Breast Cancer
in the young, the pregnant and those with family history
# Table of Contents

- **Introduction**

- **01:: Breast Lumps in Pregnancy**

- **02:: Communication within the Context of Multidisciplinary Care**

- **03:: Identification of high-risk groups**

- **04:: Mammography Screening for Women under Age 50**

- **05:: Relationships with doctors and nurses**

- **06:: Pregnancy-Related Breast Cancer case study: First Trimester Pregnancy**
GET AN INTRODUCTION TO BREAST CANCER WITH THESE KEY TITLES

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Introduction

This book is relevant to a multidisciplinary audience, for anyone working with breast cancer in pre-menopausal women. The could include breast specialists in oncology and healthcare professionals involved with pregnancy.

_Chapter 1_ looks at the differences in breast lumps in women during pregnancy. During pregnancy, changes become apparent in the breast; how does one identify a breast cancer threat opposed to a normal change?

Patients with a cancer diagnosis are at the centre of many different communications, both directly from the medical professionals and also from outside sources such as patient support groups. _Chapter 2_ advises how to explain the management at this sensitive time and to understand the importance of the input from colleagues.

Women with family history are often more likely to have a breast cancer diagnosis. _Chapter 3_ explains how to identify patients who are most at risk based on their family history.

Mammography screening in women under the age of 50 is a topic that has been the subject of much debate. _Chapter 4_ explores this ongoing controversy of screening in younger women.

Although written for the patient, _Chapter 5_ gives an effective insight into the emotional difficulties of breast cancer, and will help oncology specialists to empathise with their patients.

_Chapter 6_ is a case study of a 34-year-old woman in the first trimester of pregnancy presented with a lump that has existed for two years.

**Note to readers:** References from the original chapters have not been included in this text. For a fully-referenced version of each chapter, including footnotes, bibliographies, references and endnotes, please see the published title. Links to purchase each specific title can be found on the first page of each chapter. As you read through this FreeBook you will notice that some excerpts reference previous chapters – please note that these are references to the original text and not the Freebook.

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CHAPTER 1

Breast Lumps in Pregnancy
Chapter 1: Breast Lumps in Pregnancy

Nowadays women are asked to be 'breast aware' so that they present early with breast cancer, that is to say, as soon as they perceive any change in their breast. (Box 1)

<table>
<thead>
<tr>
<th>Box 1: Differential diagnosis of breast lumps in pregnancy</th>
<th>■ Incidental</th>
<th>■ Conditions related to pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>■ Physiological</td>
<td>■ Lipoma</td>
<td>■ Lactating nodule</td>
</tr>
<tr>
<td>■ Prominent breast lobule</td>
<td>■ Sebaceous cyst</td>
<td>■ Galactocele</td>
</tr>
<tr>
<td>■ Montgomery's tubercle</td>
<td>■ Neurofibroma</td>
<td>■ Abscess</td>
</tr>
<tr>
<td>■ Accessory breast tail</td>
<td>■ Haemangioma</td>
<td>■ Malignancy</td>
</tr>
<tr>
<td></td>
<td>■ Lymph nodes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>■ Fibroadenoma</td>
<td>■ Carcinoma</td>
</tr>
<tr>
<td></td>
<td>■ Cyst</td>
<td></td>
</tr>
</tbody>
</table>

During pregnancy, changes to the breast can be marked, and some women may seek advice for what to the examining physician are considered normal physiological developments. These changes include:

■ breast lobules becoming more prominent;

■ enlarged Montgomery's tubercle;

■ thickening of an area of the breast;

■ accessory breast tissue in the axilla, a common anatomical anomaly, which will enlarge naturally during pregnancy; it may cause a little discomfort and be perceived as a serious problem.

Pregnant women may become more conscious of their breasts and present with lesions that have been there for a long time, including lipomas, sebaceous cysts, neurofibromas, or haemangiomas. Lymph nodes adjacent to the axillary tail of the breast can fluctuate in size, and it must not be forgotten that one is occasionally situated within that part of the breast, the intramammary node. Many of these concerns can be allayed by experienced midwives.

■ Lactating nodule

This is also known as adenosis of pregnancy, and the difference between this and the very common fibrocystic disease of the breast, which is unrelated to pregnancy, is blurred. The breast undergoes huge proliferation in pregnancy, and many women may note one particular area to be more thickened than the rest, an asymmetrical swelling,
or an actual well-defined lump, such that imaging and biopsy may be contemplated. In this last case, the ultrasonographer may recognise it as a solid lump, but of similar echogenicity to the surrounding breast tissue, and the pathologist will describe it as normal breast tissue of pregnancy. Hopefully, as with other benign breast lumps seen in pregnancy, resort to excision biopsy can be avoided.

■■Fibrocystic disease

Although fibrocystic disease of the breast does not occur because of pregnancy, the condition is included for completeness. It has been labelled ‘benign breast change syndrome’, the symptoms of which include cyclical pain and thickening of the breast, typically in the upper outer quadrant. It should be emphasised that this is a very common problem and that the diagnosis begins with ‘benign’ and no ‘disease’ is mentioned. The pathologists looking at pieces of such breasts histologically might call it ‘fibrocystic disease’ because of its cyclical proliferative features and the sclerotic features that are perceived to be the basis of the mild inflammation. However, this term is very similar to fibroadenoma, which is also common but a quite different condition; hence, it is falling out of use.

■■Fibroadenoma

Fibroadenomas are common benign breast lumps seen in teenagers and women in their twenties, and there is a rise in incidence in women in their forties. Typically they appear mobile within the breast, are of a rubbery consistency on palpation, have a slightly irregular or bosselated surface, and frequently are multiple. Excision is unnecessary as long as imaging and biopsy support the benign diagnosis. The natural history of these lumps is that they enlarge over a period of months and then remain unchanged, even for years, but eventually shrink and possibly appear as a calcified spot on mammograms in later life. In pregnancy they may appear as a new diagnosis, enlarge to cause concern, or infarct. This last condition may demand a surgical excision, which is susceptible to wound complication.

■■Cyst and galactoceole

A simple breast cyst can be large compared to the multiple tiny cysts of fibrocystic disease. It may present as a lump of sudden onset. They are often found to be multiple when the breast is scanned and are most common in women in their thirties and forties, being an age group of pregnancy more common these days than for our ancestors. We assume that the explanation for not seeing this in pregnancy nearly as frequently as in the non-pregnant population is that the simple cyst is essentially a degenerative change in the breast, in direct contrast to what is happening as a consequence of pregnancy. Galactoceoles are more common in pregnancy and present as the same spherical shape with a smooth surface as does the simple cyst. The
diagnosis, for both, is confirmed by needle puncture and aspiration.

- Abscess

Abscesses are more common in the lactating woman than the pregnant one. Usually they do not present a diagnostic problem, owing to their general systemic upset, localised pain, tenderness and redness of the overlying skin, and, usually, the sign of fluctuance. The main difficulty is in determining whether it is an abscess, or (the not much less painful) mastitis. Yet even if an abscess is mistaken for mastitis and nothing is done other than to prescribe antibiotics, the abscess may become partially treated in any case and become better defined, so that one is left with a clear decision to aspirate or drain it in an operation.

- Carcinoma (Fig. 1)

This is a disastrous diagnosis for any young woman, but in pregnancy it is doubly difficult. If the appropriate scan is requested or biopsy made in good time, the prognosis is no worse than that for a similar lesion occurring in a woman of similar age who is not pregnant. The problem is that the irregular hard lump might be seen as being something to do with the pregnancy, or mastitis, and the diagnosis could be missed. It should therefore be considered mandatory to take a careful account as to what has happened to the breast and then to examine both breasts and both axillae thoroughly. In this way, failure or delay in diagnosis may be avoided. Referral to a breast specialist should be triggered by the following findings:

- slight asymmetry of the breasts;
- a subtle dimpling of the skin;
- apparent inflammation but without the commensurate tenderness;
- nipple retraction;
- an ill-defined lump.

Useful website

www.breastcancercare.org.uk
CHAPTER 2

Communication within the Context of Multidisciplinary Care
Chapter 2: Communication within the Context of Multidisciplinary Care

Modern cancer care requires the integration of many different professional groups, oncologists (medical, radiation and surgical), haematologists, gynaecologists, urologists, etc. etc. Nurses play a pivotal role and, where they are available, psychosocial oncologists can be of great value to all concerned. The patient is the central focus of all this communication, but, with access to the web and patient support groups, many patients find themselves confused by too much information, and sometimes have too little time to absorb and digest it before having to make key decisions about their management. In this chapter I offer some advice about the importance of awareness. As the oncologist, you have the primary role in designing and explaining management plans, but it is very important that you are fully aware of the input from colleagues in other medical disciplines and from your nursing colleagues, and of the information and advice that patients have gathered for themselves – from the web, patient support groups, etc. I want to illustrate specific inputs from nurses, psychosocial oncologists and patient advocacy/support groups.

**Oncology nurses**

It is impossible to overstate the importance of good communication with your nursing colleagues. The development of oncology as a specialisation within nursing has revolutionised the experience of so many patients, and it is important that during your training in oncology you learn to understand and appreciate the role that oncology nurses play. In my experience, patients relate to nurses in a different way than to their doctors. However friendly, open and compassionate the doctor appears, many patients need to keep a respectful distance from the doctor, who they see as having the primary role in the decision processes regarding their management. On the other hand, nurses are often perceived to be more accessible for sharing concerns and uncertainties about what is happening to a patient at any given time – this is most particularly seen in the outpatient setting. Whilst patients are in hospital, good doctors will make the time to talk and listen to their patients, but it is inevitable that, in the clinic, time is always a pressure. Of course this also applies to nurses, but where there is good communication between you and your nursing colleagues, the additional input from nurses can add inestimable value for both you and the patient. I have been most fortunate in having excellent clinical nurse specialists ( CNSs) attached to each of the disease-specific clinics in which I have worked. To follow the CNSs’ own assessment of new patients, and to share the information gathered about specific aspects of their disease, symptoms, anxieties, aspirations, and family and work pressures, can greatly enhance your decisions about management. Patients often confide such anxieties much more freely to a nurse than to a doctor. In my experience, patients will often ask the nurse rather than the doctor what to actually expect during treatment, and this gives the
nurse the opportunity to re-explain and amplify information that you may have given during your consultation. In my practice the CNS would give each new patient a card with their contact details, and encourage patients to use this whenever they wanted to resolve specific queries at the time that they were troubled. Few patients abused this availability, but many patients have reported to me that having this contact information in their purse or wallet was hugely reassuring.

Another area where good communication between doctor and nurse can benefit everyone concerned relates to clinical trials. Apart from the obvious need to conduct clinical research, it is well established that patients benefit from enrolment in trials. Nevertheless, many patients are initially nervous, and the amount of detail in consent forms can be overwhelming. Nurses can play a vital role in encouraging enrolment to trials by helping patients to understand what is involved, and reassuring them of the extra attention that inevitably results from trial participation. Similarly, nurses will often help to retain patients on trials, when doubts about the value of continuing cause anxieties that the patient may not wish to expose to their doctor. Nurses can also play an important role in monitoring adherence to medicines. In the days when nearly all oncology treatments were administered intravenously, adherence was not an issue. However, with the increasing use of pills, often to be taken for very long periods of time, we are becoming aware that some patients may either become forgetful or make a definite decision to stop taking their medicines. It is a patient’s right to do as they please, but it is essential that the doctor knows what is happening. In my experience, patients are more likely to tell the truth to a nurse than risk the wrath of the doctor, if they admit to having ceased taking their medication! These are but a few examples of the need for you as the oncologist to work closely with your nurses, so that, with their help and input, you are as fully informed as possible of the patient’s attitude to their illness at the different phases thereof.

**Psychosocial oncologists**

The development of the speciality of psychosocial oncology (PSO) has brought a new dimension to the holistic care of patients with cancer. As a discipline, PSO has developed with input from psychiatry, psychology and nursing. Unfortunately not every oncologist has access to psychosocial oncologists, but it is to be hoped that this will change in the years to come. For those of us who are fortunate to have such colleagues, it is essential that good communication is in place to optimise this very valuable resource. Where it is available as part of the team in which you work, then there is no excuse for poor communication, but you may have to refer outside of your institution or, in some circumstances, patients may be able to self-refer. In these situations you must make every effort to ensure good communication between both sets of professionals and the patient. As with my comments on the nurse’s role above, since this is not a
textbook or manual on the totality of cancer management, I will focus on three aspects where I believe good communication between you, the oncologist, and colleagues in psychosocial oncology is particularly relevant.

**Patients**

Not all patients need to be referred to clinical psychologists, and where you have access to a psychosocial oncologist it is important in your training years that you learn which categories of patient are most likely to benefit, or who to discuss with your PSO colleagues when you are considering a referral. A common theme throughout this entire book is your role in helping to reduce anxiety and give confidence to patients who have such a life-changing diagnosis as cancer, with all that that implies. There is considerable demand for psychological medicine in the day-to-day practice of oncology, but you must learn to detect and refer those patients for whom specific PSO support is required. Such patients are those who appear to have exceptional levels of anxiety or depression that are not being adequately managed by yourself or the patient’s family physician. Clinically significant levels of anxiety and depression are not inevitable sequela of cancer, but as oncologists we must learn to recognise patients suitable for referral to specialists in the talking therapies, for which there is now a strong evidence base. By gaining their own specialist understanding of cancer, the psychosocial oncologist can help patients to understand the reasons for their severe anxiety and depression, and address contributing issues such as the guilt that can be associated with carcinogenic lifestyle factors – for example, cigarette smoking, excess alcohol consumption, sexual practices, obesity, etc. Exploring such issues may then help patients with their relationships with partners, children, family, friends, work colleagues, and so on. For those patients who need such support, the development of coping styles will usually be of great benefit in helping them to tolerate anti-cancer treatment and the episodes of recurrent anxiety that occur during follow-up in remission. Good communication between the psychosocial oncologist and you will therefore give you very useful information about the optimal way to manage the oncological component of your patient’s care.

**Medical and nursing teams**

Psychosocial oncologists can make a major contribution in helping the medical and nursing teams to look after cancer patients. I refer briefly in the Epilogue to the demands made on oncologists over a lifetime of working with cancer patients. This is very challenging medicine, and there are times when all of us feel emotionally drained by the narrow margin between success and failure in cancer care. In my own centre, we found enormous help from our psychologists in supporting the medical and nursing staff – either collectively or individually. Communicating over a specific patient’s problem often exposes issues for doctor or nurse – either about that specific patient or
more generally. The opportunity to discuss this and seek help from our psychosocial oncologists in understanding patients and our own attitudes to them or their circumstances has often had a profound effect in helping staff with their own coping styles. As individuals, seeking the help of a psychosocial oncologist at a time of difficulty should never be seen as a personal weakness, but rather as evidence of professional maturity. Working as a team, there are times when there is a collective sense of undue stress leading to low morale – maybe a run of very challenging patients, a particularly sad death, or the loss of a key member of staff for any reason. At these times, input from a psychosocial oncologist who knows the team as a whole can be very beneficial.

**Research**

There is an ever-increasing interest in research into psychosocial oncology and it is important for oncologists to be aware of the way that they can contribute to this. A classic example is the difficult area of Quality of Life (QoL) studies. A variety of instruments have been developed to assess QoL, but the uptake of them is still very variable. Where these studies relate to the assessment of new drugs, for example, they can, when used well, make a significant contribution to the controversial area of assigning a value to “effectiveness”. Used badly, they only create noise in the system. Whilst oncologists usually agree on criteria that describe the side effects or risks of novel treatments, there is much more controversy about the “benefit”. The traditional measures of overall survival or progression-free survival are less useful than they used to be, now that so many drugs are being developed for chronic administration over several years. In these situations, the quality of a patient’s survival may be at least as important as life expectancy – or even more so. Psychosocial oncologists have a pivotal role in designing the measures required to assess this, and we as oncologists must be aware of our role in referring patients for such studies, and understanding what is involved.

**Patient support groups and the internet**

The creation of patient support groups (PSGs) offers invaluable support in many ways. The ability to share anxieties and uncertainties, to learn from the experience of others, and to have people to whom to turn for advice and comfort who are not immediate family or dependents are very powerful aids – especially to newly diagnosed patients. Some PSGs operate on a national or even international basis, providing literature and information for individuals, and lobbying on their behalf for funding, research, greater awareness, etc. Other PSGs operate on a local level to provide direct support to patients. PSGs are usually aware of the positive aspects of participating in clinical trials, and may be helpful to both patients and researchers in encouraging enrolment into trials. As an oncologist, it is important to be aware of which PSGs are appropriate and
available to your patients and, most importantly, to discuss with patients their use of such facilities. This is in no way intrusive on your part, but reflects your concern to encompass every aspect of holistic care. Most aspects of interaction between your patients and PSGs will be positive, but there are a few potential pitfalls of which you should be aware. As an oncologist, you recognise the subtle but important differences between subsets of patients with apparently the same diagnosis. Increasingly we are stratifying these subsets because they have different prognoses and therefore need different approaches to management. I have had numerous experiences of patients being confused and often upset by advice offered from fellow patients which was intended to be helpful, but did not in fact refer to their specific problem.

Obtaining misinformation is a real risk with the increasing use of the internet by patients seeking to obtain as much information as they can, especially early on but also at critical times, such as at relapse. Some websites are excellent and very helpful – especially those run by or informed by knowledgeable PSGs. Unfortunately there are other sites that are out of date, promotional in one way or another, or too superficial to be of real value.

In this book I often refer to the obvious challenge of time. The patient needs as much as possible – in consultation with you and the other professionals and whilst researching on their own before having to make key decisions. Unfortunately time is always against us for the key face-to-face encounters. In recent years I have been increasingly frustrated by the need to use precious time during consultations in unpicking information that the patient has obtained for themselves, which is inappropriate to their specific circumstance. The patient enters your consulting room brandishing pages they have downloaded from a website that they have confidence in. There is a positive message about new research, new drugs or diagnostic processes, or a revised prognosis, perhaps. You have to peruse this literature as rapidly as possible and you realise that it is either irrelevant to the specific situation of the patient in front of you, or wrong, or refers to a research study suggesting benefit, but the intervention – typically a new “breakthrough” drug – is not yet available. It takes skill and experience to handle the ensuing conversation so that you do not instantly depress your patient, completely destroy their self-confidence, or dismiss their completely understandable desire to obtain as much understanding as possible of their condition. The worst aspect of such encounters is that you are using up invaluable time for communicating the information that is relevant to this particular patient.

The use of self-acquired knowledge is likely to increase in the future and, hopefully, so will the quality and accuracy of the information available. The positive aspects of this are to be welcomed and, as oncologists, we should do whatever we can to assist in developing good web-based sources of information and to help reduce the negative
ones. In the same way, we should interact with PSGs to optimise the overall exposure of patients to an ever-increasing if sometimes confusing knowledge base. It is all about good communication.
CHAPTER 3

Identification of high-risk groups
Chapter 3: Identification of high-risk groups

Family history identifies a minority of patients at increased lifetime risk of breast cancer due to a mixture of shared environmental and genetic factors. Definitions vary, but the average lifetime risk of 8% in the United Kingdom is increased to 12%–25% if the family has just one or two first-degree relatives diagnosed with breast cancer before the age of 50 years, or two first-degree or second-degree relatives on the same side of the family with breast or ovarian cancer (these scenarios apply to 4% of the female population in the United Kingdom). Women with three or more first-degree or second-degree relatives with breast or ovarian cancer on the same side of the family, a history of bilateral tumours, male breast cancer or sarcoma or women aged more than 40 years at diagnosis have a 25%–50% lifetime risk of breast cancer (applies to 1% of the female population). Women who inherit proven BRCA1 or BRCA2 mutations have a 60%–80% lifetime risk of breast cancer and a significant risk of ovarian cancer.6,7 Nevertheless, this leaves 95% of the female population with a lifetime risk of less than 12%, including women with one first-degree or second-degree relative diagnosed with breast cancer at age 50 years or older, and women with one second-degree relative diagnosed with breast cancer at any age.

Women at intermediate or high risk according to the aforementioned factors are offered referral to a specialist risk service, comprising clinical genetics and breast oncology input, and counsellors with close links to a dedicated molecular genetics laboratory. There is currently little evidence on which to base reliable guidelines. Women at moderately increased risk (15%–25%) are advised to examine their breasts once a month and asked to attend annual clinical breast examination and annual mammography between the ages of 35 and 50 years. The frequency of screening is commonly reduced above this age but continues until the age of 69 years. Women considered or proved to have BRCA1 mutations are referred for annual pelvic ultrasound, in view of their elevated risk of ovarian cancer. Women at high risk (>25%) of breast cancer may wish to consider further measures, including bilateral prophylactic mastectomies and reconstruction (and oophorectomy in the case of BRCA1 mutation carriers). These interventions are taken only after careful consideration, including psychological counselling. Inclusion in ongoing chemical prevention trials may also be considered.
Mammography Screening for Women under Age 50
Chapter 4: Mammography Screening for Women under Age 50

Introduction

During the last 25 years, mammography screening for women under age 50 has been one of the most intensely debated topics in medicine. American and European perspectives on this issue have differed considerably for many years. Historically, after reviewing the same evidence, many experts and medical organizations have often arrived at opposite conclusions concerning its merits. For example, in February 1993, the American Cancer Society (ACS) and the European Society of Mastology (EUSOMA) met in New York and Paris respectively to review the results of mammography screening trials. After reviewing the same data, the two organizations arrived at opposite conclusions: the ACS reaffirmed its long-standing recommendations of screening women starting at age 40, while EUSOMA recommended that screening be reserved for women above age 50.

In light of more data, the US Preventive Services Task Force (USPSTF) updated its recommendations on screening mammography in 2009. In a review undertaken several years prior, the USPSTF had concluded that there was fair evidence that mammography screening every one to two years could significantly reduce breast cancer mortality for women aged 40 and older. However, in the 2009 updated guidelines, they recommend against routine mammography in women aged 40–49 years, and recommended biennial screening mammography for women aged 50–74 years. The USPSTF argued that the net benefit of screening women between age 40 and 49 years when compared with older women is much smaller, the risk of false positives is greater, and the number needed to screen to prolong one woman’s life, is much higher (1339 vs. 1904). The USPSTF guidelines have generated considerable controversy, and have been criticized by several scientific organizations. The ACS questioned the quality of evidence used in making these recommendations. It also argued that the USPSTF ignored the important concerns of incidence-based mortality and premature mortality. Although the number needed to screen in younger women may be higher, the years of potential life lost (YPLL) saved is high. It criticized that using the number needed to screen is not an appropriate justification to recommend against screening younger women. The ACS continues to recommend annual mammography starting at age 40 years. Other organizations, such as the American College of Radiologists and the American Society of Breast Surgeons, have also refuted these guidelines. Some argue that even if screening does not save a woman’s life, it may offer her the option of breast conservation and reduce the need for chemotherapy and so on. In this chapter, we discuss the ongoing controversy concerning screening in younger women and present our views on this issue.
Biases of clinical studies

More is known about screening for breast cancer than screening for any other type of cancer. Over the past four decades, various studies have been undertaken to determine the efficacy of mammography screening: case-control studies, retrospective analyses, and prospective studies. There are three biases pertinent to many of these studies: lead-time, length, and selection. An understanding of these biases is necessary before discussing the merits of mammography screening. Ultimately, the success of mammography screening should be measured by its ability to reduce mortality, rather than its ability to improve survival.

Survival refers to the period of time from cancer diagnosis to death. Lead-time bias refers to the interval between diagnosis of cancer by screening and usual clinical detection. Leadtime bias may make it appear that screening prolongs survival, when, in fact, it simply extends the period of time over which the disease is observed. As screening advances the time of breast cancer diagnosis, patients with screen-detected cancers will inevitably have better survival rates than those with clinically detected cancers, even if screening does nothing to delay the time of death. Thus, retrospective studies comparing survival between screened and unscreened populations fail to account for lead-time bias, and are flawed.

Length bias relates to the fact that screening tends to detect tumors with a better prognosis. More slowly growing tumors (those with a better prognosis) exist for a longer period in the preclinical phase and are therefore more likely to be diagnosed by mammography screening. In contrast, more rapidly growing tumors exist for a shorter period of time in the preclinical phase, and are more likely to be detected in the intervals between screening sessions. Thus, length bias invalidates comparisons of tumors detected by screening mammography with those detected by physical examination. The impact of length bias is best seen when cancers detected by screening are compared with interval cancers (cancers detected between screening sessions). Interval cancers generally carry a poorer prognosis than screen-detected cancers.

Selection bias refers to the fact that women who volunteer for screening are more likely to be health conscious, and have a lower mortality from all causes. In general, women who volunteer for screening are more likely to eat nutritional foods, exercise regularly, and maintain a healthy lifestyle. This is sometimes also referred to as the “healthy-screenee effect.” The impact of selection bias was illustrated in a case-control evaluation of the effect of breast cancer screening in the United Kingdom (UK), comparing attendees and non-attendees for screening. By comparing populations from two separate districts (one a breast cancer screening district and the other a comparison district), breast cancer mortality was found to be relatively higher among
non-attendees in the screening district. This finding was attributed to selection bias.

**Randomized prospective studies**

All of these biases can be excluded by comparing screened and unscreened populations in a randomized study with all-cause mortality as the endpoint and cause-specific mortality as a questionable surrogate endpoint. There have been nine randomized prospective trials designed to evaluate the efficacy of mammography screening, and of these eight have evaluated its impact on mortality reduction in women younger than 50: the Health Insurance Plan (HIP); the Swedish Two-County Trial; the Malmo, Stockholm, Gothenburg, and Edinburgh studies; the first Canadian National Breast Screening Study (CNBSS-I); and the UK Age trial (Table 9.1). Only CNBSS-I and the UK Age trial were specifically designed to evaluate mammography screening in women under age 50, while other trials evaluated the impact of screening in women of a broad age range.

The HIP was the first randomized controlled trial of mammography screening for breast cancer, initiated in 1963. The study involved 62,000 women in the age range of 40–64 years from the HIP medical insurance scheme of New York, who were randomly assigned to either a study or a control group of 31,000 women each. However, the HIP was not designed specifically to assess the potential benefits of screening younger women. Among women aged 40–49 at the start of the study, after a median follow-up of 14 years, there was a non-significant reduction in breast cancer mortality in the screened group, the relative risk being 0.78 [95% confidence interval (CI) 0.56–1.08]. It is also important to note that in the HIP study screening was carried out with clinical breast examinations (CBEs) as well as mammography. Ultimately, only 19% of breast cancers in women of all ages were detected exclusively by mammography, and most of them (57%) were detected by CBE alone. Thus the HIP does not necessarily justify mammography screening for any age group. If anything, it suggests that CBE may have an important role to play as a screening modality.

There have been four screening mammography trials undertaken in Sweden: the Stockholm, Gothenburg, and Malmo studies and the Two-County trial. For women aged 40–49 at entry, these trials have had median follow-ups of 14.3, 12.7, 13.3, and 13 years, respectively. For each of these trials, the relative risk of breast cancer death in the screened group in comparison with the control group was 1.52 (95% CI 0.8–2.88), 0.58 (95% CI 0.35–0.96), 0.73 (95% CI 0.51–1.04), and 0.87 (95% CI 0.54–1.41) respectively. Each of these trials examined the efficacy of mammography screening alone. CBE was not utilized as a screening modality in any of these trials. The Edinburgh trial was a randomized clinical trial involving 45,130 women between the age of 45 and 64 years, initiated in 1979. Women in the study group received screening mammography and CBE, while the control group received usual care. Of these only 5913 women were at
age below 50 years. After a median follow-up of 13 years, the relative risk of breast cancer death among women below age 50 in the screened group was 0.75 (95% CI 0.48–1.18).

CNBSS-I was the first trial specifically designed to assess the efficacy of screening for women between the age of 40 and 49 years. The total number of women enrolled in CNBSS-I was 50,430. It was designed with sufficient statistical power to detect at least a 40% reduction in mortality by screening. The screened group received mammography and CBE on an annual basis for four or five examinations, while the control group received an initial CBE upon entry and thereafter a follow-up by mail. After seven years, there was a non-significant excess in mortality in the screened group, the relative risk in the screened group being 1.36 (95% CI 0.84–2.21). However, after a median follow-up of 13 years, the relative risk of breast cancer deaths in the screened group was 0.97 (95% CI 0.74–1.27).

The CNBSS-I received far greater scrutiny than any of the other mammography screening trials, and it has withstood this scrutiny. Its critics charged that in the first 2 years of the study, over 50% of the mammograms were technically inadequate, and that neither the equipment nor the training of the radiologists was properly standardized. However, it should seem apparent that in a large study such as this, total standardization would be impractical and that CNBSS-I represented the true technology and skills of the radiologists of the communities at the time the study was undertaken. It is interesting to note that no such criticisms were leveled against the HIP study, which used techniques and standards now considered obsolete. CNBSS-I was also criticized on the grounds that there was contamination of the control group: about 26% of the unscreened population had ‘diagnostic’ mammograms to evaluate palpable breast masses. The critics argue that mammography is not particularly useful as a “diagnostic” procedure so that in a symptomatic woman, the benefit comes from screening the ipsilateral and contralateral breast for clinically occult cancer. Thus some believe that CNBSS-I in fact compared screened women with other screened women, and that this might account for the lack of mortality reduction in the study group. However, it seems unlikely that such mammograms will change significantly the outcome of such a large study. Given the standard practice of medicine in the world today, it would be impossible to run a trial in which women presenting with palpable breast masses were denied mammography, and had to proceed directly with an excisional biopsy. Finally, there have been charges that CNBSS-I may have failed to demonstrate lower rates of breast cancer deaths among women assigned to the mammography arm because the randomization of enrolled women was compromised. These concerns were raised because the mammography group in CNBSS-I contained considerably more women with four or more positive axillary nodes than the control group. Independent reviewers were therefore asked to review the randomization
strategy in CNBSS-I, and no subversion of the randomization process was ever found. The majority of the trials mentioned above were not designed to study the effect of screening in younger women. One of the reasons for the delayed benefit of screening women below age 50 might actually be attributed to screening these women after age 50.

<table>
<thead>
<tr>
<th>Screening Trial</th>
<th>Age at Entry (yrs)</th>
<th>Screening Modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Insurance Plan</td>
<td>40–64</td>
<td>MM + CBE</td>
</tr>
<tr>
<td>Swedish Two-County</td>
<td>40–74</td>
<td>MM</td>
</tr>
<tr>
<td>Malmo</td>
<td>45–69</td>
<td>MM</td>
</tr>
<tr>
<td>Stockholm</td>
<td>40–64</td>
<td>MM</td>
</tr>
<tr>
<td>Gothenburg</td>
<td>40–59</td>
<td>MM</td>
</tr>
<tr>
<td>Edinburgh</td>
<td>45–64</td>
<td>MM + CBE</td>
</tr>
<tr>
<td>Canadian (CNBSS-I)</td>
<td>40–49</td>
<td>MM + CBE</td>
</tr>
<tr>
<td>UK Age trial</td>
<td>39–41</td>
<td>MM</td>
</tr>
</tbody>
</table>

Abbreviations: CBE, clinical breast examination; CNBSS, Canadian National Breast Screening Study; MM, mammography.

With this background, the more recent age trial was initiated in UK. In this trial, 160,921 women aged 39–41 were randomized to an intervention group of annual mammography to age 48 or to a control group of usual medical care. Screening was by two-view mammography at the first screen and by a single mediolateral oblique view thereafter. At mean follow-up of 10.7 years, there was no statistically significant reduction in breast cancer mortality in women offered screening between the ages 40–48 years. The relative risk of all-cause mortality and breast cancer mortality in the intervention group was 0.97 (95% CI 0.89–1.04) and 0.83 (95% CI 0.66–1.04). The trial was designed to have an 80% power to detect a 20% mortality reduction at 10 years’ follow-up. However, the power diminished to 60% by the smaller sample size and lower than expected mortality and the non-significant mortality reduction may be a consequence of this low power. The trial has been criticized for using what is considered "non standard" single-view mammography instead of the standard two-view mammograms.

Meta-analyses

In addition to the results of the individual trials mentioned earlier, several meta-analyses of mammography screening trials have been published. Many of these indicate that, after a long-term follow-up, a statistically significant benefit to screening
women under age 50 does indeed emerge. For example, in their meta-analysis of eight trials, Hendrick et al. and Smart et al. have reported a significant decrease in breast cancer mortality in the screened group after 12.7 years of follow-up, the relative risk being 0.82 (95% CI 0.71–0.95). In a meta-analysis of the eight trials, after a median follow-up of about 12 years, Kerlikowske reported that the relative risk of breast cancer deaths in the screened group was 0.84 (95% CI 0.71–0.99). Humphrey et al. excluded the Edinburgh trial (which they considered of poor quality), and found, after 14 years of follow-up, that the relative risk of death for women under 50, in the screened group, was 0.85 (95% CI 0.73–0.99). However, Olsen and Gotzsche have argued that six of the mammography screening trials are flawed or of poor quality. In their meta-analysis, they included only the Canadian and Malmö trials, and found, after 13 years of follow-up, no benefit to screening women below age 50, the relative risk of breast cancer deaths in the screened group being 1.03 (95% CI 0.77–1.38).

The USPSTF updated its meta-analysis in 2009 to include the UK Age trial and concluded that mammography screening reduces breast cancer mortality by 15% for women aged 39–49 years [relative risk 0.85 (95% CI, 0.75–0.96); 8 trials]. This number is similar to women aged 50–59 years where the relative risk in favor of screening was 0.86 (CI 0.75–0.99). The number needed to invite for screening to prevent one breast cancer death for women younger than 50 years, was 1904 (CI 929–6378) over several screening rounds that varied by trial (2–9 rounds), and 11–20 years of follow-up. This number is 1339 for women aged 50–59 years and 377 for women aged 60–69 years.

Thus, with the exception of the results of Olsen and Gotzsche, the various meta-analyses generally suggest that, after a long-term follow-up, a benefit to mammography screening for younger women does eventually emerge. Overviews of the randomized trials suggest that mammography screening reduces breast cancer mortality by about 25% in women over age 50, and that the benefit emerges after seven to nine years of follow-up. In contrast, mammography screening in women below age 50 reduces breast cancer mortality by only 16–18%, and it takes 12–14 years for that benefit to emerge.

**Biological considerations**

Why should it take longer to see a benefit for women who are below age 50 at the start of mammography screening trials? This question remains open to speculation, but there are several possible explanations. One possibility is that screening may detect very slowly growing (indolent) tumors in younger women, so that a reduction in breast cancer mortality may take longer to emerge. However, Kerlikowske has argued that if this is indeed the case then detecting these slowly growing tumors after age 50 could perhaps produce the same reduction in risk of breast cancer deaths. Yet another possibility is that mammography screening in younger women is less effective. Thus
the delayed benefit of screening women below age 50 might actually be attributed to screening these women after 50 years of age. In their study deKonig et al. addressed this possibility with a computer simulation model known as MISCAN (microsimulation screening analysis). Their study suggested that most of the reduction in breast cancer mortality for women who were between the ages of 40 and 49 at the start of the screening trials was in fact the result of screening these women beyond the age of 50.

Another important question is why the efficacy of mammography screening should abruptly change at age 50. Indeed, some investigators have argued that there is no rational basis for such an abrupt change. Yet, age 50 corresponds approximately to the age at menopause, and the epidemiology and biology of breast cancer differ between pre- and postmenopausal women. There are, for example, changes in the incidence of breast cancer that occur in most populations around the time of the menopause: a steep rise in incidence occurs until about age 45–55 years, followed by a less rapid increase thereafter. Changes in tumor characteristics are also apparent, with tumors of younger women having a lower proportion of estrogen receptor (ER)-positive tumors and a higher labeling index. There are also differences in risk factors between pre- and postmenopausal women. In many studies, obesity is associated with a higher risk of postmenopausal breast cancer but a lower risk of premenopausal cancer. Thus the results of mammography screening trials are consistent with the results of other studies showing differences in the epidemiology and biology of pre- and postmenopausal breast cancer.

Finally, one might ask why mammography screening might be less effective in premenopausal women than in postmenopausal women. Again, there are several possible explanations. It is important to remember that the real benefit of screening is not early detection, but rather early treatment. As screening advances the time of breast cancer diagnosis, it allows for the early initiation of therapy. Thus the results from the screening trials may suggest that premenopausal women benefit less from early therapy than do postmenopausal women. Alternatively, the results of the screening trials may also be largely attributable to the fact that the sensitivity of mammography is lower in premenopausal women, making it a less effective screening test in younger women. However, breast cancer is much less common in women below age 50 than it is in women above that age, and Kopans has argued that there are insufficient numbers of women under the age of 50 in the world's screening trials to show an immediate mortality benefit to screening. Thus one might argue that the delayed benefit of mammography screening in younger women is attributable to the fact that breast cancer is much less common in this age group, and it takes longer to accrue sufficient numbers of deaths in the trials to see a statistically significant benefit to screening younger women. In fact, Kopans had estimated that a trial that could prove a 25% mortality reduction at 5 years for women between the age of 40 and 49 years.
would require about 500,000 women. It would be very difficult to undertake a screening trial involving such a large number of women. The UK Age trial included 160,921 women and a trial with significantly larger numbers is unlikely to be conducted. Proponents of screening for younger women have argued that technology has improved over the years, and that mammography equipment today is better able to detect earlier breast tumors. Thus the trials of the past would not be indicative of what can be achieved using more modern technology. This argument is not supported by the results of the Age trial that was conducted in contemporary settings. As technology is constantly improving, it would be impractical to conduct a new trial every time there is an improvement in mammography equipment.

**Hazards of screening**

If there is no clear evidence as to the point that mammography screening reduces breast cancer mortality in younger women then is it justifiable to continue to recommend screening for these women? It would seem not, because there are at least five harmful effects of mammography screening: cost, lead time, radiation exposure, false positives, and overdiagnosis (Table 2).

<table>
<thead>
<tr>
<th>Harmful Effect</th>
<th>Consequences</th>
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<tbody>
<tr>
<td>Cost</td>
<td>Increased expenditure on intervention of no proven value</td>
</tr>
<tr>
<td>Lead time</td>
<td>Advanced notice of impending death</td>
</tr>
<tr>
<td>Radiation exposure</td>
<td>Increased risk of breast cancer in women who carry the gene for ataxia telangiectasia (ATM)</td>
</tr>
<tr>
<td>False positives</td>
<td>Unnecessary breast biopsies</td>
</tr>
<tr>
<td>Overdiagnosis</td>
<td>Financial/emotional consequences of being falsely labeled as a cancer patient</td>
</tr>
</tbody>
</table>

**Cost**

In recent years, healthcare costs have increased dramatically, and governments around the world are attempting to reduce those costs. In the light of these constraints, attention has focused on the cost of mammography screening in younger women, particularly as the efficacy of screening in this age group is not clearly established. Kattlove et al. analyzed the expense and benefits of mammography screening in a hypothetical American healthcare organization in which 360 new cases of breast cancer are diagnosed each year. They concluded that the most cost-effective guideline for such a healthcare organization would be to restrict screening to women aged 50–69. Salzmann et al. have argued that screening mammography is relatively cost-ineffective among women aged 40–49 because mammography is less efficacious in women of this age group, and the incidence of breast cancer is lower than in older
age groups.

**Lead Time**

Mammography screening detects breast cancer earlier, but if this is not accompanied by a reduction in breast cancer mortality then the patient is given advanced notice of impending death, with no tangible gain. This has an adverse effect on the quality of life. This "lead time" is probably in the range of two to four years, meaning that many women will suffer needless worry and anxiety during this period.

**Radiation Exposure**

Mammography screening results in exposure to low-dose radiation, and this may actually induce breast cancer. For most of the average-risk women, the risk for death due to breast cancer from the radiation exposure involved in mammography screening is small and is believed to be outweighed by a reduction in breast cancer mortality rates from early detection.

Beemsterboer et al. developed a computer simulation model of a mammography screening program to calculate breast cancer deaths induced by exposure to low-dose radiation and the number of lives saved. Their estimates were based on data from the Swedish screening mammography trials and the Netherlands breast cancer screening program. In their model, they assumed a two-year screening interval and a mean glandular dose of 4 mGy to each breast from a two-view mammogram. They calculated that the ratio between the number of breast cancer deaths prevented and those induced as a result of mammography screening for women aged 50–69 is 242:1. When mammography screening is expanded to include screening women aged 40–49 every two years, the ratio becomes 97:1. Thus their model suggests that the potential hazards of low-dose radiation are greatly increased if screening is initiated before age 50.

Additionally, Swift et al. have suggested that heterozygous carriers of the gene for ataxia telangiectasia (ATM) are at increased risk for developing breast cancer after exposure to low-dose radiation. About 1.4% of the general population is estimated to constitute heterozygous carriers of the ATM gene mutations, and they may have a six-fold increased risk of developing breast cancer after exposure to low-dose radiation.

**False Positives**

Elmore et al. have shown that after 10 screening mammograms, a woman has about a 49% cumulative risk of a false positive result. Furthermore, the risk of false positives is dependent on age. Thus, for women between the age of 40 and 49, the risk is about 56%, while for women aged 50–79, the cumulative risk of a false-positive result after 10 mammograms is about 47%. It the UK Age trial, 23% of the regular attendees had at least one false-positive result compared with 12% of women older than 50 years screened regularly as part of the national program. False positives are a valid concern.
as they can have a detrimental effect on quality of life, resulting in unnecessary anxiety, unnecessary surgery, and additional costs. The impact of false positives on adherence to subsequent screening mammography is variable across studies and populations with some demonstrating a decreased adherence and others showing little effect. In the United States, where litigation is of paramount concern, the incidence of false positives has historically been higher than in Europe, probably due to the unwillingness of radiologists to commit themselves to a benign diagnosis. Analysis of data from the American Breast Cancer Detection Demonstration Project (BCDDP) suggested that the positive predictive value of mammography screening was only 10%, meaning that nine women had a false-positive result on screening for every cancer found. In contrast, European studies during the same time period indicated positive predictive values ranging from 30% to 60%. These figures represent the positive predictive value of screening in all age groups. If women below the age of 50 were considered alone, the incidence of false positives would be higher.

**Overdiagnosis**

Overdiagnosis of breast cancer is a very serious adverse consequence of mammography screening, and one that profoundly affects quality of life. Peeters et al. define overdiagnosis as “a histologically established diagnosis of invasive or intraductal breast cancer that would never have developed into a clinically manifest tumor during the patient’s normal life expectancy if no screening examination had been carried out.” Following the introduction of mammography screening, there has been an increase in the incidence of breast cancer, particularly a sharp increase in that of ductal carcinoma in situ (DCIS). DCIS is almost exclusively detected by screening mammography, and very rarely by palpation. Prior to screening mammography, DCIS accounted for only 1–2% of all breast cancers, but today accounts for 12% of all such cancers and for 30% of those detected by screening.

There is ample evidence to suggest that most DCIS detected by mammography will not progress to invasive cancer during a woman’s lifetime. Several years ago, Nielsen et al. reported the results of 110 medicolegal autopsies of women between the ages of 20 and 54 dying of accidents. DCIS was detected in 15%, a prevalence rate four to five times greater than the number of overt cancers expected to develop over 20 years.

Additionally, in autopsies of women diagnosed with breast cancer, Alpers and Wellings have found DCIS in 48% of the contralateral breasts, even though only 12% of all breast cancer patients develop contralateral breast cancer after 20 years of follow-up. And in two separate studies, Rosen et al. and Page et al. have reviewed benign breast biopsies and found several instances where DCIS has been overlooked by the pathologist. Only a small number of these women developed clinically manifest tumors after 15–18 years of follow-up. All of these studies suggest that not all DCIS progress.
to invasive cancer and most of the increase in the incidence of DCIS may in fact represent overdiagnosis.

However, the consequences of overdiagnosis can be devastating. Women with DCIS are generally classified as cancer patients, and, in the United States may sometimes face denial of life insurance or dramatically increased health insurance costs. In addition, they are subjected to treatments that would have been unnecessary if the lesion had not been detected by screening.

The accurate estimation of overdiagnosis in breast cancer is complicated by the need to account for temporal trends in breast cancer incidence independent of screening and lead time. In Norway where the breast cancer screening program was rolled out over 10 years over different counties, a registry study compared incidence of invasive breast cancer (DCIS was excluded) with and without screening in women aged 50–69 years (53). The percentage of overdiagnosis was calculated by accounting for the expected decrease in incidence following cessation of screening after age 69 years. A second approach compared incidence in the current screening group with incidence among women two and five years older in the historical screening groups, accounting for average lead time. The rate of overdiagnosis was estimated to be at 15–25%. For every 2500 women invited to have mammography screening in the age group of 50–69 years, 6–10 cases were overdiagnosed (20 cases were detected but not overdiagnosed).

**Advances in treatment and impact on mammography screening**

It is interesting to note that although the older mammography trials showed some benefit to mammography screening (30% mortality reduction in HIP trial) the more recent trials (CNBSS I and II and the UK Age trial) have shown no statistically significant benefit. Although screening technology has improved over time, the benefit of mammography appears to be decreasing. This is at least partly related to improvements in treatment, and also an increase in breast cancer awareness, resulting in smaller tumors in the control arms of these trials. Adjuvant treatments were widely available to patients in the CNBSS I and II and the UK Age trial, whereas the patients in the older trials were treated with surgery alone. As cancer treatments continue to improve, both the relative and absolute benefit of screening will diminish.
Conclusion

Since the 1970s, the United States has been the only major industrialized country to encourage mammography screening for women below the age of 50 years. However, age-adjusted breast cancer mortality rates in the United States continue to mirror those of other Western countries, suggesting that screening younger women has had little effect in altering overall population-based mortality trends. Thus any long-term mortality benefits of mammography screening in younger women (as suggested by some of the meta-analyses) do not translate into any real benefits in population-based statistics. Although interpretation of evidence is a scientific exercise, the formation of guidelines is largely a social exercise. This process is hence subject to individual biases of professional groups and their conflict of interest.

In the debate concerning the efficacy of mammography screening for younger women, the potential harm of screening has largely been ignored. The decision to screen women in this age group should be based on personal risk factors and preferences. Women should be helped to make an informed decision in view of not only the benefits but also the potential risks of screening. Given the doubts concerning the efficacy of mammography, screening in younger women and the potential for harm as outlined in Table 2, we believe that it is inappropriate to screen women under age 50 without first obtaining a proper informed consent. Individualized decision making and informed consent should be viewed as the middle ground in the continuing debate over whether or not to screen women under the age of 50.
CHAPTER 5

Relationships with doctors and nurses
Chapter 5: Relationships with doctors and nurses

Doctors and nurses are often grateful if we are able to be honest with them about how we feel. Unless they have been through breast cancer themselves, they cannot really know how we feel, so a major way that they can find out the reality is through us. Some will be more receptive than others. Some doctors and nurses will also be grateful if you are clear with them about what you need from them. This is easier said than done when dealing with a diagnosis of breast cancer, but it’s worth thinking about trying to do so, if you’re up to it.

As Louise says:
Talking to medical staff is really key, even if it’s hard.

If you’re not happy about something, do consider trying to talk to the people in charge of your care, as there might well be things they can do to help. If you don’t feel like saying something yourself, you could ask someone else to do it on your behalf. If you’re happy with what your doctors and nurses are doing, it might be a good idea to say so too, and positive feedback does seem to aid communication!

Sally’s experience with her oncologist was positive:
She was in the middle of radiotherapy and summoned up the courage to tell her oncologist that she felt really upset and vulnerable lying on the radiotherapy table, and was extremely relieved when her oncologist took on board what she’d said and asked the radiographers to cover her up as much as possible during treatment, so that she was not lying completely bare-chested on the table. She was really pleased she’d asked, as she’d almost bottled out of coming for treatment because she’d felt so exposed and upset. The rest of the treatment was then much easier for her to cope with emotionally.

Don’t forget that breast care nurses are there for you and they are used to helping women at diagnosis and during the initial treatment phase. Some will be more forthcoming than others, but their job is to support you emotionally as well as clinically. In the UK they do not have training in counselling skills, but they do have some training in communication and emotional support skills, so it is always worth approaching a breast care nurse at your hospital or clinic – they might well be of help to you.
Less positive experiences
Unfortunately, significant numbers of us have come across a doctor or nurse who is not as helpful or receptive as we might need them to be, and this can be very upsetting, especially when we feel vulnerable and scared.
A considerable number of women have told me they have felt variations on the following about a doctor or nurse, and felt powerless to do anything to improve the situation for themselves with the doctor or nurse in question. However, it has been helpful to them to realise that they are not alone in feeling the way they do.

These women have thought:
• 'I wish they had more time. This person is too preoccupied to attend to me as I’d like. They have to see far too many patients.’
• 'They’re comparing my situation to X and Y and wondering why I’m making such a fuss. I’m glad I’m not X or Y, but I’m sick of being dismissed because my prognosis is good and I’ve survived for several years. My situation is still hard to cope with and there are no guarantees.’
• 'They don’t recognise how stressed their job is making them. I wonder if they’re looking after themselves enough.’
• 'They still don’t seem to have much idea of how breast cancer continues to affect me psychologically, or physically, come to that, and worse still they’re too quick to judge. I’m sure they mean well, but I’m sick of their trite comments.’
• 'I’m frightened to tell them how I feel, in case it affects my care, and I don’t think they’d get it anyway.’

With the health professionals who are not so receptive
It can help if we at least recognise and try to accept that:
• they genuinely don’t understand how we’re feeling
• they’ve probably got too much on their plates
• their hands might be tied
• they’re only human
• they probably want to do the best for us, but they are just not trained to understand our emotional responses.

We can then be more realistic in our expectations, which might, in turn, enable us to get more of what we need from them clinically, if not emotionally.
Remember that there will also be doctors and nurses who are thinking the following:

- 'I wish she'd tell me how she really feels.'
- 'I don't want to ask in case I upset her even more.'
- 'I don't think I'm doing my best for her, but I want to.'
- 'I'm not sure what she needs from me.'

As a last resort, remember that you have a right to change your doctor or nurse if you are unhappy with them. This can be a hard thing to do, but is always possible and you would not be the first person to have done so! However, it is for you – and no one else – to decide whether or not you need to do this.

**Getting emotional support through breast cancer**

Many of us, including psychologists like me, need emotional support through breast cancer, and find such support invaluable. One good thing about getting support from a trained professional is that you don't have to worry about what you say to them. They are used to hearing about a vast range of experiences. They are also not part of your life, and you can speak to them about anything in confidence and expect not to be judged. Some of us are lucky enough to be offered some counselling as an adjunct to our treatments, or get such support quickly through our GP (general practitioner). Some pay for emotional support, and others cannot afford such a luxury.
Pregnancy-Related Breast Cancer case study: First Trimester Pregnancy
Chapter 6: Pregnancy-Related Breast Cancer case study: First Trimester Pregnancy

**History** A 34-year-old woman who was nine-weeks pregnant presented with a lump in the superior aspect of the right breast that had been present for approximately two years. The lump had been previously investigated elsewhere and fine needle aspiration cytology performed—the latter was classified as “C1.” The patient felt that the lump had recently increased in size and therefore sought a second opinion. There was no family history of breast or ovarian cancer and this was the patient’s first pregnancy. She had used the oral contraceptive pill for a cumulative period of more than 10 years.

**Clinical Findings** Examination revealed a rather ill-defined mass in the upper outer quadrant of the right breast measuring 3 cm in maximum diameter. There was an adjacent nodule estimated at no more than 1 cm in size and no skin tethering or axillary lymphadenopathy (E3) (Fig. 1).

![Figure 1](image1.png)  ![Figure 2](image2.png)

**Clinical Assessment** Clinically suspicious, though likely benign lump in first trimester of pregnancy.

**Investigations**

**Breast Ultrasound** This showed a dumbbell solid mass in the upper outer quadrant of the right breast measuring 37 mm in maximum diameter. The mass was ill-defined, though homogeneous with a hypoechoic pattern and posterior acoustic enhancement. The appearances were indeterminate and could not distinguish between a possible fibroadenoma or a carcinoma (U3).

**Core Biopsy** Ultrasound-guided core biopsy (14-gauge needle) of the right breast mass confirmed an invasive carcinoma (grade II, ER positive) (Fig. 2).

**Diagnosis** Early-stage right-sided breast cancer in the first trimester of pregnancy (T2N0).

**Multidisciplinary Review 1** The patient was adamant from the outset that she wished to continue with the pregnancy; this was a "cherished" pregnancy in a 34-year-old woman
with no existing children. Two potential treatment pathways were outlined and carefully discussed with the patient: 1. Neoadjuvant chemotherapy (commencing at 12 weeks) followed by surgery and a possible course of taxanes postdelivery. It was likely that surgery would involve a right modified radical mastectomy and immediate breast reconstruction could be offered in the postpartum period.

2. Proceed with mastectomy within three to four-weeks time and prescribe chemotherapy as adjuvant treatment. The patient could subsequently undergo delayed breast reconstruction at a later date.

**Treatment and Progress** The patient expressed some reluctance about receiving chemotherapy during pregnancy, but was reassured that there was no evidence for any detrimental effects on the fetus when chemotherapy is given during the second or third trimester (when organogenesis is complete). The patient enquired about the possibility of undergoing primary surgery and delaying chemotherapy until after the birth of her child. It was pointed out that any significant delay in commencing chemotherapy might impact on overall survival. It was suggested that adjuvant chemotherapy, should this be required, could be given in the third trimester. This could be followed by early induction and safe delivery of the baby and completion of chemotherapy thereafter.

After much detailed discussion, including the possibility of breast-conserving surgery after any downstaging by neoadjuvant chemotherapy, the patient opted for primary surgery with a modified radical mastectomy and level II axillary lymph node dissection (level III axillary dissection if evidence of extensive nodal disease at the time of surgery). Surgery was planned for the beginning of the second trimester and a dating scan was carried out at 12 weeks. There were no fetal complications and the patient made an uneventful recovery from surgery. She had a normal full term delivery at 39 weeks.

**Definitive Histology** This revealed a grade II invasive ductal carcinoma measuring 15 mm in maximum diameter (Fig. 3A). There was associated DCIS but this did not extend beyond the Figure 3 186 CHAPTER 11 invasive component. Lymphovascular invasion was not present and none of the 28 nodes contained metastatic tumor (Fig. 3B).

**Multidisciplinary Review 2** The final pathological tumor size was much less than the clinical and sonographic estimate. The calculated NPI was [0.2 1.5] \( \beta 2 \) 1 \( \frac{1}{4} \) 3.30 and the patient would receive an absolute benefit from chemotherapy of <3%. It was therefore recommended that she receive tamoxifen as adjuvant systemic hormonal therapy and ovarian suppression should be discussed (ER-positive tumor).
Treatment and Progress The patient declined tamoxifen and did not want any form of ovarian suppression. She subsequently become pregnant for a second time and has recently given birth to a second healthy child almost three years after her initial cancer diagnosis. She remains well and will undergo biennial mammography of the contralateral breast until the age of 50 years when she will enter the NHS Breast Screening Programme.

Discussion It is estimated that pregnancy-associated breast cancer has an incidence of approximately 3% and about 3 out of every 10,000 pregnant women are diagnosed with breast cancer. Increasing numbers of women are pursuing careers and deferring childbirth until the fourth or even fifth decade. Not only is this a likely contributory factor to the inexorable rise in incidence of breast cancer, but women will bear children at an age when breast cancer is much more common.

This 34-year-old professional woman was diagnosed with breast cancer during the first trimester of her pregnancy. This set of circumstances therefore intensified the emotional impact of a breast cancer diagnosis. Moreover, the lump had been present for almost two years and was previously investigated with an inadequate (C1) cytology specimen, which should have been repeated—or a core biopsy undertaken. It is possible the patient was falsely reassured by these earlier investigations and did not seek further medical opinion despite persistence of the lump. It was the recent increase in size of the lump that had prompted a second opinion. Perhaps ironically, physiological changes in the breast during pregnancy can obscure a breast mass and cause significant delays (6–12 months) in diagnosis. This applies to both clinical assessment and mammography where the increased breast density and water content reduce the innate sensitivity. The patient was below the age threshold for symptomatic mammography (35 years) but pregnancy itself is not a contraindication to this mode of imaging provided that appropriate abdominal shielding is employed. However, many breast units rely exclusively on breast ultrasound examination that can be used to
guide percutaneous tissue biopsy.

Management options for the pregnant patient with breast cancer can be complex; there are potentially two lives at risk with competing priorities for treatment programs. On the one hand the mother’s breast cancer must be optimally managed to maximize survival outcome. On the other, the health and viability of the fetus must be preserved and not compromised by cancer treatments.

Therapeutic abortion should be considered during the first trimester. This patient presented at nine weeks with a “cherished” pregnancy and adamantly refused to contemplate termination. The options of primary chemotherapy versus primary surgery were discussed and it was explained that there was no evidence for any overall survival difference in the absence of a complete pathological response to induction chemotherapy. The patient was particularly averse to receiving chemotherapy during pregnancy and opted for primary surgery with a modified radical mastectomy. No complications were reported among a group of 24 patients treated mainly during the second and third trimesters of pregnancy with 5-fluorouracil, cyclophosphamide, and doxorubicin (4 cycles). If chemotherapy must be given during the first trimester, it is preferable to consider termination. Sentinel lymph node biopsy was not undertaken to avoid the possibility of a delayed axillary dissection. However, there are no documented adverse side effects from injections of radiocolloid or blue dye. The tumor size and grade justified the decision to undertake axillary dissection (>50% chance of nodal involvement with a 37 mm grade III invasive ductal carcinoma in a patient under 40 years of age). Interestingly, the final histology was somewhat discordant with the preoperative assessment; not only was the tumor size less than half the sonographic estimate, but the tumor was downgraded from III to II. The patient had a favorable prognostic index (NPI 3.30) and any benefits from chemotherapy would have been minimal (<3%). Therefore any discussions of possible delayed adjuvant chemotherapy became irrelevant. Despite having a hormonally sensitive tumor, the patient declined both tamoxifen and ovarian suppression and had a further successful pregnancy. In view of this patient’s relatively young age and hormone-sensitive tumor, a two-year course of an luteinising hormone releasing hormone (LHRH) agonist immediately following the birth of her first child would have been a reasonable treatment option and may have permitted a subsequent pregnancy. Had the patient been at higher risk of relapse, she may have accepted this endocrine option.

When a first trimester pregnancy continues to term, there are potential concerns about the effect of the hormonal milieu of pregnancy (oestrogen friendly) on dormant breast cancer cells, which may persist after surgery. Studies have not revealed any statistically significant differences in 5- and 10-year survival figures for pregnant women compared with stage-matched nonpregnant counterparts. Furthermore, pregnancy subsequent to
breast cancer treatment does not have any deleterious impact on recurrence and survival.

**Learning Points**

1. Although surgery is generally safe during pregnancy, the anesthesia may pose a small risk to the fetus. Therefore, the surgeon, obstetrician, and anesthesiologist should work together to ensure a safe outcome.

2. Radiotherapy is contraindicated during pregnancy, so some surgeons maintain that breast-conserving surgery (which requires radiotherapy) should be avoided during early pregnancy. For women diagnosed with breast cancer late in pregnancy, breast-conserving surgery might be feasible because radiotherapy can be delayed until after delivery of the baby.

3. Most of the internal organs of the fetus develop during the first trimester of pregnancy, so chemotherapy should not be administered during this period.

4. The effects of hormone therapy in pregnant women are largely unknown, but there have been reports linking tamoxifen usage with birth defects.