

g (0.8-2.9) h (0.6-1.5) i (0.8-1.5)

Significance of difference from expected * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

The observed numbers of deaths from all cancers was significantly increased for female, but not male, first degree relatives of patients with ovarian cancer (n=208, relative risk 1.5, 95% confidence limits 1.29-1.71, and n=148, relative risk 0.8, 95% confidence limits 0.67-0.94; respectively). Table 22 shows the observed number of deaths from ovarian cancer and the relative risks. Overall, the relative risk of ovarian cancer in first degree relatives of all index patients was 4.5. The risk was most marked for those women who were younger than 55 and who were relatives of patients diagnosed before age 45.

Table 23 shows the observed number of deaths from breast cancer and relative risks. Overall, a 1.3-fold increase in risk for first degree relatives was seen. The risk was greatest for those relatives of patients diagnosed with ovarian cancer before age 55. The association of ovarian cancer and breast cancer was shown clearly in some pedigrees. Although no significant increase in risk of uterine cancer was seen overall (relative risk 1.1), a 3.7-fold increase in risk was observed in younger relatives (aged less than 55) of patients diagnosed before 55 (Table 24).

There was no significant overall increase in the risk of cancers of the colorectum, lung, prostate or stomach. The relative risks were 1.1, 0.5, 0.8, and 1.1 respectively (Tables 25, 26, 27, 28 respectively).

2.4.3 Segregation Analysis: Results

Table 29 shows the 8 liability classes for women with the calculated risks of ovarian cancer. A total of 861 nuclear families were derived from the 462 pedigrees. Table 30 shows the results of complex segregation analysis for the 861 nuclear families under conditional likelihood. A model not providing for family resemblance can be rejected (X^2 3 d.f. = 67.5, $p < 0.001$). Of the various models incorporating a major gene ($q>0$), a recessive model ($d=0$) did not explain the observed segregation pattern as well as a dominant model ($d=1.0$). The dominant model provides for a similar likelihood to the

Table 29. Liability classes and risks of ovarian cancer in England and Wales, 1975-1979 [OPCS].

Age range	Cumulative incidence* I	Cumulative mortality** M	Risk of having ovarian cancer dead or alive R
20-24	0.000106	0.000045	0.000086
25-29	0.000201	0.000085	0.000156
30-34	0.000336	0.000150	0.000251
35-39	0.000571	0.000305	0.000421
40-49	0.001600	0.001545	0.001355
50-59	0.004359	0.004400	0.002817
60-69	0.008243	0.008310	0.003860
70+	0.014448	0.013750	0.006190

* To mid point of interval

** To end of interval

Table 30. Results of segregation analysis for total sample of ovarian cancer pedigrees under conditional likelihood.

Model	d	t	q	H	Z	-2lnL+c	AIC
Sporadic	-	-	(0)	(0)	(0)	-4281.2	-4281.2
Polygenic	-	-	(0)	0.51	(1)	-4343.6	-4341.6
Multifactorial	-	-	(0)	0.53	0.60	-4344.3	-4340.3
Major locus							
Recessive	(0)	2.36	0.059	(0)	(0)	-4343.4	-4339.4
Dominant	(1)	1.86	0.0026	(0)	(0)	-4347.8	-4343.8
Generalised single locus	0.46	3.85	0.0033	(0)	(0)	-4348.7	-4342.7

d = dominance

t = displacement

q = gene frequency

H = childhood heritability

Z = ratio of adulthood to childhood heritability

AIC = Akaike Information Criterion

Table 31. Results of segregation analysis for total sample of ovarian cancer pedigrees under joint likelihood.

Model	d	t	q	H	Z	-2lnL+c	AIC
Sporadic	-	-	-	(0)	(0)	1522.5	1522.5
Polygenic	-	-	-	0.60	(0)	1376.0	1378.0
Multifactorial	-	-	-	0.44	2.03	1361.9	1365.9
Major locus							
Recessive	(0)	2.62	0.066	(0)	(0)	1380.1	1384.1
Dominant	(1)	2.20	0.0015	(0)	(0)	1356.6	1360.6
Generalised single locus	0.47	4.60	0.0017	(0)	(0)	1355.4	1361.4

d = dominance

t = displacement

q = gene frequency

H = childhood heritability

Z = ratio of adulthood to childhood heritability

AIC = Akaike Information Criterion

Table 32. Heterogeneity tests for the dominant model of ovarian cancer according to type of family and mating type under conditional likelihood.

	t	q	-2lnL+C
Complete ascertainment (473 families)	1.89	0.0034	+114.04
Incomplete ascertainment (391 families)	1.83	0.0024	-4462.5
All	1.86	0.0026	-4347.8
Heterogeneity			0.7
d.f			2
Mating type			
Normal x normal	1.92	0.0023	-4174.7
Other	1.74	0.0035	-173.3
All	1.86	0.0026	-4347.8
Heterogeneity			0.2
d.f.			2

Table 33. Characteristics of the major locus for ovarian cancer for each liability class when analysed under conditional likelihood (d=1, q=0.0026).

Age range	*P* (affection I genotype)		*P* (G' I affection) *	Penetrance, Pj
	GG	GG' or G'G'		
20-24	0.00002	0.01271	0.774	0.013
25-29	0.00005	0.02104	0.706	0.029
30-34	0.00009	0.03087	0.644	0.047
35-39	0.00018	0.04582	0.570	0.072
40-49	0.00082	0.10222	0.395	0.147
50-59	0.00200	0.15858	0.295	0.308
60-69	0.00289	0.18886	0.256	0.509
70+	0.00495	0.24169	0.204	0.738

* The probability of a G' carrier (GG' or G'G') among affected individuals at this age.

Table 34. Characteristics of the major locus for ovarian cancer for each liability class when analysed under joint likelihood (d = 1, q = 0.0015).

Age range	*P* (affection | genotype)		*P* (G' | affection) *	Penetrance, P_j
	GG	GG' or G'G'		
20-24	0.00001	0.02463	0.830	0.024
25-29	0.00004	0.04069	0.756	0.051
30-34	0.00008	0.05910	0.683	0.077
35-39	0.00017	0.08595	0.592	0.116
40-49	0.00084	0.17699	0.379	0.226
50-59	0.00208	0.25695	0.264	0.403
60-69	0.00301	0.29682	0.223	0.589
70+	0.00515	0.36243	0.170	0.789

* The probability of a G' carrier (GG' or G'G') among affected individuals at this age.

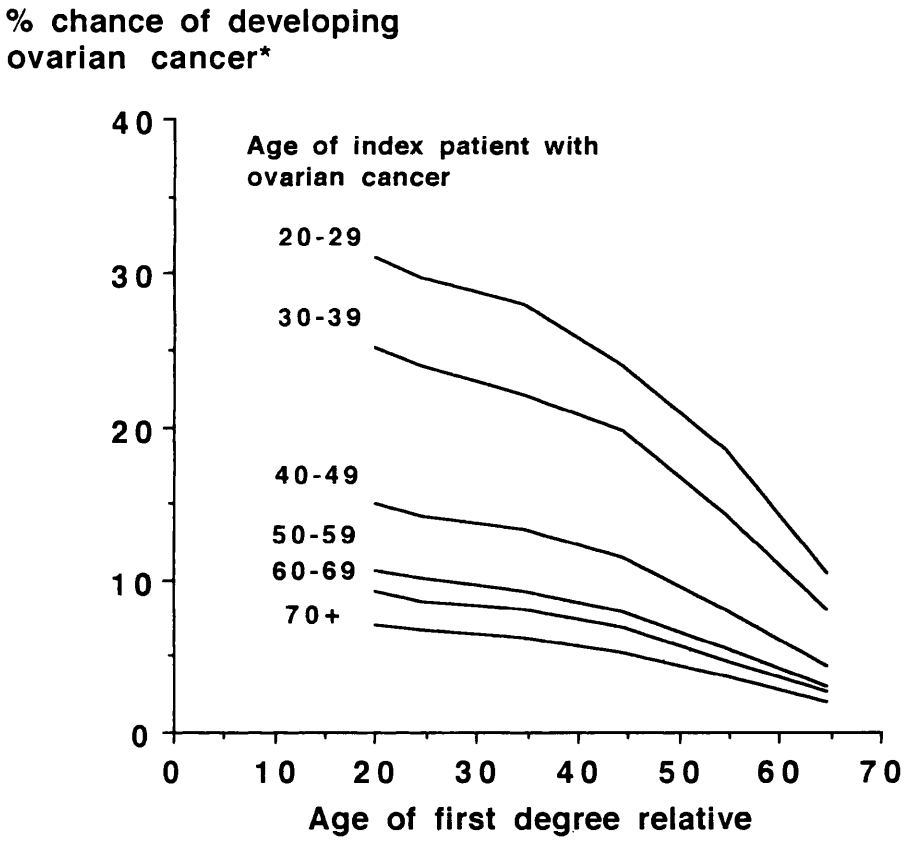


Figure 7. Chance of developing ovarian cancer with increasing age in first degree relatives of patients with ovarian cancer.
(* defined as B_i-B_j / 1-B_j ; refer section 2.1.2.6)

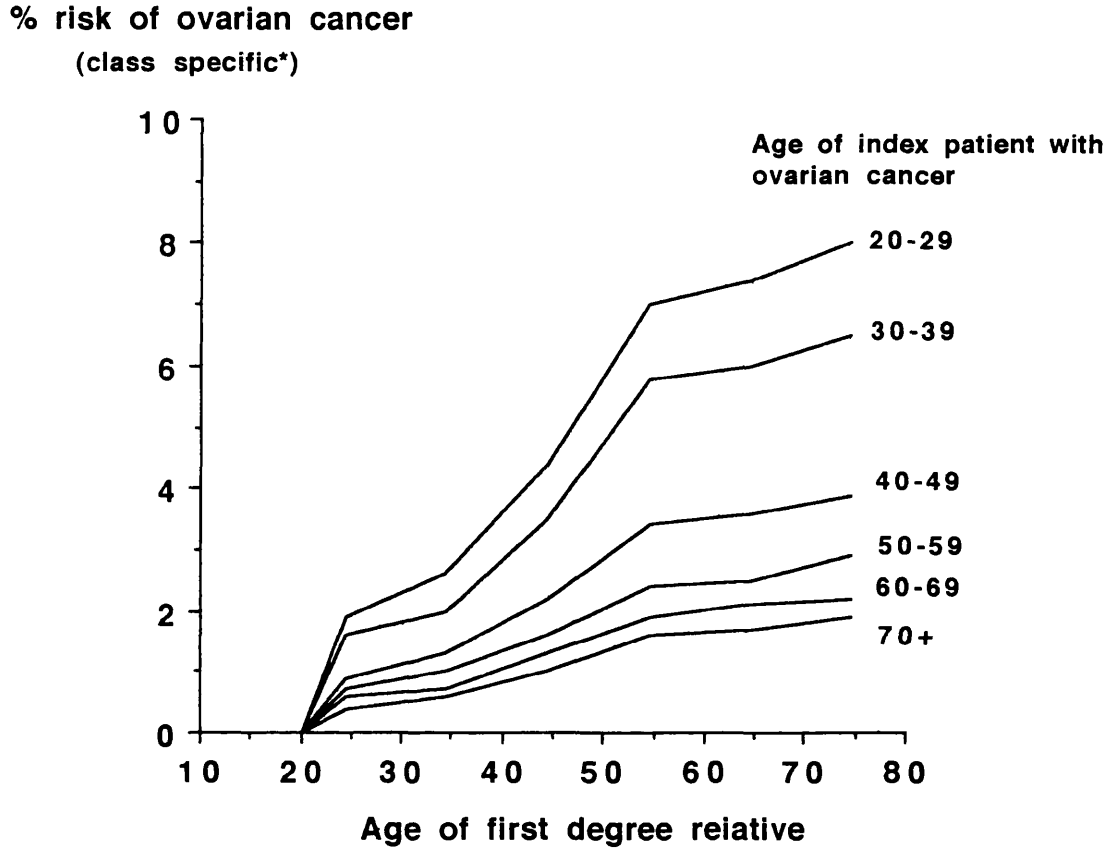


Figure 8. Actual risk of ovarian cancer with increasing age in first degree relatives of patients with ovarian cancer.
(* defined as B_i- B_j ; refer section 2.1.2.6).

general model and provided a better likelihood than either polygenic or multifactorial models. An analysis under joint likelihood provided even greater support for the dominant model (Table 31).

Families were partitioned according to the mode of ascertainment and mating type and analysed for the likelihood of the dominant model under conditional likelihood. The results were compared with the pooled material (Table 32). No difference was seen. This internal consistency provides a measure of the confidence in the most likely model, as previously discussed (section 2.2.3). Tables 33 and 34 show the characteristics of the major locus model when analysed under conditional and joint likelihood approaches respectively. The lifetime penetrance of the deleterious allele, taking age specific mortality into account, is 0.74 under the conditional likelihood approach and 0.79 under joint likelihood.

Penetrance of the abnormal gene (G') increases with age. An affected woman belonging to a low risk liability class is more likely to be a gene carrier than an affected individual in a high liability class. This is reflected in Tables 33 and 34, where an affected individual aged between 20 and 24 has a 77-83% chance of possessing the major gene compared with 22-26% for a woman aged between 60 and 69. Figures 7 and 8 show the chance of developing ovarian cancer with increasing age in first degree relatives of patients affected at different ages and the actual risk with increasing age.

2.4.4 Discussion

The results from this pedigree analysis are similar to a number of studies which have demonstrated an increased risk of ovarian cancer in relatives of patients with ovarian cancer [Hildreth et al., 1981; Cramer et al., 1983; Schildkraut and Thompson, 1988; Mori et al., 1988 Koch et al., 1989; Ponder et al., 1990]. In this study the relative risk was dependant on the age at diagnosis of ovarian cancer. The highest risk was for those relatives aged less than 55 of women who developed ovarian cancer when they were

young. Some studies have, however, suggested that late-onset ovarian cancer may be 'more familial' than early-onset ovarian cancer [Schildkraut et al., 1989; Ponder et al., 1990].

An assumption in this study is that ovarian cancer is a single disease. There are however, a number of histological variants of ovarian cancer [Scully, 1983]. Despite the likelihood of heterogeneity diluting or obscuring any evidence for a genetic effect, it was possible to show evidence for the contribution of a dominant gene to the development of ovarian cancer. The gene frequency accounts for a significant proportion of ovarian cancer in young women, but in later years the majority of cases are sporadic. With an early age of onset, the genetic risk to offspring is high, but with increasing age of onset the genetic component to overall risk diminishes. Furthermore, with increasing age of the relative, the risk of any inherited liability is reduced because the genetic risk has been outlived.

The estimated frequency of the dominant gene is between 0.0015 and 0.0026, with a lifetime penetrance of between 0.74 and 0.79, making it responsible for at least 17% of the total burden of ovarian cancer. Lynch et al., [1990a] has suggested that between 5 and 10% of ovarian cancer is due to hereditary factors.

The possibility of unrecognised bias in pedigrees ascertained through a normal consultand cannot be overlooked and there is a need for confirmation in a sample of pedigrees ascertained through probands. Only cancers of the ovary were verified by death certificates or hospital records; other information was obtained by history-taking alone.

Despite potential bias in ascertaining pedigrees through normal consultands attending an ovarian cancer screening unit, there was no significant increase in risk of cancers of the prostate, stomach, uterus or colorectum. The risk of lung cancer in relatives was reduced and whilst the possibility of under-reporting cannot be excluded, the observation is concordant with the findings of Koch et al., [1989].

A significant increase in risk of 1.3-fold of breast cancer was seen. The genetic relationship between cancers of the ovary, breast and uterus has been examined in a case-control study by Schildkraut et al., [1989]. A significant correlation was found between cancers of the ovary and breast (R_{12} = 0.484), but no significant overlap was observed between either ovarian or breast and endometrial cancer. This data supported the existence of a breast-ovarian cancer syndrome, and although endometrial cancer is heritable, it appears to be genetically unrelated to the breast-ovarian syndrome. The association of breast and ovarian cancer has been postulated to result from a common genetic aetiology by the segregation analysis of a small number of extended families [Go et al., 1983].

Chromosome studies of ovarian tumours have demonstrated loss of heterozygosity for 17q [Lee et al., 1990]. The long arm of chromosome 17 has also been shown to be linked with early onset breast cancer [Hall et al., 1990] suggesting possible involvement of 17q in the aetiology of the breast-ovarian association in at least a proportion of families. This inference was subsequently confirmed by Narod et al., [1991] with the demonstration of linkage in 3 families between breast and ovarian cancer and 17q. Whilst both breast and ovarian cancer may be pleiotropic effects of the same gene in some families, the genetic correlation between these two cancers reported by Schildkraut et al., [1989] was less than unity, suggesting the existence of heterogeneity. Current data from the International Linkage Consortium [Easton et al., 1992] suggests that it is likely that about 50% of breast cancer pedigrees and approximately 75% of breast-ovarian cancer pedigrees are linked to the BRCA1 gene on chromosome 17q.

2.5 CONCLUSIONS

The genetic epidemiology of colorectal, breast and ovarian cancer was investigated in order to examine the role of family history in the aetiology of these cancers, and to provide risk estimates for use in clinical practice.

Life table analyses of the colorectal, breast and ovarian cancer pedigrees showed that the risk of cancer at the same site in first degree relatives is greatest for relatives of patients diagnosed at a young age. The age-specific risks are compatible with a gene or genes conferring a high lifetime risk of colorectal, breast and ovarian cancer.

Although empiric risks can be used in clinical practice for counselling, every family history is unique and in many circumstances an empiric risk may be non-specific or unavailable. In contrast, where the mode of inheritance is inferred, a risk can be calculated for any pedigree structure. One objective of segregation analysis is therefore to define a more accurate estimate of risk than that obtained through empiric calculations which ignore the aetiology of the disorder, unlike a prediction of risk based upon an underlying model.

Complex segregation analysis showed that the familial aggregation of colorectal, breast and ovarian cancers is most compatible with the inheritance of dominant genes. Using estimates of the probability of inheriting the deleterious genes for these cancers and the age-specific penetrances enables the genetic component of risk at different ages for relatives to be calculated. With an early age of diagnosis the genetic risk of cancer in offspring is high, but with increasing age at diagnosis the risk diminishes. This information can be used to identify more precisely those family members who are at high risk and estimate the chance that a dominant gene is responsible for any family aggregation of colorectal, breast or ovarian cancer and hence the chance of developing the cancer at subsequent ages. However, for all but the simplest of pedigree structures such risk calculations will be complex and are best carried out by computer programs (e.g. MENDEL devised by Lange [1988]).

The identification of genes predisposing to colorectal, breast and ovarian cancer resides in the process of linkage. The use of linkage analysis for cancer makes the results of segregation analysis important because a wrongly specified model leads to difficulties. Misprediction of allele frequencies, especially in the presence of sporadic cases of cancer, will greatly influence the power of any linkage study. For breast cancer, segregation analysis suggests that a dominant gene accounts for a significant proportion of early onset cases, but that in later life the majority of cases are phenocopies. It is therefore not surprising that King and co-workers found linkage of early onset, but not late onset breast cancer to chromosome 17q [Hall et al., 1990].

Table 35. Expected number of cases (n) of colorectal, breast and ovarian cancer due to dominant genes at defined ages in a population of 5 million.

Ascertainment	gene frequency (q)	p*	n**
Colorectal cancer			
< age 35	0.006	0.01	300
Breast cancer			
< age 30	0.009	0.007	315
Ovarian cancer			
< age 35	0.0016	0.047	376

* penetrance within age limit
** expected number of cases in a population of 5 million (N), n = q. P. N

Table 35 shows the expected numbers of cases of colorectal, breast and ovarian cancer in a population of 5 million which could be used to ascertain families suitable for linkage analysis.

Highly selected families, whilst useful for linkage do not, however, permit estimation of gene frequency, penetrance and other genetic parameters. This is the unique role of segregation analysis, and is best achieved by analysis of families ascertained through sequential probands.

One problem in using complex segregation analysis to study cancer is the temporal differences in the age specific cancer risks. This can be minimised by limiting analyses to nuclear families rather than extended pedigrees.

A more significant problem for segregation analysis in general is the interaction between a rare gene and common trait. A major gene will inevitability be inferred to be common if modelled inappropriately. This has been suggested by Morton et al., [1991] to be the likely explanation for reports of very common genes underlying the development of adenomas and colonic cancer [Cannon-Albright et al., 1988] and fibrocystic breast disease and breast cancer [Skolnick et al., 1990].

In the reported segregation analyses of breast cancer there are differences in the relationship between phenotypes and genotypes. In particular, for an affected individual with a given age of onset, the estimated probabilities of being a mutation carrier differ. This problem is not likely to be unique to breast cancer. Underestimation of the proportion of sporadic cases may lead to false linkage exclusion in some families, simulating genetic heterogeneity [Clerget-Darproux and Bonaiti-Pellie, 1992], and leading to inaccuracies in determining risks in relatives of affected individuals.

The accuracy of estimates of gene frequency and penetrance predicted by complex segregation analysis are clearly governed not only by how pedigrees are ascertained, but also by how well the underlying models are implemented.

A specific problem in the implementation of the mixed model in POINTER is the inability to incorporate ancillary information such as age at onset, bilaterality of cancers and variables predictive of liability among

affected, associated cancers and premalignant states such as colonic polyps. This may be overcome in future segregation studies using the model COMDS (COMbined segregation and linkage analysis with Diathesis and Severity) proposed recently by Morton and co-workers [Morton et al., 1991] which attempts to integrate ordinal polychotomies into the liability model.

SECTION 3: USE OF RISK ESTIMATES IN CLINICAL PRACTICE: SCREENING AND GENETIC COUNSELLING IN FAMILY CANCER CLINICS.

3.1 SCREENING AND GENETIC COUNSELLING FOR RELATIVES OF PATIENTS WITH COLORECTAL CANCER IN A FAMILY CANCER CLINIC

3.1.1 Introduction

The lifetime risk of colorectal cancer in England and Wales is approximately 1 in 25 [OPCS 1985] and increases rapidly from age 50. Unfortunately, the results of treatment are disappointing with an acknowledged survival rate of 50% in patients undergoing surgery with a view to cure. In 1974 Morson pointed out that the majority of colorectal carcinomas arise in pre-existing adenomatous polyps and this hypothesis of the adenoma-carcinoma sequence offers an opportunity for early diagnosis and treatment if polyps can be identified.

Population screening using faecal occult blood tests, though low in cost, has so far been found to have a disappointing uptake and poor yield [Hardcastle et al., 1989]. A screening programme targeted at high risk individuals should be more efficient. Furthermore, compliance is likely to be high among individuals who perceive themselves to be at increased risk and have a good understanding of the reasons for screening. To test this hypothesis a family cancer clinic was opened at St. Mark's Hospital, London offering counselling and screening for relatives of patients with colorectal cancer.

3.1.2 Patients

In the latter half of 1986 a family cancer clinic for relatives of patients with colorectal cancer was opened at St. Mark's Hospital, London as part of

the North East Thames Regional Genetic Service. The clinic was supported by the Imperial Cancer Research Fund and publicised in the national press. Clear guidance was given that screening was available for first degree relatives of patients who had developed colorectal cancer before the age of 45 and for members of families in which multiple cancers had occurred. Self referrals were accepted as well as those referred by medical practitioners. Pedigrees were obtained from those attending, risks were estimated and explained, and a screening programme was offered.

3.1.3 Screening Policy

The screening policy for first degree relatives of patients with colorectal cancer was devised around lifetime risks of colorectal cancer.

For first degree relatives of index patients diagnosed with colorectal cancer at or below age 45, the relative risk is 6.4 and for first degree relatives of index patients over 45 the risk is 2.7 (derived from data presented in section 2.2). Relative risks were used to estimate lifetime risks; because of large confidence limits, rounded figures were used in clinical practice and are shown in Table 36.

For those whose lifetime risks were between 1 in 17 and 1 in 10, annual screening by faecal occult blood testing was offered using the Haemoccult test (Norwich-Eaton Ltd., Newcastle. U.K.). For those whose risk was 1 in 10 or greater, colonoscopy was chosen for two reasons; firstly, large bowel lesions in high risk families tend to be right sided with only 26% being detectable by sigmoidoscopy [Mecklin and Jarvinen, 1986; Lynch et al., 1988], and secondly, colonoscopy allows the removal of small adenomas at the time of screening. Among affected members of high risk families the mean age of developing colon cancer is 40 years, and 77% of the risk of having colorectal cancer is passed by 69 years [Mecklin and Jarvinen, 1986]. Adenoma follow up studies suggest that three-yearly examinations are adequate for those with pre-existing polyps [personal communication -

Table 36. Lifetime risks of colorectal cancer in first degree relatives used in clinical practice.

Population risk	1 in 50
One relative affected	1 in 17
One first degree and one second degree relative	1 in 12*
One relative < 45 years	1 in 10
Dominant pedigree	liability 1 in 2, risk 1 in 3

* Estimated originally from a polygenic model.
Figures based on mortality data from OPCS, [1974] up to age 70.

Table 37. Screening policy for colon, breast and pelvic cancer in the Family Cancer Clinic at St. Mark's Hospital.

Colon cancer (Ages 25-65)	
Risk < 1 in 10	Faecal occult blood
Risk > 1 in 10	Colonoscopy 5 yearly, 3 yearly if polyps found
Breast cancer	
Ages:	
25-39	Baseline mammogram, yearly ultrasound
40-49	Yearly mammogram
50+	DHSS National Breast Screening Programme
Pelvic cancer	
Age 25+	Yearly pelvic ultrasound

C. B. Williams, St. Mark's Hospital]. It was therefore decided to offer colonoscopy every 3 years to those between the ages of 25 and 65 if polyps were detected on initial examination, but 5-yearly if no polyps were detected. In clinical practice where there was evidence of dominant inheritance, family members over 65 at a 1 in 2 risk of inheriting the liability, were offered a single colonoscopic examination but were not included in the regular screening programme.

Women from families with pedigrees compatible with the Lynch syndrome type II were offered additional screening for breast, uterine and ovarian cancers, starting at age 25. Table 37 shows the screening strategy for colonic, breast and pelvic cancers.

3.1.4 Results

Eighty per cent of the patients attending the clinic in the first two years were self referrals; subsequently more patients were referred by medical practitioners. Table 38 shows the detailed source of the referrals. Of the 715 patients who attended the clinic from 1986 to 1990, 461 had a lifetime risk of 1 in 10 or greater, 103 had a risk of between 1 in 10 and 1 in 17, and 42 patients were themselves affected but required further screening. In all, 608, or 85% of those who attended the clinic required screening and 508, or 71% were at high risk requiring colonoscopy.

One hundred and fifty one patients with lifetime risks of less than 1 in 10 were offered screening by Haemoccult. Compliance rates were 136 out of 151, or 90%, for the first screen and 69 out of 79, or 87%, for the second screen. Three patients with positive occult blood tests proceeded to colonoscopy. Two were found to have polyps, one in association with enterocolitis, the third had ulcerative colitis.

Haemoccult tests were also performed on 59 high risk patients prior to colonoscopy. Two were positive due to bleeding from ulcerative colitis.

Table 38. Source of referrals to the Family Cancer Clinic at St. Mark's Hospital.

Source of referral	**n**	**%**
Self	362	51
Patient via general practitioner	64	9
General practitioner	159	22
Hospital consultant	120	17
Other (screening programmes)	10	1
Total	715	

However, of the 57 negative tests, 13 had adenomatous polyps, one with carcinoma in situ, giving a negative predictive value for polyps of 78%.

This report covers 382 relatives who underwent the first of their regular screenings by colonoscopy during the period 1986-1990. Table 39 shows the number of relatives with varying risks, their ages, and the number in whom polyps or colorectal cancers were detected. In two patients at a 1 in 2 liability, polyps were too numerous for control though colonoscopy and colectomy was performed. There was no evidence of adenomatous polyposis coli in either of these patients. Polyps were detected in 9 relatives who were already known to have colon cancer; 2 had metachronous colon cancer. Eighteen relatives were screened by colonoscopy because, whilst their risks were less than 1 in 10, they reported rectal bleeding or had positive occult blood tests; three had polyps.

Table 40 shows the anatomical distribution of adenomatous polyps detected. Twice the expected number of polyps were found in the proximal and mid colon.

Of the 715 patients seen, 83 had pedigrees compatible with Lynch syndrome type II (Table 41); 19 were found to have polyps at the first screen and 3 had colon cancer. Of 110 patients with evidence of the Lynch syndrome type II in their pedigrees, 16 were found to have polyps and one had colon cancer. Thirty five women with Lynch syndrome type II were offered breast and pelvic screening; 4 were found to have breast cancer (ages 57, 42, 35 and 45) , two asymptomatically (ages 35 and 45). No pelvic cancer was detected on initial screening.

Nine patients attended the clinic from three previously undiagnosed families with adenomatous polyposis coli; 2 had multiple polyps requiring colectomy. Twenty five patients had stigmata compatible with other syndromes known to be associated with colon and other cancers including Cowden's, Muir-Torre and Gorlin's syndromes. Two patients were seen to have multiple lipomata in association with colorectal cancer, and in addition

Table 39. Results of screening by colonoscopy in relatives at a high risk of colorectal cancer.

Risk	Number of relatives (%) Screened	With polyps	With cancer	Mean (SD) age of relatives with polyps
Dominant pedigree	202	36 (17.8)	3	46.4 (9.9)
> 1 in 10	132	14 (10.6)	0	48.7 (9.8)
Affected	30	9 (30)	2	45.2 (7.0)
< 1 in 10 with symptoms	18	3 (16.6)	0	43.7 (11.1)

Table 40. Number of patients at risk of colorectal cancer who had colorectal polyps.

	Site in colon		
Risk	**Proximal ***	**Middle ****	**Distal *****
Dominant pedigree	7	8	22
> 1 in 10	2	4	8
Affected	2	3	4
< 1 in 10 with symptoms	1	1	2
Total 64 adenomas	12 (19%)	16 (25%)	36 (56%)
St. Mark's series 1187 adenomas+	8.2%	13.6%	78.2%

* Caecum and ascending colon

** Hepatic flexure to splenic flexure, including transverse colon

*** Descending and sigmoid colon and rectum

+ Morson et al. [1983].

Table 41. Syndromes identified in 715 patients at risk of colorectal cancer.

Syndrome	**Number of patients at risk**	**Number with polyps**
Lynch syndrome type I	83	19
Lynch syndrome type II	110	16
Adenomatous polyposis coli	9	2
Other syndromes: (Cowden's, Muir's, Gorlin's, multiple lipomata)	25	1

8 first degree relatives at risk were found to have lipomas. Multiple lipomas are common in the population at large and these observations could be fortuitous.

3.1.5 Discussion

In the Family Cancer Clinic at St. Mark's Hospital, risk estimates for first degree relatives of patients with colorectal cancer were obtained from family histories, enabling screening to be offered to relatives based on their probability of developing colorectal cancer.

Screening by faecal occult blood test seems to be unsuitable for high risk patients as it has a poor negative predictive value, and this supports the observations of Rozen et al. [1986]. Colonoscopy, however, is an efficient method of detecting malignant polyps. In this series polyps were detected and removed through the regular screening programme in 62 out of 382, or 16%, of patients within the high risk groups.

Other studies have reported a higher prevalence of colorectal neoplasms in individuals with a family history of colorectal cancer than in unselected individuals; the detection rate using colonoscopy has been variously reported as 12% [Guillem et al., 1989; McConnell et al., 1990], 18% [Grossman and Milos, 1988], 20% [Orrom et al., 1990], 25% [Guillem et al., 1988] and 27% [Baker et al., 1990]. Although autopsy studies have shown that about one third of colons carry neoplasms [Rickett et al., 1979; Vatn and Stalasberg, 1982], it is not entirely valid to compare endoscopic data with autopsy data. Endoscopy tends to under-estimate the prevalence of adenomas, especially those less than 1 cm in size, and the mean ages of screened individuals are lower than in most autopsy series.

The young age of the patients and the right-sided distribution of the polyps in this study was consistent with the observations of other workers [Anderson, 1980b; Mecklin and Jarvinen, 1986; Lynch et al., 1988], and supports the view that colonoscopy is an appropriate screening method for

this high risk group [Anderson, 1980b; Rozen et al., 1986]. It has been suggested that flexible sigmoidoscopy would be appropriate for screening high risk groups [Stephenson et al., 1991]; however, this technique has a sensitivity for detecting colonic neoplasms of only 55% and a negative predictive value of 88% [Dunlop, 1992]. It therefore seems wholly inappropriate to carry out an incomplete examination in individuals at a high risk of proximal colonic disease.

The high frequency of patients with family histories compatible with the Lynch syndromes types I and II was not wholly unexpected; their contribution to the overall incidence of colon cancer has been estimated as 6-10% [Lynch et al., 1988]. Twenty seven per cent of the patients who presented to the family cancer clinic because they had recognised the high frequency of bowel cancer in their family had pedigrees compatible with the Lynch syndromes type I or II. Any strategy targeting screening to high risk colorectal cancer patients must recognise that screening of the breasts and pelvis should be available to patients from families with Lynch syndrome type II.

Seven out of 14 patients over age 65 with a liability of 1 in 2 were found to have colonic polyps on colonoscopy, one contained a carcinoma in situ. These patients were not included in a regular screening programme because they were over 65, but were offered colonoscopy for clinical management because their risk was high and the result would contribute to the genetic information relevant to other family members. The numbers are too small to draw any conclusion about the possible benefits of screening older relatives, but the question perhaps merits further consideration.

Although a prophylactic effect of polypectomy on the natural history of subsequent colorectal cancer has been reported [Murakami et al., 1990], it is accepted that not all adenomas undergo malignant transformation and the value of polypectomy in reducing the risk of colorectal cancer in the general population is largely based on indirect evidence [Stryker et al., 1987; King's Fund consensus statement, 1990; Pollock and Quirke, 1991].

Targeting screening to those at high risk of colorectal cancer may not only be an effective strategy in itself, but may provide an opportunity to answer many of the questions on the overall efficacy of polypectomy in reducing the risk of colorectal cancer.

3.2 SCREENING AND GENETIC COUNSELLING FOR RELATIVES OF PATIENTS WITH BREAST CANCER IN A FAMILY CANCER CLINIC

3.2.1 Introduction

For women in Britain the lifetime risk of developing breast cancer is approximately 1 in 12 and it is the most common cause of death in women aged between 35 and 55 [OPCS, 1986]. Recently there has been considerable interest in screening to detect breast cancer at an early stage and maximise the potential benefit of treatment [The Health of the Nation, 1991]. Although between 5 and 10% of breast cancer may be due to an inherited liability [Claus et al., 1991; Iselius et al., 1992], the majority of breast cancer is sporadic and population risks are highest overall for those women over age 50 (Figure 9). This level of risk underlies the availability of breast screening to women through the National Breast Screening Programme [The Health of the Nation, 1991], however, there is an equivalent risk of developing breast cancer below the age of 50 for those relatives of patients diagnosed before 45 (Figure 9).

A large proportion of women in the general population are aware that having a close relative with breast cancer places them at increased risk [Fallowfield et al., 1990]. Those whose relatives have died young and who are below age 50 themselves cannot be reassured through the National Breast Screening Programme though their risk may be equivalent to women who are eligible for screening.

Experience in the development of a genetic counselling clinic for those at risk of colorectal cancer (Section 3.1) led to the recognition of a need for a similar service for families with breast cancer.

3.2.2 Patients

In 1988 a family cancer clinic was opened at the Royal Free Hospital as part of the North East Thames Regional Genetic Service. This family cancer

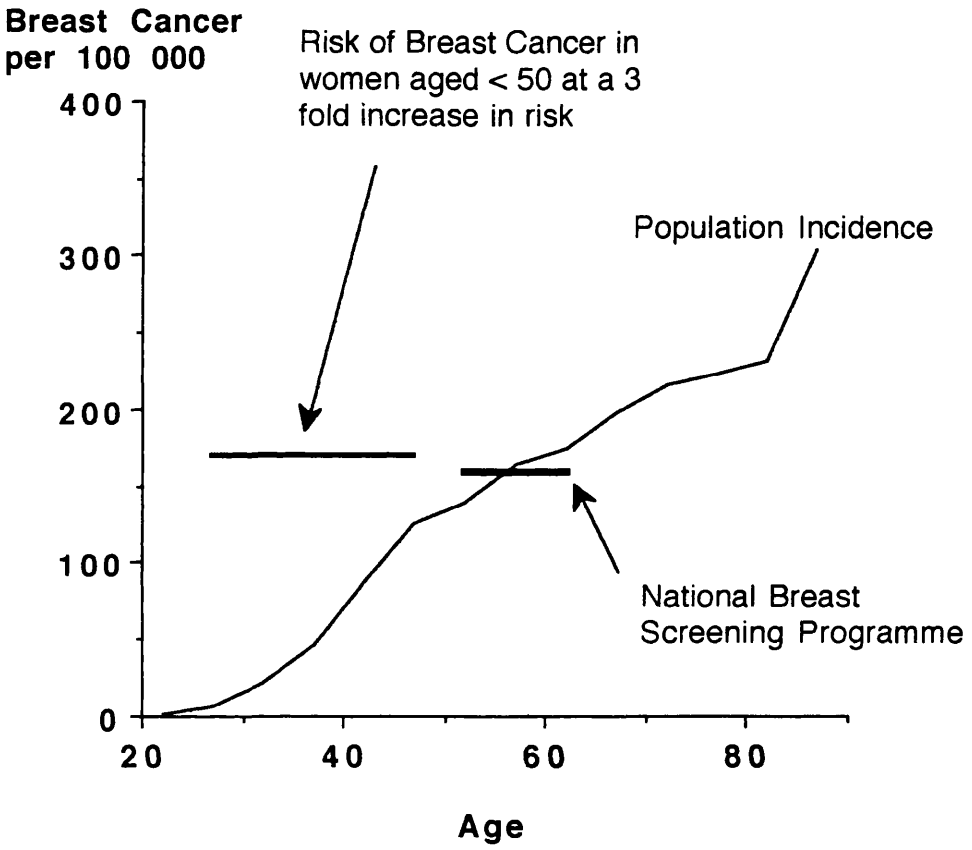


Figure 9. Incidence of breast cancer by age showing risks at which screening is offered through the National Breast Screening Programme.

clinic, like the clinic at St. Mark's Hospital (section 3.1), was supported by the Imperial Cancer Research Fund and publicised in the national press. Guidance was given that the clinic was available for first degree relatives of patients who developed breast cancer premenopausally or who had multiple cases of breast cancer within their families.

3.2.3 Screening Policy

The risk of breast cancer for each woman attending the clinic was estimated from her family history. Annual radiological breast examination was offered to the relatives of patients diagnosed young who had a three-fold or greater increase in risk or whose pedigrees showed a dominant mode of inheritance of breast and/or other cancers. The risk of breast cancer in these women is equivalent to that of women in the general population aged between 50 and 64, whose risk is approximately 0.0016 per year [OPCS, 1986]. From age 25 to 39 women were offered a baseline mammogram and yearly ultrasound examination of the breasts, from 40-49 annual mammography and after 50 years of age they were encouraged to participate in the National Breast Screening Programme. All the women including those whose risk was not substantially increased (i.e. less than 3-fold), were taught breast self examination and were encouraged to join the National Breast Screening Programme at 50. All ultrasound examinations and mammograms performed at the Royal Free Hospital were reported by consultant radiologists.

Women whose pedigrees were consistent with one of the multiple cancer syndromes such as the Lynch syndrome type II were offered additional screening for pelvic and colonic cancers using the protocol outlined in Table 37.

3.2.4 Results

From 1988 to 1990, 851 patients attended the Royal Free Hospital Family Cancer Clinic concerned about their risks of developing breast cancer. Table 42 shows the source of referrals to the clinic. Initially 91% of patients were self-referrals, subsequently a greater proportion of patients were referred by medical practitioners.

Table 43 shows the age profile of patients attending the clinic. Of those aged 50 or over and who were eligible for screening through the National Breast Screening Programme, 45% (35 out of 75) were referred by medical practitioners.

Table 44 shows the pattern of risk and syndromes identified in patients attending the clinic. Fifty per cent of women (56 out of 111) whose risks were not substantially increased, or whose risks were no more than the population risk, were referred by medical practitioners. Of the cancer family syndromes showing dominant inheritance of cancer, site specific breast cancer and the Lynch syndrome type II were most frequent, accounting for 39% of all those at increased risk.

Of the women who were estimated to be at a high risk of developing breast cancer 595 were offered screening at the Royal Free Hospital and it is the experience of these women that is reported, rather those who chose to participate in screening at other centres. Table 45 shows the results of radiological screening and compliance rates for those offered screening at the Royal Free Hospital. Compliance rates in both age groups were in excess of 83% throughout the period of study 1988 to 1990. All suspicious results from physical or radiological examinations were referred to breast surgeons. Altogether 1028 radiological breast examinations were carried out at the Royal Free Hospital and five cancers were detected. Three cancers were detected by screening, one was a palpable breast lump detected on initial examination (patient aged 38) and two were detected by radiology; one by ultrasound examination and one by mammography (patient ages 49

Table 42. Source of referrals to the Family Cancer Clinic at the Royal Free Hospital.

Source of referral	Year 1 n (%)	2 n (%)	3 n (%)
Self referral	361 (91)	135 (58)	127 (58)
By general practitioner	29 (7)	90 (38)	88 (40)
By hospital practitioner	7 (2)	9 (4)	5 (2)

Table 43. Age profile of patients attending the Family Cancer Clinic at the Royal Free Hospital.

Age range	n (%)
<25	66 (8)
25-39	500 (59)
40-49	210 (25)
50+	75 (9)

Table 44. Pattern of risks and syndromes identified in patients attending the Family Cancer Clinic at the Royal Free Hospital.

Pattern of risks	**n (%)**
Less than 1.7	111 (13)
Greater than 3.5	740 (87)
Specific syndromes identified	
Site-specific breast cancer	179 (21)
Breast-ovarian cancer	20 (2)
Lynch syndrome type II	108 (13)
Li-Fraumeni syndrome	4 (0.5)
Cowden's syndrome	2 (0.2)
Muir-Torre syndrome	5 (0.6)

Table 45. Compliance rates and results of breast screening in women attending the Family Cancer Clinic at the Royal Free Hospital.

		Years of screening		
		1	2	3
Women aged 25-39				
Compliance		96%	84%	89%
Results	Normal	388 (92%)	217 (95%)	70 (95%)
	Benign lesions	21 (5%)	11 (4%)	4 (5%)
	Suspicious lesions	12 (3%)	1 (1%)	
	Biopsy confirmed breast cancer	1	0	
Women aged 40-49				
Compliance		93%	89%	97%
Results	Normal	132 (91%)	97 (95%)	51 (89%)
	Benign lesions	10 (7%)	4 (4%)	5 (9%)
	Suspicious lesions	3 (2%)	1 (1%)	1 (2%)
	Biopsy confirmed breast cancer	0	1	1
Compliance overall		95%	89%	97%

and 46 respectively). Two interval breast cancers occurred in women who had in each case had at least two preceding negative annual screens; one aged 49 by three annual mammograms and one aged 38 by mammogram followed by ultrasound. Both were found by breast self examination. All breast cancers were confined to stage T_1 N_0 M_0 [TNM Classification of malignant tumours: Hermanek and Sobin, 1987].The false positive rate was 1% and the predictive value of a negative screen was 99%.

Of those women offered additional screening because of their multiple cancer syndrome pedigrees, no pelvic or colorectal cancers were detected.

3.2.5 Discussion

Breast screening is currently available in the United Kingdom to women over 50 in whom population risks are high. The detection rate of radiological screening for breast cancer in young women is acknowledged to be lower than for post-menopausal women [Rodgers and Witcombe, 1991]. This reflects the lower incidence of breast cancer and the reduced efficacy of mammography in young women. It is therefore not surprising that Eddy and co-workers provided evidence that population screening by mammography of asymptomatic women before age 50 does not show sufficient health or economic benefit to offset the costs and risks [Eddy et al., 1988]. However, their findings did not consider women at a high risk for breast cancer. Mammography, initiated at age 50, or even at age 40 which is now under evaluation in some regions of the United Kingdom, is inadequate for women predisposed to breast cancer through family history; many will have completed the majority of the evolution of the disease's natural history years before.

Young women generally have much denser breast tissue, potentially obscuring the early signs of malignancy. Some studies have shown however, that it is still possible to detect breast cancer early in premenopausal women [Meyer et al., 1983; Sickles et al., 1986] and,

although numbers are small, evidence from the Royal Free Family Cancer Clinic suggests that screening a high risk group can give a pick-up rate similar to the 6 per 1000 currently achieved through the National Breast Screening Programme for women over 50 [Chamberlain et al., 1992].

The accepted consensus on the radiation risk associated with regular mammography is that the risk is negligible for women over the age of 50 (1 cancer induced per 1 million women screened). The risk is presumed to be greater for younger women, with an effect delayed for 10 to 20 years [Royal College of Radiologists, 1991]. Although use of ultrasound to detect breast cancer avoids exposure to radiation, making it more acceptable for screening of women at young ages, it is a less sensitive technique than mammography [Fung and Jackson 1990]. Furthermore, the suggestion that women under 50 are put at a survival disadvantage by undergoing mammography seems unlikely, at least in studies of women from the general population [Stacey-Clear et al., 1992; Miller et al., 1992.].

At present family history is a useful criterion for selection of patients for screening, but molecular genetic analysis will further refine this process. The first gene responsible for early onset breast cancer has been localised to the long arm of chromosome 17 [Hall et al., 1990; Easton et al., 1992] and gene markers useful for diagnosis will soon become available. In addition germ line point mutations of the tumour suppresser gene p53 are reported to underlie a proportion of cases of the Li-Fraumeni syndrome [Malkin et al., 1990; Srivastara et al., 1990].

The screening programme used in this study detected only 3 out of 5 breast cancers in 851 young women at risk. Those at risk will soon be identified with more certainty, but the best protocol for screening younger women still needs to be defined. The best screening programmes and other management strategies will only be determined by long term follow-up studies.

3.3 SCREENING FOR OVARIAN CANCER: USE OF FAMILY HISTORY

The risk estimates determined for relatives of patients developing ovarian cancer were not implemented in clinical practice by the author. However, screening for ovarian cancer of women who have a close relative with this disease is ongoing in the Department of Obstetrics and Gynaecology, Kings College Hospital, London [Bourne et al., 1991].

Seven hundred and seventy six asymptomatic women who all had a first or second degree relative who had developed ovarian cancer (677, 87% and 98, 13% respectively) were screened using transvaginal ultrasound. Forty three women underwent surgical investigation and of these, 3 cases of primary ovarian cancer were detected (prevalence 3.9 /1000) all at FIGO stage Ia [International Federation of Gynaecology and Obstetrics staging of ovarian cancer: Hermanek and Sobin, 1987]. None of the women developed ovarian cancer within the first year following the initial scan, giving a detection rate of 100%. The false positive rate was 5.2% and the predictive value of a positive screen 7.7% Both the positive predictive value of the screening procedure and the prevalence of ovarian cancer were significantly higher than in population based screening programs [Campbell et al., 1989; Van Nagell et al., 1990].

3.4 CONCLUSIONS

Experience gained in the two family cancer clinics presented supports the view that family history of cancer provides a useful method of identifying those placed at highest risk of cancer and who may benefit from targeted screening.

It is impossible to estimate the economic benefits of screening high risk groups until long term follow up has demonstrated effects on mortality or morbidity. However, there is clearly an opportunity to identify individuals

predisposed to common cancers through family history and potentially to detect cancer at an early stage through intensive screening programmes.

With the imminent availability of linked gene markers for early onset cases of breast cancer and the likelihood of a similar development for colorectal cancer, debate over the possible introduction of screening for those at highest risk is likely to seem inappropriate in clinical practice.

As well as concern over the efficacy of screening for cancer, there is controversy over the possible psychological morbidity associated with screening programmes; most widely voiced in connection with breast cancer [Roberts, 1989; Ellman et al., 1989; Bull and Campbell, 1991]. In the development of the two family cancer clinics reported in this thesis, all workers taking part were aware that anxieties might be heightened by discussing actual risks during counselling and that false expectations regarding screening could develop. Both these problems were discussed freely with all patients attending. Formal psychological testing of 41 unselected patients attending the Family Cancer Clinic at the Royal Free Hospital before and after attending the clinic did not suggest that perceptions of health were significantly altered [M. Van Duijin and T. Marteau, Dept. Psychology, Royal Free Hospital; personal communication]. There is a great variation in peoples' requirements for reassurance about their risk of cancer and the high proportion of self-referrals to both of these clinics who were found to be at high risk suggests that individuals can be adept at self-selection for this type of screening programme. However, it is accepted that this may not be the universal experience. In a study from the U.S.A by Kash and co-workers into anxiety and breast screening in women with a family history of breast cancer a higher anxiety score was directly related to poor attendance for clinical breast examination [Kash et al., 1992].

SECTION 4: CONCLUDING REMARKS

The studies reported in this thesis on the genetic epidemiology of colorectal, breast and ovarian cancer suggest that the inheritance of dominant genes underlies the development of these cancers in a significant proportion of cases, particularly those of early onset. Family history therefore, enables those placed at highest risk to be identified.

Empiric estimates of risk, gene frequency and penetrance have been used in clinical practice in the development of two family cancer clinics offering counselling and screening to relatives of patients with colorectal and breast cancer. Screening was targeted to young individuals at a high risk of cancer. Detection rates for adenomas of the colon and colorectal cancer, and breast cancer using mammography and ultrasound were high and comparable to those older individuals in the general population with a high liability.

From the experience in two family cancer clinics it is clear that as well as the need to optimise screening programmes for those at a high risk of developing cancer, there is a need for psychological studies into the health beliefs of those screened in order to maximise the efficacy of screening and reduce any associated psychological morbidity [Calnan, 1984; Vernon et al., 1990].

In conclusion, family history offers an opportunity to identify those placed at high risk of colorectal, breast or ovarian cancer and to determine screening requirements. Furthermore, controlled studies of screening in high risk individuals may be more effective than population studies in determining the efficacy of screening programmes for the early detection of cancer.

SECTION 5: APPENDICES

APPENDIX A. Diseases and their corresponding ICD numbers [International Classification of Diseases 1978].

Disease	Corresponding ICD number	
All causes	-	
All cancers	-	
Breast cancer	174	
Colorectal cancer	153	large intestine except rectum
	154	rectal cancer
Lung cancer	162	trachea, bronchus, lung, pleura, mediastinum and unspecified respiratory site
Ovarian cancer	183	ovary, fallopian tube and broad ligament
Prostatic cancer	185	
Stomach cancer	151	
Uterine cancer	189	uterus unspecified

APPENDIX B. Transformations for running the computer program POINTER [Morton et al. 1983b].

Where:

AF = affection status
ID = family identification
FM = format
LI = liability indicator
PI = ascertainment probabilities
PO = position of an individual within family
PT = specifies degree of relationship to pointer
PT = order of data entry
PR = proband field
TR = transformation

COLORECTAL CANCER PEDIGREES

PT (ID=1, PO=2, AF =3, PR=4, Li=6,) (*)
FM (24) (F5.0, 1X, F1.0, F 1.0, F 1.0, F2.0, 2X, A2)
PI (0.001, 1.00)
LI (0.000163, 0.00121, 0.0063, 0.0414, 0.00017, 0.001169, 0.0054, 0.0054, 0.0302)
TR (27) (6) (6) (1,2,3,4) (20-35, 35-50, 50-65, 65-100)
TR (8) (6) (6, 5) (10)
TR (27) (6) (6) (1,2, 3, 4, 5, 6, 7, 8) (11,12,13,14, 21, 21, 23, 24)

BREAST CANCER PEDIGREES

PT (ID = 1, PO = 2, AF = 3, PR = 4, LI = 6, PT = 7) (*)
FM (24) (F 5.0, 1 X, 3 F 1.0, 1 X, F 2.0, A 1, 6 X, A 2)
PI (0.001, 1.0)
LI (0.00005, 0.0002, 0.00012, 0.00228, 0.00986, 0.01903, 0.02792, 0.03356, 0.04759)
TR (27) (4) (4) (0,1,2) (0,1,2)
TR (27) (3) (3) (0,1,0,9) (0,1,8,9)
TR (27) (6) (6) (2, 3, 4, 5, 6, 7,8, 9, 1) (A, 2, 3, 4 , 5, 6, 7, 8, 9)
TR (25) (5) (5) () (0 - 20)

OVARIAN CANCER PEDIGREES

PT (ID =1, PO = 2, AF = 3, PR = 4, LI = 5, PT = 6) (*)
FM (74) (F 5.0, 2X, F 1.0, 3X, F 1.0, 3X, F 1.0, 4 X, F 1.0, 2 X, A2)
PI (0.001, 1.0)
LI (0.0000001, 0.000086, 0.000156, 0.000251, 0.000421, 0.001355, 0.002817, 0.00386, 0.00619)

* J or C inserted for analysis under joint or conditional likelihood respectively.

SECTION 6: REFERENCES

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SECTION 7: PUBLICATIONS RESULTING FROM WORK CARRIED OUT IN PREPARATION OF THIS THESIS

1. Houlston, R.S., Murday, V., Harocopos, C., Williams, C.B. and Slack, J. (1990) Screening and genetic counselling for relatives of patients with colorectal cancer in a family cancer clinic. British Medical Journal **301**: 366-368.

2. Itoh, H., Houlston, R.,S., Harocopos, C.J. and Slack, J. (1990) Risk of cancer death in first degree relatives of patients with hereditary non-polyposis cancer syndrome (Lynch type II): a study of 130 kindreds in the United Kingdom. British Journal of Surgery **77**: 1367-1370.

3. Houlston, R.,S. and Lemoine, L. (1991) Medical and psychological perspectives on breast screening: a comment on Pitt's, McMaster and Wilson. Journal of Community and Applied Social Psychology **1**: 43-44.

4. Houlston, R.,S., Collins, A., Slack, J., Campbell, S., Collins, W.P., Whitehead, M.,I. and Morton, N.E. (1991) Genetic epidemiology of ovarian cancer: segregation analysis. Annals of Human Genetics **55**: 291-299.

5. Buckley, C., Thomas, V., Crow, J., Houlston, R.S., Slack, J. and Rustin, M.H.A. (1992) Cancer family syndrome associated with multiple malignant melanomas and a malignant fibrous histiocytoma. British Journal of Dermatology **126**: 83-85.

6. Houlston, R.S., McCarter, E., Parbhoo, S., Scurr, J. and Slack, J. (1992) Family history and risk of breast cancer. Journal of Medical Genetics **29**: 154-157.

7. Houlston, R.S., Collins, A., Slack, J. and Morton, N.E. (1992) Dominant genes for colorectal cancer are not rare. Annals of Human Genetics **56**: 99-103.

8. Houlston, R.S., Fallon, T., Harocopos, C., Williams, C.B., Davey, C. and Slack, J. (1992) Congenital hypertrophy of retinal pigment epithelium in patients with colonic polyps associated with cancer family syndrome. Clinical Genetics **42**: 16-18.

9. Houlston, R.S., Lemoine, L., McCarter, E., Harrington, S., MacDermot, K., Hinton, J., Berger, L. and Slack, J. (1992) Screening and genetic counselling for relatives of patients with breast cancer in a family cancer clinic. Journal of Medical Genetics **29**: 691-694.

10. Houlston, R.S., Bourne, T.H., Davies, A., Whitehead, M.I., Campbell, S., Collins, W.P. and Slack, J. The use of family history to identify relatives at high risk of ovarian and other cancers. Gynaecological Oncology : In press.

11. Houlston, R.S., Bourne, T.H., Davies, A., Whitehead, M.I., Campbell, S., Collins, W.P. and Slack, J. Risk of ovarian cancer and relationship to other cancers in families. Human Heredity :In press.

12. Houlston, R.S., Hampson, J., Collins, W.P., Whitehead, M.I., Campbell, S. and Slack, J. Correlation between age at death from ovarian cancer in sisters. Gynaecological Oncology :In press

13. Eccles, D.M. and Houlston, R.S. Letter: Ovarian cancer and prophylactic choices. Journal of Medical Genetics :In press.