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Predicting the severity of radiation skin reactions in women with breast cancer

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PREDICTING THE SEVERITY OF RADIATION SKIN REACTIONS IN WOMEN WITH BREAST CANCER.

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USE OF THESIS

The Use of Thesis statement is not included in this version of the thesis.

ABSTRACT

Skin reactions are unavoidable side effects of radiotherapy for breast cancer that may limit the amount of treatment a patient is able to receive. As well, the discomfort associated with the treatment may negatively affect the patient's quality of life and their willingness to complete a course of treatment that typically extends over seven weeks.

Prior literature suggests that variations in patients' tissue reactions to radiation may be related to individual patient characteristics. Before health care providers can intervene to prevent or minimise skin reactions, a clinical model that helps predict which patients will experience more skin reactions is needed. The purpose of the study was twofold: firstly, to test the theoretical relationships between factors that impair healing and the severity of radiation skin reactions; and secondly, to develop a model to predict the severity of radiation skin reactions in women being treated for breast cancer.

The theoretical framework for the study was based on two bodies of knowledge, radiobiology and wound healing. This framework specified three sets of potential predictors of radiation induced skin reactions. These were radiation factors (e.g. dose, fractionation), genetic factors (e.g. personal and family history of cancer, radiosensitive conditions) and personal factors (e.g. age, smoking history, nutritional status). It was hypothesised that the severity of the skin reaction was a function of the relationship between these constructs.

A sample of 126 women was recruited to the study over a 14-month data collection period. All the women had undergone lumpectomy and were commencing a standard radiation protocol of 45 Gray to the whole breast delivered in daily fractions of 1.8 Gray over five weeks, and a 20 Gray electron boost to the lumpectomy site delivered in daily fractions of 2 Gray over two weeks. After

obtaining written informed consent, data on potential factors were collected by interview at the commencement of treatment and from the medical records. Weekly observations of the skin using the Radiation Therapy Oncology Group scoring system were recorded throughout the seven weeks of treatment. The breast was divided into eight anatomical sites to increase specificity in the final analysis. The mean inter-rater reliability of RTOG scoring between the three observers was 0.85.

Chi square analysis revealed that several factors were associated with a more severe reaction. Significant factors from the "personal construct", included smoking, chemotherapy, history of skin cancer, reaction of the skin to UV radiation, lymphocele aspiration, condition of the lumpectomy scar at the commencement of treatment, weight, and the size of the breast.

Stepwise logistic regression analysis revealed the relative risk and predictive value of the factors. A predictive model was developed for each of the eight anatomical sites of the breast for weeks three to seven of radiation treatment. The principal predictors were a large breast size, smoking during the treatment period, and having had a lymphocele aspirated on at least one occasion prior to radiotherapy. The results show that it is possible to predict the severity of skin reactions in individual patients.

The research contributes to theory development in radiation skin reactions and to the practice of radiation oncology nursing. Practice implications centre on individualising the preparation, education and management of women undergoing radiation therapy for breast cancer. Further research with larger samples and using different anatomical sites will contribute to the development of a skin reaction risk assessment tool for general use in radiation oncology nursing.

DECLARATION

I certify that this thesis does not, to the best of my knowledge and belief:

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Davina Porock

Date: March 18, 1998

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LIST OF CONTENTS

Chapter Three The Research Process

Chapter Four Results

Chapter Five Discussion

Appendices

List of Tables Page

List of Figures

CHAPTER ONE

INTRODUCTION

Radiotherapy is an important non-surgical treatment for cancer that can be used alone or in conjunction with surgery and/or chemotherapy. It is a principal treatment modality in the cure of breast cancer. Effective radiotherapy treatment depends, in large part, on the patient's compliance and willingness to complete a course of treatment that typically extends over seven weeks.

Radiotherapy for the treatment of breast cancer can be stressful for several reasons. Whilst adjusting to the diagnosis of cancer, the patient must commence a treatment that is unfamiliar and time consuming. Patients often begin radiotherapy with limited information about the treatment, or with inaccurate information from sources such as other patients or well meaning people who have known someone who has had radiotherapy. One area of concern to patients who undergo treatment for breast cancer, and one fraught with misinformation, is the occurrence of skin reactions as a side effect of treatment.

Skin reaction is the most common side effect of radiotherapy with as many as 95% of patients experiencing some degree of reaction (De Conno, Ventafridda & Saita, 1991; King, Nail, Kreamer, Strohl & Johnson, 1985). Given that in developed countries such as the United States of America, Europe and Australia, at least 50% of all cancer patients will receive radiotherapy at some stage during the course of their illness (Bentzen & Overgaard, 1994a; Holmes, 1988), this represents a substantial number of people who can expect to experience a radiation skin reaction.

The ionizing radiation used in radiotherapy causes damage to all living cells, both normal and malignant. Side effects from radiotherapy are caused primarily by

damage to normal tissue. The acute side effects result from damage to cells that divide rapidly and frequently such as skin, bone marrow and gastrointestinal mucosa. Some side effects: for example fibrosis and loss of pigmentation, can be observed months or even years later. These permanent effects occur in cells such as connective tissues that divide less frequently.

Acute radiation reactions of the skin are the focus of this study. Acute radiation reactions typically appear between 10 and 14 days from commencement of radiotherapy and continue to increase in severity until the completion of treatment. The appearance of the skin is often described as a severe sunburn with peeling (dry desquamation) and itching. The reaction may become more severe with varying degrees of epidermal loss (moist desquamation) and in very rare occasions, necrosis. Discomfort ranges from mildly irritating to severe pain.

Many texts and journal articles on radiotherapy include information on radiation-induced side effects in normal tissue. The variation in side effects experienced by individuals is often raised and is explained as being dependent on several variables or factors. The factors are usually listed as: radiation dose; quality (type or energy) of radiation; time period over which the dose is administered; size of field (volume); anatomic location; and other factors (Casarett, 1980: Sitton, 1992; McDonald, 1992). Holmes (1988) describes the "other factors" as being previous or concurrent chemotherapy or surgery and individual susceptibility dependent on age and general health. Sitton (1992) includes poor nutritional status and age as factors impairing normal tissue repair and thus worsening the skin reaction.

Common knowledge in radiotherapy is the role of radiation factors in producing variations in the expression of side effects. Without radiation, there would be no skin reaction and work continues on the manipulation of these factors:

for example, hyperfractionation protocols. The advances made using knowledge of radiotherapy have already made a significant impact in reducing the severity of radiation reactions: for example, megavoltage linear accelerators have earned the name "skin-sparing" machines because of their protection of the skin by the delivery of higher energy radiation.

Despite advances in radiotherapy knowledge and probably because of the importance of tumour eradication, development of knowledge in the role of personal characteristics or factors has not received the same research attention. Now the necessity to know more about personal factors has arisen due to consumer pressure for knowledge about what will happen to the individual; calls for professional accountability for interventions and advice on the management of reactions; and the need for knowledge to aid decision making in respect to treatment choices.

Several notable authors in the medical literature have identified the potential importance of personal factors, recognizing that the degree of radiation skin reaction experienced is not due solely to the radiation received but that particular individual characteristics contribute to its expression (Bentzen & Overgaard, 1994b; Tucker, Turesson & Thames, 1992).

Furthermore, the need for research investigating the impact of personal factors on normal tissue reactions has been documented. Dische (1991) called for research that not only included large numbers of patients but also gathered detailed data about the patients in order to identify predictive factors. More recently, the need for prospective research focussing on the influence of gender, age, site and previous sun exposure on the manifestation of early skin reactions was suggested by Hamilton et al. (1996). These studies will be discussed in greater detail in subsequent chapters.

There has been increased interest in the medical and nursing literature on the individual differences in radiation skin reactions experienced by patients receiving radiotherapy (Bentzen & Overgaard, 1994b; Dische, 1994; Tucker, Turesson & Thames, 1992). This work has led to the identification of factors in the patient that may predict the degree of skin reaction. Patient factors are those that impair the normal processes of tissue healing, such as smoking, infection and nutritional deficits. An assumption underlying this research was that by considering both radiation and patient factors together a clearer picture of patient-to-patient variation in radiation skin reactions would emerge making possible the prediction of individual risk.

The Benefits of Risk Prediction in Radiation Skin Reactions

Skin reactions are currently viewed as an unavoidable part of treatment and nursing management is often directed toward the palliation of skin reaction symptoms. Skin care guidelines given to patients usually entail a change in hygiene routine, restrictions in clothing and, in some cases, restriction on activities such as swimming. The rationale behind these guidelines is not to prevent the development of skin reactions, but to prevent exacerbation of the inevitable radiation damage. In addition, there are no studies that have described the proportion of patients who suffer mild, moderate or severe radiation reactions. This lack of information means that skin care guidelines are applied to all patients even though it is apparent clinically that only a small proportion of patients will develop a severe acute radiation skin reaction.

Self-regulation theory specifies that when a patient is prepared for a stressful event, accurate concrete descriptions of the event guide the patient's coping mechanisms (Johnson, Fieler, Wlasowicz, Mitchell & Jones, 1997). According to this theory, a schema (or mental picture) is formed in anticipation of an impending

stressful event. Schemata are formed from various sources, including the patient's own experiences and new information from health professionals, family members or the media. Based on this schema, the patient's expectations about the nature of the event are formed. Patients use their interpretations of the schema to cope with the physical and functional aspects of the event.

Application of self-regulation theory leads to the postulation that providing patients with an accurate description of what is most likely to happen to them, rather than what is the general rule for all patients, will help them cope and prepare for treatment. This hypothesis was tested in earlier research which found educational preparation of this kind results in a significant reduction in anxiety and improvement in patients' satisfaction with nursing care (Poroch, 1995).

The development of accurate individual predictions for radiation skin reactions means that if the patient were likely to have no reaction or a mild reaction, then s/he would be reassured. The description of a mild skin reaction would be given and options for skin management tailored appropriately. If the patient were likely to have a more severe reaction then s/he would be prepared for the experience and options for skin management could be discussed on the basis of individual need.

Benefits to the nurse, in addition to the ability to individualise skin management information, would be prioritisation of care through identification of high-risk patients and consideration of interventions that may counteract the risk factors. For example, the nurse might advise the patient regarding smoking cessation, or nutritional needs.

There are also research benefits associated with accurate prediction of skin reactions. To date, methodological problems occur when attempting to assess the efficacy of different skin care guidelines or dressing materials due to the patient-to-

patient variation in severity of skin reactions. This problem makes matching subjects or controlling for extraneous variables virtually impossible. Therefore, if it were possible to predict the severity of reactions, new dressings and changes to guidelines could be tested against the prediction. For example, if a patient was reliably scored as high risk, then the difference between the prediction and the final appearance of the skin when trying a new dressing would indicate the advantages (or otherwise) of the dressing.

In summary, radiation skin reactions are a well recognised, common problem in the cancer patient population. To date, research has proved difficult due to the patient-to-patient variation in reactions. Although the benefits of predicting the severity of radiation skin reactions are evident, and there has been discussion in the literature to suggest some causal relationships, no attempt has been made to quantify these relationships or use them to predict patient outcomes. This study aimed to address this empirical gap.

Statement of Purpose

The principal purpose of this work was the investigation of relationships between personal characteristics of patients and their differing responses to ionizing radiation revealed by the severity of the radiation skin reactions. Sufficient literature and clinical knowledge were available to suggest that the degree of radiation skin reaction experienced by the patient is not due solely to the radiation received, but that particular individual characteristics contribute to the expression of radiation damage in normal tissues (Bentzen & Overgaard, 1994b; Tucker, Turesson & Thames, 1992). Two assumptions underscored the research: firstly that factors known to impair wound healing would also affect the development of skin reactions; and secondly that these factors had a measurable effect.

The findings of this study will ultimately lead to the development of an instrument for clinical and research use that would enable nurses to predict the severity of radiation skin reactions for individuals commencing radiotherapy. The research process proceeded in three phases:

1. Development of hypotheses for testing relationships between the severity of radiation skin reactions and potential predictors identified from the wound healing and radiation oncology literature and from clinical experience.
2. Development of the research protocol and testing of hypotheses with a sample of women with breast cancer receiving post lumpectomy radiation therapy.
3. Development of predictive models and calculation of relative risks associated with significant predictors using stepwise logistic regression analysis.

Organisation of the Thesis

Chapter Two presents the conceptual framework for the study and critically examines the research and knowledge of radiation oncology and wound healing in relation to patient-to-patient variation in the severity of radiation skin reactions. Chapter Three details the research process including the development of new measures and the validity and reliability testing conducted. Chapter Four reports the findings of the statistical analysis commencing with descriptive statistics followed by testing the hypotheses on univariate and multivariate levels and presenting the prediction models. The final chapter includes an interpretation and discussion of the findings in light of previous research and literature. Clinical implications and future research directions are also presented.

CHAPTER TWO

THEORETICAL FOUNDATIONS AND LITERATURE REVIEW

The purpose of this chapter is to review the published literature and clinical knowledge on normal tissue reactions to ionizing radiation in order to construct a testable model of potential predictors of severe radiation skin reactions. This review will show that patient-to-patient variability expressed in normal tissue reactions to radiation can be explained theoretically by the interplay of three groups of factors: radiation, genetic and personal. These factor groups form the constructs of the conceptual model. The proposed relationships between the constructs form a hypothesis to test the theoretical explanation of the variation of radiation reaction expressed in individual patients. The arguments supporting the hypothesis are based on current knowledge in radiobiology and wound management as well as a critical review of relevant research.

Conceptual Framework

The conceptual framework proposes the physiological factors that may have value in predicting the severity of radiation reactions in individual patients. Two assumptions underpin the framework: firstly that factors known to impair wound healing would also affect the development of skin reactions; and secondly that these factors have a measurable effect.

The constructs are comprised of factors (concepts) arranged together to form a theoretically meaningful framework to guide empirical study. Some concepts overlap, finding a theoretical home within more than one construct. For example, skin type could be located in both the personal construct and the genetic construct, or chemotherapy could be located in both the personal construct and as a

radiosensitiser in the radiation construct. The theoretical underpinnings and substantive evidence for the constructs and concepts of the framework are analysed in the following discourse. Figure 2.1 presents the model used to design the study and guide the analysis of potential predictive factors.

The model is also used to organise the information presented in this chapter. The published and clinical knowledge relevant to the outcome variable, radiation skin reactions, will be reviewed first followed by the three constructs. The chapter will conclude with discussion of the hypothesised relationships between the constructs and the dependent variables.

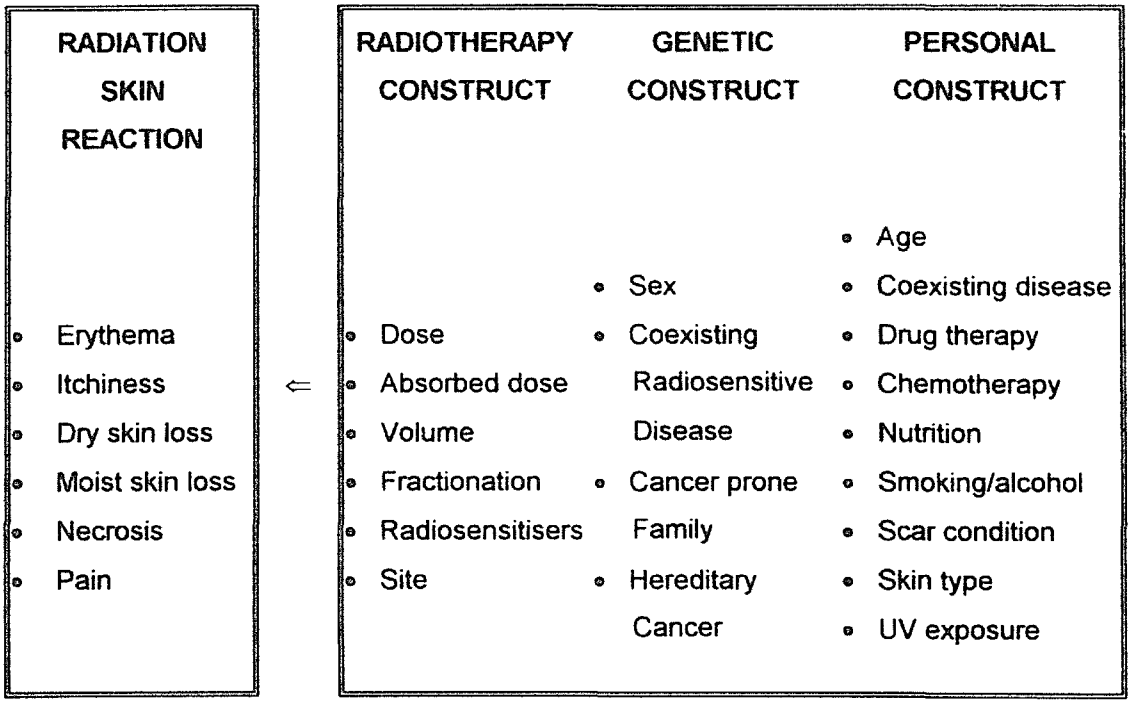


Figure 2.1 Conceptual Framework of Radiation Skin Reaction Predictors

Radiation Skin Reactions

The skin forms an important function in the protective mechanisms of the body providing a specialised covering based on an epithelial outer layer and a

deeper connective tissue layer. The health of the skin and the body's ability to repair damage significantly affects the quality of life of patients undergoing anticancer treatment. A review of the normal anatomy and physiology of skin can be found in Appendix A.

Radiation Histopathology of the Skin

Histopathologic changes of the skin range from minimal degenerative changes in epidermal germinal cells to total necrosis and are categorised as either acute or chronic. Acute reactions in normal tissues manifest damage early, that is, within a few weeks to a few months after irradiation. Damage to normal tissues exhibited months to years after irradiation is described as chronic reaction. However, acute reactions are the focus of this research and specifically those reactions occurring during the treatment period.

An acute skin reaction develops within two to three weeks of irradiation as manifested by erythema, then dry and/or moist desquamation erosions, epilation and ultimately healing. The germinal epithelial cells of the skin respond to the effects of irradiation immediately. Damage to these cells can be dose-limiting, meaning that the severity of acute reactions may require time off treatment, potentially interfering with the effectiveness of radiotherapy in terms of tumour eradication. Although the skin may not always represent the critical dose-limiting normal tissue reaction for megavoltage radiotherapy, the skin is recognised as the model for other acute reacting normal-tissues, therefore knowledge of its response is important in understanding all normal-tissue reactions (Hamilton, et al., 1996).

Recovery from acute effects is also variable, ranging from complete recovery by primary intention to healing solely by secondary intention, if healing occurs at all. The following points, taken from Casarett (1980, p. 94), describe the main sequence of histopathologic changes occurring after irradiation.

1. Early mitotic inhibition, degeneration and necrosis of the sensitive germinal cells of the epidermis, hair follicles and sebaceous glands.
2. Degenerative and inflammatory changes in the moderately sensitive fine vasculature.
3. Vascular and circulatory responses with erythema and oedema.
4. Depilation and functional and morphologic changes in the glands of the skin.
5. Desquamation (dry or moist) and sloughing of the epidermis.
6. Pigmentation.
7. Recovery processes.
8. Chronic and delayed or late changes including epidermal atrophy, sclerotic changes in underlying vessels and connective tissue, late necrosis.

The presence of erythema indicates histopathologic changes to vascular and connective tissue. Erythema manifests progressively, and has been categorised into four phases by Casarett (1980, p. 96) as follows:

1. The initial phase occurs within minutes or an hour or so after irradiation and lasts for a few hours.
2. The second phase occurs in a day or so and lasts a day or so.
3. The third phase (erythema proper) begins in the second or third week and lasts for several days to a week.
4. The fourth phase (and possibly additional subsequent phases) may occur a month or later after irradiation.

The first three phases are most significant to the study of acute skin reactions All the phases of erythema are associated with vasodilatation and

vascular congestion, increased permeability of the endothelium, plasmatic extravasation and oedema into and/or through vessel walls as a result of the inflammatory response

After subsidence of initial erythema (phases one and two), there is a latent period before phase three. Phase three includes residual oedema with thinning of the epidermis and reduced secretion of sebum and sweat indicating damage to epithelial cells and degeneration of glands. Obstructive changes in arterioles causing hypoxia also seem to be associated with erythema proper. Consequently, an increased dilation and hyperaemia may occur in surviving capillaries through collateral channels of circulation to the area (Casarett, 1980).

Damage to epithelial cells and degeneration of sebaceous and sweat glands manifests as dry desquamation during the phase of erythema proper. Temporary or partial permanent depilation may occur concurrently with dry desquamation. If dry desquamation is the most acute reaction experienced, then the recovery of the epidermis will be functionally normal. However, the following permanent changes will have occurred: fibrosis of fine vessels in vasculoconnective tissue; hyperpigmentation in melanocytes; thinning of the epidermis; and changes to hair follicles and sebaceous glands. If damage to the basal cells and glands is more severe, moist desquamation occurs.

Casarett (1980) described moist desquamation in terms of the consequences of vasculoconnective tissue changes in the epithelium. The manifestation of moist desquamation results from the formation of small blisters in and around the basal layer of the epidermis that may also extend into the more superficial layers. The epidermis sloughs when these blisters rupture and coalesce, denuding the dermis and causing permanent depilation.

Epithelialisation occurs after one to two weeks following sloughing of the epidermis if the dose has not been prohibitive and the acute vasculoconnective tissue damage has not been too severe. Provided the blood supply is adequate, surviving basal cells will re-epithelialise the area.

Doses at which moist desquamation occur vary by mode of delivery. Fowler and Stein (1960) experimented with pigs' skins and found that similar moist desquamation was produced by: 20Gy in one fraction; 30Gy in five fractions over five consecutive days; and 50Gy in 20 fractions over 28 days. The ability to increase the total dose through fractionation, thereby achieving more effective tumour eradication, without exacerbating the normal skin reaction may be a result of what is known as the four Rs of radiotherapy: repopulation (regeneration), redistribution, repair, and reoxygenation which are discussed as part of the radiotherapy construct.

Furthermore, recent research by Denham, et al., (1995) suggests that the inflammatory response alone does not explain the patient-to-patient variability. Denham, et al., continue that in addition to the effect of inflammatory mediators, other factors such as age, gender and prior sun damage, may influence the reactivity of vascular tissue.

Radiotherapy Construct

The aim of radiotherapy is described by Perez and Brady (1992, p. 1) as follows:

> deliver a precisely measured dose of ionizing radiation to a defined tumour volume with as minimal damage as possible to surrounding healthy tissue, resulting in the eradication of the tumour, a high quality of life, and prolongation of survival at reasonable cost.

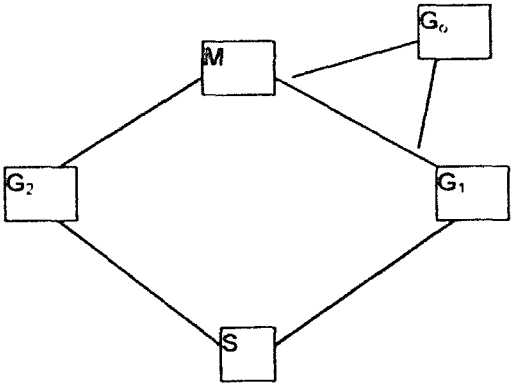
The importance of this objective lies in the fact that radiation affects all living cells both malignant and normal. A balance between the destruction of malignant cells and the preservation of normal cells must be maintained in order to achieve the best possible results for the patient with cancer. The science studying the effects of radiation on cells is radiobiology.

Fletcher (1980, cited in Hilderley, 1992, p. 10) describes radiobiology as an essential part of radiotherapy stating "As pharmacology is to the internist, so is radiation biology to the radiotherapist". Hilderley goes on to say, "...radiobiology is no less important to the radiotherapy nurse" (p 10).

Overview of Radiobiology

The cell can be damaged by ionizing radiation directly, through immediate damage to DNA synthesis, or indirectly, through the production of free radicals in the cell. The mechanism of damage occurs at the cellular level and is intimately connected with the process of replication. The process of replication is similar for both normal and malignant cells and comprises a progression through four distinct phases known as the cell cycle. Figure 2.2 illustrates the phases and briefly outlines the functions of each phase.

The cell is most vulnerable to direct damage from ionizing radiation during the phases of the cell cycle when DNA synthesis or mitosis can be disrupted. Specifically, radiation damage affects the following three phases: G_1, when substances necessary for DNA synthesis are altered; G_2, when protein synthesis is inhibited and changes occur in the chromosomes; and during mitosis, when the altered chromosomes lose their ability to reproduce. The mechanisms of injury to DNA are summarised in Table 2.1.



G_0 = Quiescent, resting phase. Cell functions continue but the cell is unable to divide.

G_1 = Pre-synthetic phase. Enzymes needed for DNA synthesis are produced.

S = DNA synthesis occurs in preparation for cell division.

G_2 = Pre-mitotic gap during which specialised proteins and RNA are synthesised in preparation for division.

M = Mitotic phase. Cell divides to produce two identical daughter cells

Figure 2.2 Phases of Cell Cycle (Holmes, 1988, p 23).

Table 2.1

Mechanism of direct damage to DNA from ionizing radiation

Mechanism of injury to DNA
• Breakage in one or both chains of the DNA molecule
• Faulty crosslinking of chains after breakage
• Damage or loss of the nitrogenous base
• Breakage of the hydrogen bond between the two chains of DNA molecule

However, the primary cause of damage is induced by the ionization events derived from the indirect action of radiation, as, at the moment of irradiation, most cells are more likely to be in cell cycle phases other than active mitosis. The cellular response to radiation involves the creation of free radicals in the cell by the interaction of cell water and electrons ejected from atomic structures by the passage of radiation through the cell. Free radicals alter the atomic and molecular structures damaging the DNA in the cell nucleus. It is estimated that approximately 70% of the biological damage produced by X-rays is due to the indirect action mediated by free radicals (Hall, 1985). The presence of oxygen acts as a sensitiser in the cell causing further damage to DNA through the formation of oxidising substances, such as hydrogen peroxide, which occurs when oxygen reacts with free radicals (Hilderley, 1993; Holmes, 1988). Ultimately the effects of radiation, whether direct or indirect, damage the cell's DNA, leading to the inhibition or failure of mitosis. Depending on the dose of radiation, cell death may occur immediately or within hours but is usually preceded by one or more cell cycles post radiation (Hilderley, 1993).

Radiation Factors

The radiation factors associated with normal tissue reactions are well documented and used to advantage wherever possible in clinical practice. Underlying these factors is the principle of balancing tumour eradication with damage to surrounding normal tissue. Perez and Brady (1992) call this principle the therapeutic ratio providing a formula thus:

$$\text{Therapeutic Ratio} = \frac{\%\ \text{tumour control}}{\%\ \text{major complications}}$$

The higher the therapeutic ratio, the more efficient the particular therapy. The formula can be used to make comparisons between treatment protocols. It has

been used this way in both clinical practice and research. However, Andrews (1981) noted that although the development of a formula was a logical step in decision making for optimal radiotherapy, it could not be absolute because clinical considerations were important. The most important of these clinical considerations are the interaction of total radiation dose, the volume treated, the fractionation schedule and the overall treatment time

Absorbed Radiation Dose

The close relationship between total dose, volume of treated tissue, fractionation and treatment time is fundamental to predicting the severity of radiation skin reactions. Normal tissue tolerances, that is the point at which erythema, dry or moist desquamation or necrosis occur, are usually reported in terms of the dose of radiation received. However the dose absorbed by the body is affected by a number of factors which are used to enhance the efficacy and accuracy of radiation

The quality (type and energy) of radiation directly affects skin reaction and is related to the amount of energy absorbed by the skin. The skin-sparing effect achieved with the megavoltage linear accelerators is somewhat diminished when the beams hit the body's surface at a tangent, that is, at an angle other than 90°. This is because penetration is lost as the beam travels more along the surface than straight through the body.

Electrons are high energy, low mass particles which have only superficial penetration and are used to treat the skin surfaces thereby increasing the severity of the skin reaction. An increased dose may be desired in some treatment protocols such as in breast cancer where the lumpectomy scar is treated with electrons following treatment to the whole breast with photons.

The application of a tissue-equivalent material, or bolus, to the skin surface also increases the dose to the skin. The bolus acts as tissue and the skin absorbs the higher dose that underlying tissue would have received; thus the use of a bolus increases the skin reaction.

In an Australian study of 110 patients being treated palliatively, Denham et al (1995) was unable to demonstrate a dose-rate effect on the development of erythema in the range of 3 to 8.2 Gy. Although it is logical to assume that such an effect exists, the patient-to-patient variability associated with a heterogeneous group of patients was enough to obscure the dose-rate effect. The variables Denham and colleagues found that affected skin reactions were: age, gender, site of treatment and a history of prior sun damage.

Volume

From the 1940s until the 1980s it was thought that normal tissue tolerances decreased when larger volumes of tissue were treated (Perez & Brady, 1992). Maciejewski, Withers, Taylor and Hliniak (1990) disputed this belief in a retrospective study of 268 patients with head and neck cancers treated with various total doses and fractions. The researchers observed no difference in the acute or chronic effects in patients treated with large or small fields. The differences in conclusions from these two studies may be due to the advantages of contemporary techniques, in particular, megavoltage radiation. Due to the limitations of retrospective design, however, the findings of Maciejewski et al. must be viewed with caution. Thus the volume of tissue treated remains a factor that cannot be discounted with current empirical evidence.

The number of fields radiated is logically linked with the total volume because more surface area is exposed to radiation. In some instances the dose is divided between the fields to ensure that normal tissue, particularly of vital organs, is

spared higher doses. In the treatment of breast cancer, however, additional fields usually indicate more extensive disease and each field has an equivalent dose. The significance therefore, of volume of irradiated tissue lies more in the fact that the patient may have: reduced tolerance to the effects of radiation with the increased volume (a small area of skin loss is quicker and easier to heal than a large area); increased discomfort or skin breakdown with a larger treatment volume; and/or a greater variation in skin dose as the beam strikes the varying contours of the skin's surface.

Fractionation and Treatment Time

Fractionation is the division of the total dose of radiation into smaller doses (fractions). By the 1970s, giving multiple small daily doses of radiation over a period of time, was found to lead to better tumour control than the large single dose of early treatment protocols (Kaplan, 1970). The relationship between dose and time is directly associated with increasing the therapeutic ratio and substantial research effort is currently being invested in refining fractionation schedules. The conventional or standard fractionation is one fraction of 2Gy given daily, five days per week over two to eight weeks. Fractionation is based on the four Rs of radiotherapy: repopulation, redistribution, repair and reoxygenation. These four basic factors are considered to be the mechanisms by which fractionation improves tumour eradication and minimises normal tissue damage (Hilderley, 1993; Withers, 1992).

Repopulation

Germinal cells of the skin and mucous membranes show an early regenerative response through increased rates of cell proliferation. Repopulation may begin before the course of radiotherapy has ended and as with the physiological response to any trauma, the repopulation rate accelerates, creating

what is termed an 'avalanche effect' (Withers, 1992). In a standard course of treatment, where a daily fraction of 2 Gy is given five days per week, repopulation begins about day 28 for the skin (Turesson & Notter, 1984).

Research by Turesson and Notter (1984) on women treated for breast cancer indicates that radiation-induced accelerated repopulation of the basal cells of the epidermis began with an abrupt onset after four weeks of standard fractionation. This group had a significantly more pronounced skin erythema as measured by reflectance spectrometry than a comparison group who received twice-a-week fractions of 4 Gy.

Thus fractionation is assumed to have a protective effect on the skin. The assumption is limited however, by the fact that repopulation of cells may occur over a prolonged period (Fowler, 1979). If the overall treatment time is over-extended or interrupted unexpectedly, the extra time between fractions or any time off treatment allows regeneration of tumour cells as well as normal cells. In order to achieve optimal tumour eradication, additional fractions would be required resulting in a higher total dose. A higher total dose has implications for the overall normal tissue damage both in the acute and chronic phases. The optimal effect is achieved by planning for the overall treatment time to be as short as possible.

Redistribution

As stated previously, the effect on tumor eradication can be enhanced if the treatment is given over a shorter time. This effect is further enhanced if smaller, more frequent fractions are also given (accelerated hyperfractionation). Cells vary in their radiosensitivity as they move through the phases of the cell cycle, with the greatest radiosensitivity for direct damage occurring in the late S-phase and the G_2 – M. Following each fraction of radiation, surviving cells, which are in relatively radiation resistant phases of the cell cycle, progress to more sensitive phases. The

net gain in this process, in terms of tumour eradication, is that cells 'self-sensitise', resulting in more cells reaching the mitotic phase as the next dose is given (Hilderley, 1993; Withers, 1992). Protocols exploiting this phenomenon are the subject of current clinical trials and redistribution is the mechanism thought to be responsible.

Redistribution is a phenomenon of acute-responding tissues (such as tumour, and normal skin, mucosa and bone marrow) and not of late-responding tissues (such as spinal cord, brain or kidney). Therefore hyperfractionation exacerbates acute effects, but reduces, theoretically, the late effects.

Combining radiation with chemotherapeutic agents, such as methotrexate and hydroxyurea, is proving to be another method of exploiting redistribution (Hilderley, 1993). The effect of multiple modalities on skin reactions will be discussed in detail in a later part of the radiation construct.

Repair

The ability of the cell to repair following each fraction of radiation is the key to the survival of acute-responding normal tissues. Withers (1992) cites research from as long ago as 1959 that showed cells could be repaired following radiation given a few hours of normal metabolic activity. A review of the process of normal tissue repair can be found in Appendix B.

Repair is initiated by the body immediately and continues in acute-responding tissues for three to four hours following each fraction of radiation. The quality and speed of the repair response depends on personal factors to be described in section on the Personal Construct. It is this aspect of the individual's capacity to repair damage that is the focal point of this study.

Tumour cells also can repair between fractions, but the assumption underlying all radiation treatment is that less repair of radiation damage occurs in

tumour cells than in normal tissues. In addition, reoxygenation further radiosensitises the tumour resulting in improved tumour kill when the next fraction is given.

Reoxygenation

As discussed in the previous section on radiobiology, oxygen is necessary for the production of some free radicals important in the mechanism for indirect damage to DNA. Hypoxia, therefore, causes the cellular response to radiation to be reduced (Holmes, 1988; Noll, 1992). The importance of oxygen concentration at the time of radiotherapy has been known for over 60 years (Hall, 1985). In the laboratory it has been shown that the dose required to eradicate all tumour cells may be doubled where just 2-3% of the cells are hypoxic (Gray, Conger, Ebert, Hornsey & Scott, 1953; Dische, 1991). As a result, studies have been undertaken to identify methods to increase the radiosensitivity of hypoxic tumour cells.

Reoxygenation occurs after each fraction of radiation as part of the normal tissue repair process. Fractionation optimises the reoxygenation process by increasing the oxygen concentration in the tumour. Cater and Silver (1960, cited in Perez & Brady, 1992) found that reoxygenation relates primarily to tumour cells and oxygen changes in normal tissues were slight or non-existent.

The use of oxygen to deliberately sensitise tumours led to experimentation with hyperbaric (high-pressure) oxygen therapy. Dische (1991), in a review of the literature, cited research using hyperbaric oxygen to sensitise tumour cells to the effects of radiotherapy. He concluded that the effect of oxygen is just as great on normal cells as on malignant cells when the patient is subjected to hyperbaric oxygen therapy. Dische concluded that the therapeutic ratio (improved tumour cell eradication versus damage to normal tissue) is altered with hyperbaric oxygen to the degree that the increase in damage to normal tissue may outweigh the benefits

of the increased tumour eradication. As a result, the technique has largely been abandoned (Noll, 1992). Nevertheless, the mechanisms of injury caused by ionizing radiation and the substances that enhance its effects are important to consider when applying this knowledge to the radiohistopathology of the skin.

Radiosensitisers

Radiosensitisers are substances that enhance the damaging effects of ionizing radiation. Oxygen, as discussed in the previous section, is an important radiosensitiser. However, more pertinent to this study are the anticancer drugs.

The combined use of radiotherapy and some chemotherapy agents, known as combined modality treatment (CMT) has been well documented as potentiating skin reactions. A significant amount of research has been conducted on the effect of combining these two modalities. Although most of the research has been conducted in laboratories on mice, there is sufficient evidence from clinical research to identify specific chemotherapeutic agents that enhance cutaneous effects of radiotherapy (Bentzen & Overgaard, 1993; Fu, 1985; O'Rourke, 1987; von der Maase, 1994).

There are three classifications of drug interactions with radiation: independent action, protection, and enhancement action. The radiation-drug interaction is said to have independent action when the drug has no effect on the irradiated tissue. Some experimental drugs have a protective effect on irradiated tissue, reducing the toxic effects on normal tissue and thereby allowing a higher cancerocidal dose of radiation to be delivered to the tumour (Brown et al., 1984; Hirshfield-Bartek, 1992). Drugs specifically used for a protection effect were not in use at the study site and so are not included in any further discussion.

Enhancement interactions.

Enhancement interactions occur when damage to normal and tumour tissue is greater with the combined effect of radiation and chemotherapy than either of the treatments alone. Enhancement is determined by looking at the cell survival curves for each agent, radiation and chemotherapy, and then mathematically determining the theoretical amount of tumour kill (Phillips, 1980). Enhancement interactions are further classified as additive, superadditive and sensitising. Hirshfield-Bartek (1992, p. 255) explains the difference between classifications thus:

> Additive reactions occur if the cell killing obtained with CMT is equal to the cell killing produced by each modality alone (i.e., 1+1=2)... Superadditive reactions occur when the amount of cell kill is greater than would be expected from either modality alone (i.e., 1+1=3)...Sensitisation responses result when agents that are relatively nontoxic when given alone produce an increase in tumour kill when given with radiation.

It is logical to assume that chemotherapeutic agents that enhance the effect of radiation on tumour cells will have a similar effect on normal cells thus increasing the severity of normal-tissue reactions. The agents with the highest likelihood of an additive or superadditive effect on the skin are adriamycin, actinomycin D, bleomycin sulfate, hydroxyurea, 5-fluorouracil, and methotrexate (McDonald, 1992). Fu (1985) lists six possible mechanisms to explain the interaction between chemotherapy and radiotherapy that result in an enhanced effect (see Table 2.2). Appendix C lists 15 commonly used chemotherapeutic agents along with their mechanism of cytotoxicity and the possible mechanism of enhancement.

The first three mechanisms focus on preventing the tumour cells from repairing following each fraction of radiation. The fourth mechanism, perturbation in

cell kinetics, relies on the effect of redistribution The fifth and sixth mechanisms, the improved blood supply and increased drug delivery and uptake, rely on the effect of reoxygenation. The enhancing effects of CMT have positive outcomes in terms of tumour eradication but the same effects on normal cells, such as the skin, will impact negatively.

Table 2.2

Possible Mechanisms of Interaction between Chemotherapy and Radiotherapy Resulting in an Enhanced Effect

Mechanism of interaction
◦ Modification of the slope of the response curve
◦ Decreased accumulation of or inhibition of repair of sublethal damage
◦ Inhibition of recovery from potentially lethal damage
◦ Perturbation in cell kinetics with an increased proportion of cells in sensitive cell cycle phase and proliferative state
◦ Decrease in tumour bulk → improved blood supply → reoxygenation and recruitment → increased radiosensitivity and chemosensitivity
◦ Increased drug delivery and uptake

Fu, K (1985). Biological basis for the interaction of chemotherapeutic agents and radiation therapy. *Cancer* (Suppl), May 12, p. 2125.

Site of Treatment

The variability in skin reaction by anatomic location has been documented. For example, the scalp has the greatest tolerance for radiation, followed in decreasing order by the face, neck, trunk, ears, groin, and extremities (Dutreix, 1986). Hamilton et al. (1996) found that anatomical site was a significant factor in the variation of skin reaction severity. Interestingly, the relational factor suggested was sun exposure. In looking at the order Dutreix documented, the face and neck would be expected to have had greater sun exposure than the groin. Hamilton's

study shows that increased sun exposure increases the early erythema rather than making the skin more tolerant. Thus, there is a contradiction between the findings of the two studies. It is important to note that the study by Hamilton et al was conducted in Australia, known for its high levels of Ultra Violet (UV) radiation. The impact of chronic exposure to UV radiation is discussed in greater detail in the section on the Personal Construct.

Sitton (1992) discussed differences in skin reactions at sites where there was appositional skin. Areas such as that found in the axilla, inframammary area, groin and perineum, well known clinically to have more severe reactions, are situated where there is close skin-to-skin contact. There is increased moisture, warmth and friction along with poor aeration at these sites. The mechanism increasing the reaction in these areas probably relates to the *stratum corneum* being shed at a faster rate than the newly forming epithelium can maintain. Any anatomical site at which friction is common, whether it be due to movement or clothing, is at risk of a more severe reaction. Typical trouble spots are the neck, where the collars of clothes rub; the axilla, where clothes and movement cause friction, and the inframammary fold, where there can be friction from a brassiere. Obesity or the wearing of tight clothing can further exacerbate this problem.

Prediction Models

Some fairly sophisticated models for predicting normal tissue damage have been proposed, including the Nominal Standard Dose (Ellis, 1969), and the Cumulated Radiation Effect (Kirk, Gray & Watson, 1971). Some criticisms of these methods are evident in the literature. Notable authors such as Peters and Withers (1981) suggest that no single set of correction factors can be universally applied to an exact relationship of dose and time and that good clinical observation and judgement are necessary in dealing with normal tissue damage.

More recently, predictions of acute and chronic effects have been based on the Linear Quadratic Equation (LQE) (Perez & Brady, 1992) which has been used widely since the early 1980s. However, Hamilton et al. (1996) found, in a well controlled clinical study of 65 patients being treated palliatively, that erythema was much greater at low doses of radiation than the LQE would predict. The researchers noted the effect of pre-treatment erythema, gender, age and site of treatment. Erythema was measured in the study by reflectance spectrometry. These findings highlight the need to complete the 'picture' of normal tissue radiation reactions by including other factors other than radiation factors alone.

Summary of the Radiation Construct

The principal radiation factors influencing normal tissue damage are total dose, dose per fraction, volume treated, overall time taken for radiotherapy to be completed, quality of radiation, use of tangential beams, site of treatment and the presence of bolus material. Although it is well known that these factors impact on the severity of skin reactions, their predictive value has not been calculated on an individual patient basis. The literature presented has also highlighted the need to explore individual characteristics of patients to explain more fully patient-to-patient variation.

Genetic Construct

Observation and scientific investigation into the differences in radiosensitivity of cells began in the early 1900s when the French scientist, Regaud, found that seminiferous epithelia became less radiosensitive as they differentiated (Regaud, 1906 cited in Peters, 1990, p. 178). These differences in radiosensitivity were noted, not only in different cell types from the same person but also in the same cell type from different people. This led to the hypothesis that genetically based

radiobiologic prognostic factors or predictive assays were possible (Peters, 1990). Although the research in this area has focussed on the radiosensitivity of tumour cells, some extrapolation has been made to normal cells. The concept that individual differences can be explained by genetic diversity is supported by the existence of inheritable syndromes that are partially characterised by hypersensitivity to radiation. The most well known of these disorders is ataxia telangiectasia and clinical papers have been published considering the treatment modifications required in the case of such striking hypersensitivity (Abidir & Hakami, 1983; Hart, Kimler & Evans, 1987). Although rare, other genetic syndromes associated with increased susceptibility to cancer and hypersensitivity to radiation and chemical agents are Bloom's syndrome, Fanconi's anaemia, retinoblastoma, Down's syndrome, basal cell naevus syndrome, progeria and cancer prone families (Mahon & Casperson, 1995; Peters, 1990).

Because hypersensitivity to radiation can be observed both in tissue reactions, and in cell cultures derived from them, the techniques used to develop predictive assays have found fibroblast and keratinocyte cultures to be particularly useful (Geara, Peters, Ang, Wike & Brock, 1992). Thus far, the research on the radiosensitivity of normal tissue has concentrated mainly on the late effects of treatment, often using telangiectasis as a model of late normal-tissue damage (Burnet, Nyman, Turesson, Wurma, Yarnold & Peacock, 1992; Turesson, 1989; Turesson, 1990; Turesson & Thames, 1989). There is little work on the acute effects despite a long standing assumption that the acute skin reaction influences the course of the radiation reaction (Jolles & Harrison, 1966; Tucker, Turesson & Thames, 1992) and despite clinical research suggesting that moist desquamation in the acute phase is highly associated with the risk of developing telangiectasia (Bentzen & Overgaard, 1993).

The research, using cell cultures, is progressing and is gradually revealing the relative sensitivities of cell types. For example, fibroblasts show more variation in radiosensitivity between individuals than keratinocytes (Geara et al., 1992). Geara and colleagues call for further studies using the techniques developed to predict normal tissue responses to radiotherapy. Burnett et al. (1992) suggest that these techniques may be most useful in detecting patients at the extremes of reaction severity. Nevertheless, Burnett et al. suggest that there are practical problems associated with the processes of cell culture prediction: namely that they are slow, they require a high level of expertise and they are labour intensive. These features mean that cell culture predictive assays in their present form could not be used in clinical practice. These practical problems will no doubt be solved as the research in this area continues.

The ability to identify genetic markers capable of predicting radiosensitivity of both tumour and normal cells and the development of cell culture techniques to test radiosensitivity in individuals would at first seem to negate the need for any other method of predicting radiosensitivity of normal tissue. However, the extensive effort that has been invested in the development of predictive assays has not yet explained why the same cell type (whether tumour or normal) in different people has such variability in its radiosensitivity (Bentzen, Overgaard & Overgaard, 1993; Tucker, Turesson & Thames, 1992). Tucker et al. also suggest that radiosensitivity is not the same for all cells in an individual, contrary to the prevailing theory that intrinsic radiosensitivity is dominated by a genetic component common to all cells. Bentzen and Overgaard (1993) support this suggestion deducing from their clinical research that the hypothesis specifying that all normal tissues of individual patients have a generally high or low radiosensitivity cannot be corroborated.

Moreover, in an extensive review of the literature, Peters (1990) concluded that cellular radiosensitivity, determined by *in vitro* diagnosis, is but one factor influencing treatment outcomes. This view is supported by Tucker et al., (1992, p. 1783) who state "...whether these [individual] differences are dominated by heterogeneity in intrinsic cell sensitivity or by other factors has yet to be determined". The other factors which Tucker et al., suggest are personal characteristics, such as age and smoking. These comments regarding the interplay of genetically based prediction and the role of "other factors" form the foundations for developing the conceptual framework and hypothesis of this study.

Hendry (1994) applies the knowledge of these relationships, suggesting the possibility of moderating normal tissue damage through modifying individual characteristics such as diet and supporting the individual's resistance to infection with prophylactic antibiotics. Hendry recognises the impact of surgery and chemotherapy on the promotion of cell proliferation and suggests that appropriate supportive therapy in the form of fluids, electrolytes and antibiotics may positively affect morbidity, ultimately resulting in an ability to give higher doses of radiation. Hendry's conclusions are based on animal models, but it is an interesting proposition to suggest that not only can "other factors" affect the individual expression of radiation reactions, but also the modification of these factors may in fact moderate the impact of genetically determined radiosensitivity. The importance of determining the relationship between these "other factors" is clear. Such knowledge could lead to preventative and supportive nursing management approaches.

Summary of the Genetic Construct

Understanding the impact of genetic make-up on the variability of radiosensitivity between people is vital to completing the picture of individual

differences in radiation reactions. It is clear there is substantial support for a genetic basis to individual differences in radiation reactions, but at this time the gene markers have not been identified and a feasible clinical method of determining prediction through cell cultures has not been developed.

'Cancer proneness' may well be an indicator of heritable radiosensitivity, but the relationship between individual radiosensitivity expressed as a skin reaction and coming from a cancer prone family or having a hereditary cancer may, at best, be tenuous.

There is also support for the influence of "other factors" in the expression and perhaps even moderation of the genetic radiosensitivity component. The strength of the relationships between potential factors has not yet been determined in humans. The "other factors" suggested in relation to the genetic component of individual differences in the expression of radiation reactions are discussed as concepts in the Personal Construct of the conceptual framework.

Personal Construct

The concepts included in the Personal Construct are those which are unique in combination to each individual. Although some may be considered as hereditary, such as allergy, or due to uncontrollable environmental factors, such as exposure to UV radiation, their impact is expressed uniquely in each individual. A principal argument in this construct is that the patient-to-patient variability in the expression of damage to normal tissue relates to the presence in the individual of factors known to affect tissue repair generally. To date there has been no empirical research investigating the relationship between the presence of factors that impair normal tissue repair and normal tissue damage in radiation skin reactions.

Many factors affect the repair of normal tissue and those most pertinent to radiation reactions will be described. Although specific headings have been used to

organise this information, it should be noted that tissue repair is often affected by the interplay of several factors. Each factor is considered in the light of research on the healing of normal tissue and radiotherapy or cancer.

Age

The impact of increasing age on healing is difficult to isolate because of the general deterioration of all body systems and the likelihood of coexisting disease such as diabetes. The effects of ageing on the skin are as follows. Epidermal turnover decreases with age resulting in extended healing times and a greater likelihood of secondary infection following trauma. The ageing of cell lines results in thinning of the epidermis, particularly in sun exposed areas and atrophy of the dermis through loss of collagen and reduction in the capillary network. Elastin fibres thicken and fragment while the vascular bed, collagen layers and fibroblasts diminish. Thinning of vascular walls explains the tendency of the skin in the older adult to bruise. Blister formation and the susceptibility to skin tear injuries occur as collagen fibres lose their elasticity (Staab & Hodges, 1996).

It is logical that sun damage to the skin would accumulate with age due to the time available for exposure. Lifestyle habits, anatomic site and geographic location of course, temper this factor (Goldfarb, Ellis & Voorhees, 1990). Sun exposure also causes hyperplasia of sebaceous glands with a resulting increase in cyst, comedone and papule formation (Ogawa, 1975; Staab & Hodges, 1996).

The vasculoconnective damage caused by ionizing radiation, as described in the section on radiohistopathology, when combined with the degenerative changes to the epidermis and underlying structures as described above, points to an exacerbation of the skin reactions as age increases.

Age also brings with it an increased risk of malnutrition (Goldfarb et al., 1990). Exton-Smith (1971) divided the causes into primary and secondary. Primary

causes included ignorance, social isolation, physical disability, mental disturbance, iatrogenic disorder and poverty. Secondary causes were impaired appetite, masticatory inefficiency, malabsorption, alcoholism, and medications. As the skin is composed of rapidly proliferating cells, they are among the first tissues to be affected by nutritional deficiency.

Obesity, which is associated with increasing age and mature onset diabetes, may have a negative effect on the efficiency of healing (Carville, 1995; Dealey, 1994). Excessive adipose tissue can compromise healing principally due to the poor vascularity of adipose tissue. Obesity can also cause excessive wear and tear on skin through increased friction on movement, causing abrasion. Obesity in surgical patients is also a factor in increased risk of postoperative infection.

It is estimated that 50% of cancers occur in persons over the age of 65 years (Strohl, 1992). With the presence of co-existing illness or conditions and the ageing of normal cell lines, it is accepted that increasing age limits the healing ability of skin. It would seem logical to assume that any skin reaction will be more severe as age increases. Many authors cite age as one of the probable "other factors" (Denham et al., 1995; Hamilton et al., 1996; Holmes 1988; Tucker et al., 1992; Turesson, Nyman, Holmberg & Odén, 1996). However, the reducing frequency of mitosis that accompanies ageing needs to be considered. Less frequent mitosis may reduce the severity of acute reactions because the effects of ionizing radiation damage become apparent on cell replication. There may, then, be a balance between these two mechanisms with age not making a significant contribution to the skin reaction.

Coexisting Disease

Several illnesses directly impede the healing process and others affect healing through medication or reduced physical mobility inhibiting nutritional intake

and hygiene respectively. Age is a significant factor in increasing the likelihood of these problems.

Diabetes mellitus.

Uncontrolled glycosuria weakens the inflammatory phase and impairs macrophage production. The increased risk of infection and the retarded healing that results are further compounded by the presence of the diabetic complications of neuropathy and ischaemia. Diabetes mellitus has been investigated as a possible factor in unusually severe reactions to radiotherapy. Kucera, Enzelsberger, Eppel and Weghaupt (1987) found no differences between diabetics and non-diabetics in any side effects although a significant increase in urinary complications in diabetics was suggested by Bentzen and Overgaard (1994b). In view of the lack of published research in this area there is insufficient evidence on which to draw a conclusion about the role of diabetes on radiation reactions with normal tissue.

Autoimmune diseases.

There are two general categories of autoimmune disease: collagen diseases (including systemic lupus erythematosis [SLE], dermatomyositis, poly-arteritis nodosa, scleroderma and rheumatoid arthritis); and haemolytic diseases (including idiopathic thrombocytopoenic purpura, acquired haemolytic anaemia and autoimmune leucopoenia).

Autoimmune disorders retard healing in the inflammatory phase of tissue repair and the risk of infection is increased due to reduced leucocyte numbers. In addition to these conditions predisposing the patient to problems of pain and immobility, which of themselves inhibit healing, treatment of autoimmune diseases centres on the use of steroids, anti-inflammatory drugs, and immunosuppressive drugs.

A common assertion in the literature is that patients with a collagen vascular disease (CVD) such as rheumatoid arthritis or SLE, dermatomyositis and scleroderma are at greater risk for radiation side effects (Fleck, McNeese, Ellerbroek, Hunter & Holmes, 1989; Teo, Tai & Choy, 1989). Although case reports have highlighted the differences between CVD and non-CVD patients, a study using a retrospective matched pair design found no difference in the incidence of early or late side effects (Ross, Hussey, Mayr & Davis, 1993).

There is convincing evidence that patients with certain genetic diseases such as ataxia telangiectasia (AT) differ in their radiosensitivity. These diseases have been discussed in the section titled, Genetic Construct.

Stress and Depression.

The physiological responses to stress are well documented. The primary biochemical response to stress is the increased production of adrenocorticotrophic hormone (ACTH) stimulated by the release of adrenalin. ACTH stimulates the adrenal cortex in the production of glucocorticoids, cortisol and hydrocortisol (Vander et al., 1994). Glucocorticoids break down the body's glucose stores, raising the blood sugar. They also suppress the inflammatory response mediated by the immune system by reducing the mobility of granulocytes and macrophages, impeding their migration to the wound. Glucocorticoids also increase protein breakdown and nitrogen excretion which in turn inhibits endothelial cell regeneration and delays collagen synthesis (Dealey, 1994).

Stress and anxiety can also be exacerbated by pain (Hayward, 1975) and socioeconomic problems including social isolation and poor housing (Dealey, 1994). Grief and depression also affect appetite and represent yet another layer of complexity in the interplay of factors affecting the repair of normal tissue. The measurement of stress and depression was not within the scope of this study.

Allergy and/or Skin Sensitivities.

Skin sensitivities or allergies may have an impact on the severity of reaction. The response of the skin to radiotherapy can be described in the same terms as a response to any physical trauma. When an abrasion, a cut or a burn damages skin, the body responds initially with inflammation. The inflammatory response, mediated by the immune system, rallies the body's resources to repair tissue and prevent infection. Similarly, when a known allergen is brought in contact with the skin, the immune response is rapid and an exaggerated reaction is noted. Clinical observation suggests that patients who have a history of allergic reaction may respond to irradiation in a similarly exaggerated way, potentially exacerbating the radiation skin reaction. This may also include patients who have a family history of allergic response.

Pruritus is a common symptom of radiation skin reaction. The principal risk associated with pruritus is the overwhelming urge to scratch, causing further skin damage including skin loss. In addition to skin allergies, there are many benign and malignant diseases associated with pruritus. Benign diseases include diabetes, hyper- and hypothyroidism, parasitic infections, multiple sclerosis, psychophysiological or idiopathic conditions, drug reactions, chronic renal failure, iron-deficiency anaemia and non-malignant obstructive biliary disease. Malignant conditions particularly associated with itching are lymphoma, leukemia, sarcoma and carcinomas of the lung, biliary tree and pancreas (McDonald, 1992). In addition, pruritus is known to occur in the advanced and terminal stages of many carcinomas (De Conno et al., 1991).

Infection

The presence of infection or immunosuppression may also affect normal tissue response to radiation (Bentzen & Overgaard, 1994b; Chak, Gill, Levine,

Meyer, Anselmo & Petrovich, 1988). Immunosuppression may be part of the causal chain in the development of infection in radiation reactions where the integrity of the skin has been compromised.

Bacteria exist as part of the natural flora of the skin and mouth and will cause infection, given the opportunity that epithelial loss allows. There are four levels for classifying infection in wounds as described by Carville (1995):

1. Clean, where the wound is made under aseptic conditions but does not interfere with the integrity of mucous membranes.
2. Clean/contaminated, where either a surgical wound does interfere with mucous membranes or there is contamination by resident flora of the cavities, but there is no host reaction.
3. Contaminated, where bacterial contamination results in a host reaction but no pus formation.
4. Infected, where the clinical signs of infection are present with increased leucocyte and macrophage levels.

Contamination in an open wound does not affect healing, but clinical infection does by prolonging the inflammatory phase and inhibiting the ability of fibroblasts to produce collagen (Senter & Pringle, 1985). Healing is also affected by the presence of infection due to the competition for white cells and nutrients. Healing may be delayed until the body has dealt with the infection. In addition, systemic infection causes fever, raising the metabolic rate, thus increasing catabolism and tissue breakdown. Pain, also produced by infection, may further increase the metabolic rate.

There are also many factors that may predispose an individual to infection. Some of these are age, obesity, diabetes (Cruse & Foord, 1973); and drugs, particularly immunosuppressive drugs and steroids (Bibby, Collins & Ayliffe, 1986).

Drug Therapy

The effect of drugs in radiation skin reactions fall into two categories, those that enhance the effects of ionizing radiation and those that impair healing. The drugs that enhance the effects of radiation, specifically the anticancer chemotherapy agents, have been discussed under the heading Radiosensitisers, in section one of the chapter. Here, the focus will be on the impact of drugs on tissue repair.

Steroids and Non Steroidal Anti-inflammatory Drugs [NSAIDs].

Both steroids and NSAIDs are used for a range of chronic and acute inflammatory conditions to reduce the swelling and pain of the inflammatory response by blocking prostaglandin synthesis. As prostaglandins are the principal mediators of inflammation, both drugs impair the healing process, particularly if they are used over a long term (Laurence & Bennett, 1987).

Steroids also suppress the inflammatory and reconstruction phases of the healing process through inhibiting fibroblast proliferation (Westaby, 1995).

Chemotherapeutic agents.

Chemotherapeutic agents used to destroy cancer cells are unable to differentiate between normal and malignant cells. The majority of drugs destroy DNA in replicating cells or interfere with protein synthesis, directly affecting fibroblast production and collagen synthesis. In addition to the direct effect of cytotoxic drugs on normal tissue, the side effects often cause nausea, vomiting and diarrhoea thereby affecting nutritional status. Alopecia caused by some cytotoxic

drugs may result in changes in body image that may cause or exacerbate stress and feelings of depression.

It would be expected that the effect of chemotherapy on normal cells when given prior to, or concurrently with, radiotherapy would impair the normal processes of tissue repair. The body would be less able to cope with the demands on the healing process in response to treatment with both radiotherapy and chemotherapy.

In addition to their damaging effect on normal cells, cytotoxic drugs also have a suppressing effect on the immune system. The principal risks of immune suppression are infection and bleeding. Healing is specifically impaired by a delay in clearance of debris through reduced white cell activity (Laurence & Bennett, 1987). As a result, patients receiving chemotherapy are expected to be at risk of infection. This would be extended to patients receiving chemotherapy as an adjuvant to radiotherapy thereby increasing the risk of infection in any skin reaction particularly where moist desquamation has occurred.

Other drugs may cause photosensitivity reactions (see Appendix D for a list of these drugs). The major difficulty with photosensitivity reactions is in masking the severity and recovery of skin reactions.

Nutritional Status

A balanced diet rich in essential nutrients is necessary to provide an ideal environment for optimal tissue repair. Malnutrition causes delay in healing and is generally the result of either insufficient intake or a problem of malabsorption.

Several factors affect nutritional status and often their impact has a compound effect on healing. Age and obesity have already been discussed in the light of their influence on healing and nutritional status. Hospitalisation, undergoing medical procedures, and surgery also affect patients' nutrition. Patients who are

not obviously at risk of undernutrition may fail to eat adequately for optimal healing whilst in hospital. Brown (1993) studied medical and surgical patients considered to have no special dietary requirements. Due to a failure to eat the food provided, 68% of the patients had intakes of less than 1000 kcal and large deficits in a range of vitamins and minerals. Many patients with cancer, having had recent hospitalisations for surgery, are at greater risk of malnourishment given the additional nutrient depletion that can occur with malignancy (Smale, Mullen, Buzby & Rosato, 1981).

Malignant disease is well recognised in compromising nutritional status. Bruera and MacDonald (1988) discuss malnutrition as one of the most frequent complications of advanced cancer, alleging that the prevalence is far greater in patients with solid tumours, children and the elderly. From their research, they found 51% of patients with advanced cancer and 80% of patients with terminal cancer were malnourished compared with just 2.3% of patients with breast cancer in the early stages of the disease. In reporting other studies with a total sample of 3,047 patients, Bruera and MacDonald revealed that weight loss ranged from 37% of a sample of lymphoma patients to 87% in a sample of patients with gastric or pancreatic carcinomas. In a study of 54 hospitalised cancer patients, almost all patients had loss of adipose tissue, skeletal muscle or visceral protein (Nixon, Heynesfield & Cohen, 1980). The use or abuse of alcohol, smoking and prescribed or illicit drugs may also have an impact on the nutritional status of the patient generally.

Some drugs, commonly used in the treatment of cancer and associated side effects, affect nutritional status directly or indirectly. The following are examples of drugs with a direct effect on nutrition: Neomycin, used for treatment of candidiasis, reduces the absorption of vitamins K and D; and Methotrexate, a cytotoxic agent

used in the treatment of breast cancer, interferes with folic acid and vitamin metabolism ultimately affecting the synthesis of DNA. Smoking can have a direct effect on nutritional status as smokers in general have been found to be deficient in vitamins B_1, B_6, B_{12} and C

A number of drugs are well known to affect nutritional status indirectly by decreasing appetite. Indomethacin, morphine, digoxin, and cytotoxic drugs in general cause anorexia and they are in common use amongst patients with cancer (Dealey, 1994). Nicotine and excessive amounts of alcohol also act as appetite suppressants. Continued smoking and alcohol use during the treatment period is well known to potentiate the normal tissue damage in the mouth and throat (Bentzen & Overgaard, 1994b; Browman et al., 1993).

Reduced Vascularity and Impaired Oxygenation

Turesson et al., (1996) tested the predictive value of several patient characteristics in a sample of 402 women having 45Gy to the whole breast. The treatment protocols were varied as the sample was drawn from a larger study so a score was specially devised to represent the "total effect (TE)" of the radiation. Other than the TE, hypertension and specifically a high systolic blood pressure, was found to be predictive of more severe erythema as measured by reflectance spectrometry. These two variables accounted for about 30% of the variance in patient-to-patient variability. This study was published after the data collection for the present study was well underway, so measurement of blood pressure was not included in the research protocol.

A good blood supply and an adequate supply of oxygen are essential to healing. Impaired oxygenation can be due to a number of illnesses affecting the haematological, respiratory, cardiovascular and/or peripheral vascular systems. Although tissue hypoxia stimulates angiogenesis (Knighton, Silver & Hunt, 1981)

continued hypoxia impairs all metabolism and the overall growth rate (Dealey, 1994).

Anaemia is important in radiotherapy because of its role in the transport of oxygen. No studies have specifically investigated the effect of haemoglobin level on normal skin exposed to radiotherapy and the study of the effect on other normal tissues has been minimal. One group of investigators identified a significant correlation between high haemoglobin concentration and the risk of radiation myelitis and speculated that the haemoglobin concentration affected the oxygen concentration in the spinal cord (Dische, Saunders & Warburton, 1986; Dische, Warburton & Saunders, 1988). It was also suggested in the 1986 study that a slightly depressed haemoglobin level led to a reduction in late normal tissue damage. However, in these reports no allowances were made for the smoking habits of the subjects which would alter the oxygen unloading capacity of haemoglobin (Overgaard, Nielson & Grau, 1992).

Research from the wound healing literature suggests that cigarette smoke contains three to six percent carbon monoxide that in turn produced carboxyhaemoglobin. In addition to limiting the oxygen-carrying capacity, elevated carboxyhaemoglobin levels have been associated with changes in the endothelium and increased platelet stickiness. The latter problem can add to the limitation of local blood flow particularly in the presence of atherosclerosis (Cohen, Diegelmann & Lindblad, 1992). Also, in a review of literature on the effects of smoking on wound healing, Siana, Frankild and Gottrup (1992), found that nicotine affected macrophage activity and reduced epithelialisation.

Early research by Moseley, Finseth and Goody (1978) investigated the effect of nicotine alone on the healing capacity of rabbit's ears. The rate of healing in the

experimental group was significantly retarded up to day 10, although healing continued at equal rates from day 12 to day 20.

The primary mechanism of smoking on wound healing seems to be cutaneous vasoconstriction. The effect may be due to one or more of the constituents of cigarette smoke (Cohen, Diegelmann & Lindblad, 1992). In terms of radiotherapy where increasing the oxygenation of tissues is associated with increasing radiosensitivity, smoking may seem to have a potentially protective effect. The degree of reduced oxygenation due to cigarette smoking is probably insufficient to decrease radiosensitivity. In all likelihood, however, the reduced oxygenation will be sufficient to reduce the body's ability to heal.

Cigarette smoking and nicotine abuse has been studied in regard to radiotherapy-related morbidity. The focus of most studies has been the early or late reactions of the mucosa in head and neck cancers, that is, anatomical sites that are in direct contact with the cigarette smoke (Browman et al., 1993; Des-Rochers, Dische & Saunders, 1992; Rugg, Saunders & Dische, 1990). No studies have specifically investigated the severity of skin reactions and smoking. In a study of the effects of cigarette smoking and diabetes mellitus, a greater proportion of smokers were found to suffer from severe irreversible side effects than the non-smokers (Kucera, Enzelberger, Eppel & Weghaupt, 1987). Unfortunately, these side effects were not described in any detail. Nevertheless, the research is on oxygenation is conclusive that it is an important component in influencing the response of tumour and normal tissue to irradiation.

Skin Colour and Condition

There is no research available on the possible impact of the colour or condition of the skin in the treatment field. However, there is some anecdotal support to suggest that individuals with fair or pale skin have more severe skin

reactions. The colour of the skin is, as previously described, created by the number of melanocytes present, the basic yellowness of the subcutaneous fat and the vascularity of the area. Basic skin colour has a genetic basis but the colour is modified through exposure to the elements, in particular UV radiation. Melanocytes protect underlying structures from the effects of UV radiation and are activated whenever exposure occurs. The mechanisms for damage to skin cells from ionizing radiation and UV radiation are not the same: it may be that where the skin has suffered damage from chronic UV exposure its ability to heal may be impaired.

The type of skin reaction to the sun in terms of tanning and burning, which individuals experience may determine the extent of UV damage. If an individual burns easily in the sun and does not tan readily then the probability that they have spent a lot of time in the sun unprotected by clothing or sunscreen is reduced. Individuals with a propensity to tan and not burn are more likely to spend time in the sun unprotected and therefore have more chronic sun damage.

The condition of the skin, whether it is dry, normal or oily indicates the normal rate of desquamation of the *stratum corneum*. If dry skin is present in the radiation treatment area then the effects of the ionizing radiation may be more pronounced and the usual management of skin in reducing the normal rate of desquamation from the *stratum corneum* less effective.

Exposure to Ultraviolet Radiation

Ultraviolet (UV) radiation, emitted by the sun, can be divided into three components UV-A, UV-B and UV-C. UV radiation has some beneficial effects, such as its role in Vitamin D synthesis; in the treatment of neonatal jaundice; and in the treatment of skin conditions such as psoriasis but the effects, particularly of UV-B, can also be detrimental. UV-B is known for its role in mediating damaging photochemical reactions in the skin, including DNA damage, through the

generation of free oxygen radicals (Browder & Beers, 1993). These reactions can cause mutation, death or transformation in a number of cells including epidermal cells, with the resultant effect of causing carcinogenesis (Young, 1990).

Most of the research in this area focuses on the development of skin cancer. Of relevance here, however, is that the mechanism for carcinogenesis is based on systemic immune suppression caused by UV-B (Jacobson & Flowers, 1996). This alteration to the immune system may also have a suppressing effect on the inflammatory phase of normal tissue repair.

Melanocytes are activated by UV radiation to produce melanin, creating a protective chemical barrier against the effects of UV radiation. The effects of UV radiation are cumulative and, therefore, the evidence of exposure is a noticeable aspect of ageing skin. Chronic sun exposure thins the epidermis and atypical keratinocytes become more prevalent (Jacobson & Flowers, 1996). Although melanocytes are normally activated by UV radiation, with chronic exposure, some melanocytes are destroyed by UV radiation and some are stimulated. This non-uniform reaction manifests as spotty hypopigmentation juxtaposed with areas of hyperpigmentation (Goldfarb et al., 1990).

Marked changes occur to the dermis with years of UV exposure. The connective tissue forms irregular clumps in a process called solar elastosis. The first noticeable change of solar elastosis is wrinkling. Wrinkling does not occur in some of the most sun exposed areas such as the nose or ears, thus it seems to be confined to skin that is elastic (Goldfarb et al., 1990). Solar elastosis is also responsible for the yellowing and roughened texture of skin giving it a "weather-beaten" appearance (Gilchrist, 1984).

Cutis Rhomboidalis Nuchae is a common condition in men after many years of sun exposure characterised by deep furrows on the back of the neck forming a

rhomboid pattern (Ogawa, 1975). The skin is thickened and may be yellow or red (Goldfarb et al., 1990).

UV exposure is known to have a detrimental effect on the condition of the skin, affecting its ability to protect the body from UV radiation damage and impairing the healing of the skin. It seems logical to suggest, then, that the effects of UV radiation may also exacerbate the severity of radiation skin reactions. This phenomenon has received only fleeting mention in the published radiation oncology nursing literature (Sitton, 1992). It has, however, been noted clinically that the reaction observed in areas commonly exposed to UV such as the head, neck and upper chest can be dramatically worse than adjacent areas of skin that are less commonly exposed.

Furthermore, work published by a radiation oncology research group in Australia suggests that prior sun damage increases the baseline erythema when measured by reflectance spectrometry (Denham et al., 1995) and increases the severity of early erythema. Neither of these studies specified how prior sun damage was assessed. Whether this phenomenon is exaggerated in Australian patients due to the intensity and aspect of sunlight in Australia is not known.

Summary of the Personal Construct

Radiation has a damaging effect on normal tissue and inhibits the process of tissue repair through damage to vasculoconnective tissue. The variation in expression of radiation skin reactions may be attributed not only to the known radiation factors but also to the genetic and personal factors that combine differently for each individual.

Patients with cancer facing radiotherapy may be experiencing many of the factors that impair healing: anorexia-cachexia, malnutrition, anaemia, some metabolic alterations, impaired mobility, old age, disturbances in blood circulation,

stress, anxiety and neurological disorders. These conditions have the potential to be detrimental to the repair of the epithelium (Bruera & MacDonald, 1988; Jacobson & Flowers, 1996; Taylor, Moran & Jackson, 1989). In addition, such patients are likely to have been hospitalised for surgery and may have had, or are having, chemotherapy. To date, the interplay of these factors and their effect on radiation skin reactions has not been empirically tested.

Relationships Between the Constructs of the Conceptual Framework

To have a radiation skin reaction one element is essential, ionizing radiation. The relationship between the Radiotherapeutic Construct and the severity of the radiation reaction is undisputed, although the degree to which the patient-to-patient variation can be explained by the radiation alone is not known. When the same treatment protocol is used, such as in the treatment of early breast cancer, then the radiation becomes more constant and investigation of individual variations can be more clearly related to the presence of "other factors"

Events occurring in normal tissues following irradiation, as described in the section on radiation histopathology, highlight the recovery or repair process as an essential component affecting the severity of the reaction. If the individual's ability to repair damaged normal cells is poor, then it would be expected that the reaction would be more severe. Therefore, the presence of factors known to have a detrimental effect on wound healing such as smoking, poor nutrition, coexisting chronic illnesses and some drugs, would also have a detrimental effect on radiation reactions.

The role of the Genetic Construct in this conceptual framework is in the genetic predisposition to factors which impair healing, such as chronic illness or factors which potentiate the effects of radiation; for example, the genetic condition, Ataxia Telangiectasia, known to produce a highly radiosensitive response.

Theoretical relationships between the constructs and the resultant radiation reactions formed the main hypothesis of the study: That the patient-to-patient variation in radiation normal tissue reactions results from the combined effect of some or all of the personal and genetic factors plus the radiation factors.

This can be illustrated in the formula:

Radiation Skin Reactions		Radiation Factors	+	Genetic Factors	+	Personal Factors
	⇐					

Measurement Issues in Operationalising the Conceptual Framework

Dependent Variable - Radiation Skin Reactions

Previous studies investigating skin reactions have relied on highly technical equipment that is not available in the average radiotherapy department; for example, reflectance spectrometry for measurement of erythema (e.g. Denham et al., 1995; Hamilton et al., 1996; Tucker et al., 1992; Turreson & Notter, 1986; Turreson & Thames, 1989). However these are not available on a day to day basis and, more importantly, nurses are not skilled in their use. Therefore, to make the final instrument useful in day-to-day practice the equipment must be available to nurses at all times.

A number of scales have been devised for clinical use to assess the progressive development of skin reactions. The most commonly used scales are those devised by Yasko (1983), McNally, et al. (1985) and the Radiation Therapy Oncology Group [RTOG] and the European Organisation for Research and Treatment of Cancer [EORTC] (Cox, Stetz & Pajak, 1995). There are some similarities in the scales in that the progression of increasing severity is conceptualised as an ordinal scale and each level of the scale is given a brief description.

Yasko's (1983) system has four stages (1 - 4) and follows the pattern of the acute skin reactions for the first three stages and then in the fourth level introduces chronic reactions. McNally, et al's (1985) system also has only three stages with each stage encompassing a broad range of possible reactions. The system is not specific to the skin alone, but the lack of adequate description in the stages makes its validity questionable.

The scoring criteria for acute radiation reactions were developed by the RTOG/EORTC in 1985 to complement the long-standing scoring system for late (chronic) reactions (Cox et al., 1995). The acute scale has six levels with '0' meaning an absence of radiation reaction and '5' meaning that the effects of the radiation led to the death of the patient. The severity of reactions is graded from one through four although in fact a grading of three is considered severe.

No psychometric testing has been reported for any of these scales. The RTOG/EORTC, by the nature of its development by a group of expert radiation oncologists (Perez & Brady, 1992) and its subsequent use in many research studies (Dische. 1994), has established a measure of content validity. Only one study was found that tested clinicians' scoring of skin reactions with the RTOG/EORTC scale by comparing it with reflectance spectrometry. Denham et al., (1995) found that RTOG scores were lower than spectrometry readings in male patients, melanin pigmented and sun-exposed anatomical sites. Other than this discrepancy, the relationship between the two methods did not vary substantially during the development of the reaction. However, whilst a reasonable correlation was found between spectrometry readings and RTOG scoring, inter-rater reliability among clinicians was poor. The article does not indicate how many clinicians were involved in the observations, or if the conclusion was reached through statistical

analysis. Reliability is, however, an important aspect to consider in controlling an observational study based on visual assessment with the RTOG scoring system.

Independent Variables - Predictive Factors

Factors included in the Radiation Construct are objective items. The collection of this data requires only an easy-to-use method of transferring data from the medical record to the data collection form to ensure accuracy in documentation. The measurement of factors included in the Genetic Construct was not within the scope of this project. However, secondary measures such as a personal and/or family history of cancer were included.

The Personal Construct includes the collection of some objective data, such as age or type of chemotherapy and some measured phenomena such as cumulative UV radiation exposure. Although factors which impair optimal healing such as age, nutrition, medications and coexisting disease are well recognised, no previous research in the wound care literature has attempted to quantify them. In other words, there is no known effect size for any of these factors. Thus, despite there being a logical theoretical relationship between the constructs, there is little or no empirical evidence to assist in overcoming the pragmatics of testing the model.

Therefore, to determine which of the identified factors or combination of factors best predict the individual differences in skin reactions, an inclusive approach was considered appropriate. This means that as many factors as possible were measured to explore individual and combined effects. Also, wherever possible, similar characteristics (such as disease or treatment factors) were grouped together to provide as much control as possible over the multitude of potential extraneous variables. Details of the measures used to collect data for the Personal Construct are presented in Chapter Three.

Chapter Summary

The purpose of this chapter was to review and critique the literature to construct a conceptual framework upon which the empirical study of factors impacting on the severity of skin reactions to radiation therapy could be based. The conceptual framework, draws together two bodies of knowledge, radiation oncology and wound management. The scientific research and clinical knowledge presented here shows that the interplay of radiation, genetic, and personal factors explains to some degree, patient-to-patient variability in normal tissue responses encountered in radiation oncology practice.

The complexity of conducting research that considers the impact of personal factors on the severity of skin reactions is evident in the few studies that have been published. To overcome some of the difficulties, Denham et al. (1995) recommend that future research be confined to the study of one site and one gender.

Management of radiation skin reactions provides a daily challenge to the interdisciplinary team in radiation oncology. For clinically utility it is not only important to determine the influence of the aforementioned concepts on patient-to-patient variability, but also find practical measures that can be used on a day-to-day basis.

CHAPTER 3

THE RESEARCH PROCESS

This chapter presents the methods used to collect and analyse data for the study. Details of the sample and setting, design, measures, procedures, analysis and ethical considerations are described.

Sample

The sample was drawn from the population of patients commencing radiotherapy for cancer of the breast. A total of 128 women who met the following selection criteria were approached to join the study:

- Adult women (≥ 18 years old)
- Able to verbally communicate sufficiently well in English to understand the purpose and nature of the study in order to give consent, and complete the interview.
- Diagnosed with primary breast cancer at any stage who had undergone surgical removal of the breast tumour (lumpectomy) with or without axillary node clearance.
- Commencing the standard post-lumpectomy radiotherapy protocol of 45 Gy to the whole breast delivered by two tangential fields in daily fractions of 1.8 Gy for 25 days, five days per week, followed by a 20 Gy electron boost (6MeV or 9 MeV) to the lumpectomy scar delivered by one field in daily fractions of 2 Gy for 10 days, five days per week.

Of the 128 women who were approached, 126 agreed to participate in the study. One person refused because she was too busy and the other felt too weak. There were no withdrawals from the study. Recruitment continued over a 12-month

period. The entire data collection period including a follow-up of all cases was 14 months from May 1996 to June 1997 inclusively.

Setting

The setting for the study was the Radiation Oncology Department of a major metropolitan, public teaching hospital located in Perth, Western Australia (WA), hereafter known as the Department. During a 12-month period the Department receives over 1200 new referrals and administers approximately 1350 treatment courses. An average of 105 patients are treated each day.

Design

A prospective, descriptive correlational, repeated measures design was used to determine predictors of skin reaction severity in patients being treated with radiotherapy for breast cancer. This design facilitated the correlation of identified factors with the development of radiation reactions experienced by participants. The dependent variable was the severity of radiation skin reaction as measured by the RTOG scoring system. The independent (predictive) variables were the factors identified in the theoretical framework through review of the literature and clinical knowledge.

Data were collected at weekly intervals over the seven weeks of treatment. In addition to the observation of the skin reaction at each time point, a pain score was recorded along with a description of the nursing interventions that had been instigated. Comments from participants and observers were also recorded.

Instruments

Operationalisation of the conceptual framework is described in this section. Figure 3.1 depicts the concepts and constructs that will be detailed subsequently.

CONSTRUCT LEVEL	RADIATION SKIN REACTION	RADIATION FACTORS	GENTETIC FACTORS	PERSONAL FACTORS (Disease related)	PERSONAL FACTORS (Treatment related)	PERSONAL FACTORS (General health)	PERSONAL FACTORS (Skin condition)
CONCEPT LEVEL	a. Erythema	Dose	Previous cancer	Tumour histology	a. Condition of scars	Age	Skin condition
	a. Itchiness	Fractionation		Stage of disease	b. Lymph drainage	Chronic illness	Skin allergies
	a. Dry skin loss	Treatment length	Family history of cancer	Time since diagnosis	c. Chemotherapy for this cancer	Prescribed drugs	Family history of allergies
	a. Moist skin loss	Energy		Recurrences	b & c Chemotherapy or radiotherapy for previous cancer	Self-medication/ alternative drugs	Reaction of skin to UV radiation
	b. Pain					Smoking history	Cumulative UV exposure
						Alcohol intake	Geographic location
						Weight (kg)	
						Height (cm)	
						Breast (bra) size	
						Nutritional intake	
						Alternative diet	
MEASURE-MENT LEVEL	a. RTOG scoring system	Radiation prescription	Participant report	Medical notes	a. Observation	Participant report	Participant report
	b. VAS - pain				b. Participant report		
					c. Medical notes		

Figure 3.1 Operationalisation of the Conceptual Framework

Dependent Variable - Severity of Radiation Skin Reactions

As shown in Figure 3.1, the severity of radiation skin reactions was indexed with two instruments, RTOG scoring system and a visual analogue scale (VAS) to measure pain. The breast area was divided into eight anatomical sites and a score recorded for each site at each observation. The sites were: midline chest (sternum); axilla; inframammary fold; nipple; and the four quadrants of the breast, upper outer quadrant (UOQ), upper inner quadrant (UIQ), lower outer quadrant (LOQ), and lower inner quadrant (LIQ). The data collection form for recording weekly observations is presented in Appendix E.

The RTOG Scoring System

The RTOG Scoring System for Acute Radiation Morbidity was developed by groups of expert physicians as part of the RTOG over some 25 years (Dische, 1994). The scoring has been used extensively in empirical studies (Dische) and is used routinely in the Department as a standard measure for documenting skin reactions.

Other scoring systems have been devised; however, they have fewer categories and do not distinguish between acute and chronic reactions (see literature review). The RTOG, therefore, was judged to have more specificity, is used extensively in clinical research and is accepted generally in the medical and nursing communities. The validity of the scoring system is based on these credentials as no formal psychometric testing of the RTOG has been published. The current form of the scoring system was published in 1995 in a special issue of the *International Journal of Radiation Oncology Biology Physics* (Cox, Stetz & Pajak, 1995). Descriptors for skin reactions used in the study are detailed in Table 3.1.

Table 3.1

RTOG Score System for Acute Radiation Skin Reactions

RTOG * SCORES			
1	2	3	4
Follicular, faint or dull erythema, epilation, dry desquamation, decreased sweating.	Tender or bright erythema, patchy moist desquamation, moderate oedema.	Confluent, moist desquamation other than skin folds, pitting oedema.	Ulceration, haemorrhage, necrosis.

* RTOG Score of 0 = No change over baseline

The RTOG system scores radiation reaction severity on an ordinal scale from zero to four. Zero represents no change from the baseline observation with each subsequent category depicting increasing severity as the score increases.

Interrater Reliability

Interrater reliability (IRR) in the use of the RTOG was tested at the commencement of data collection and at random times throughout the data collection period. Over the 14 months of data collection, 30 sets of observations (observation of the eight anatomical areas made one set) were included in the IRR testing, occurring approximately at fortnightly intervals.

Over the study period, three people were involved in the observation of skin reactions, two research assistants and the researcher. All three observers were experienced in radiation oncology nursing. IRR was tested between two observers at a time because the use of three observers would have been practically difficult and intrusive to the patient. The researcher was always one of the two observers. The procedure for IRR testing was to examine a patient's skin together and then record the observation on separate sheets.

IRR scores were generally high with an overall reliability of $r = 0.85$. The IRR for each observation site of the breast are detailed in Table 3.2. Discrepancies arose most often when the skin was changing from a RTOG 1 to RTOG 2 rating.

Table 3.2

Overall Interrater Reliability by Site on Breast over the Study Period.

Site	Average IRR Coefficients (range)
Sternum	r = 0.90 (0.80 - 1.00)
Axilla	r = 0.90 (0.80 - 1.00)
Upper Outer Quadrant	r = 0.90 (0.75 - 1.00)
Upper Inner Quadrant	r = 0.85 (0.70 - 1.00)
Lower Outer Quadrant	r = 0.80 (0.70 - 1.00)
Lower Inner Quadrant	r = 0.80 (0.70 - 1.00)
Nipple	r = 0.75 (0.60 - 1.00)
Inframammary Fold	r = 0.90 (0.80 - 1.00)

Modifications to the RTOG Scoring System

After completing the data collection on the first 20 patients, a problem emerged in the definition of RTOG 2. There was a clear difference in the participant's perception of the skin reaction severity between "bright tender erythema", and "patchy moist desquamation". That is, patients perceived loss of even a small patch of skin worse than tender bright red skin. The decision was made to differentiate between these two reactions recording bright tender erythema as "2", and patchy moist desquamation as "2.5" as this would provide more specific information for predicting outcomes.

A recent study (Denham et al., 1995) also found it necessary to modify the RTOG scoring. They split RTOG 1 rather than RTOG 2. The decision in this study to split RTOG 2 was based on what participants saw as a discrepancy in skin reaction severity scores as described by the RTOG system.

Another modification was made due to the use of retention tape dressings to prevent fragile skin from breaking down. The use of retention tape dressings, such as Fixomull, Hypafix and Mefix) for the management of radiation skin reactions was

developed by nursing staff in the Department and was a standard feature in the skin care protocol (Downes, Porock & Upright, 1997). Retention tape is placed over areas of moist desquamation to reduce pain and the risk of infection. However, when the skin is assessed to be very fragile and breakdown is seen to be imminent, the tape is used to prevent skin loss. Retention tapes, when used as wound dressings, adhere to the skin and can remain intact for up to three weeks. Radiotherapy can continue with the tape *in situ,* as it is thin enough not to create a significant bolus effect (Downes et al.). This protocol could not be disrupted during the course of the study. Thus, when a retention tape was recorded, a score of 2.5 was given to that site even when moist desquamation had not actually occurred as it was anticipated that had the tape not been used, the skin would have broken down.

Pain

Pain is an aspect of radiation reactions that is not included on the RTOG scoring system other than by the term "tender" in RTOG 2. Pain was, therefore, measured separately using a VAS where "zero" represented no pain and "ten" represented the worst pain the patient could imagine. The VAS is a unidimensional measure of the perception of pain based on the premise that pain is what the patient describes it to be. Participants were asked to rate the worst pain they had experienced with the skin reaction during the week preceding each observation. The pain score was recorded on the data collection form for recording weekly observations of skin reactions (Appendix E).

Independent Variables

As indicated in the conceptual framework, and illustrated in Figure 3.1, there were many possible independent variables acting alone or in concert to increase the severity of the radiation skin reactions. The data collected and tools used to

measure factors from each construct are presented first, followed by a description of content validity and reliability testing.

Radiotherapy Construct

The factors identified in the conceptual framework that comprise the Radiotherapy Construct required careful documentation from the prescription for radiotherapy. At the end of the treatment period, a treatment summary was written by a radiation therapist from the planning section of the Department indicating the total dose, dose per fraction, energy used for the electron boost and the total number of days of treatment (including weekends and missed days).

Genetic Construct

The data collected for this construct were indirect indicators of personal or familial genetic makeup. Other tests of radiosensitivity or cancer proneness were beyond the scope and purpose of this study. The two items used were previous personal history of cancer, and a family history of any type of cancer.

Personal Construct

The personal construct was the largest construct and the main focus of the study. For ease of discussion the construct has been divided into four categories: disease related factors, treatment related factors, general health factors and the condition of the skin at commencement of radiotherapy.

Personal Construct - Disease-Related Factors

Data for disease-related factors were obtained from the medical record of each participant. Specifically, the histology and staging of the tumour were obtained from the pathology report after surgery. Time since diagnosis was calculated from the date of surgery to the start of radiotherapy.

Personal Construct - Treatment-Related Factors

The two main areas of data to be collected as treatment-related factors were in relation to the surgical and chemotherapeutic effects of cancer treatment prior to commencing radiation. In addition, data from treatment with radiation or chemotherapy from any previous cancer treatment were documented.

The condition of the surgical scars at the lumpectomy site and from axillary clearance was an important aspect in assessing the condition of the skin at the commencement of treatment. In consultation with a microbiologist and a clinical nurse consultant for wound care, an ordinal scale was developed. The scale was reviewed informally for content validity by four experts in surgical wounds (two surgical nurses and two wound care consultant nurses) and an agreement of r = 1.00 was achieved. The scar was observed during the first week of treatment and recorded as follows.

The scar: (1) is fading; (2) is inflamed (3) has haemoserous discharge (4) has purulent discharge

Details of concurrent and completed chemotherapy in relation to treatment of the current breast cancer were taken from the participant's medical record. Information regarding any previous chemotherapy or radiotherapy for the treatment of any previous cancer was documented from the participant's self-report and cross-checked in the medical record.

Personal Construct - General Health

Data for the general health section of the Personal Construct were primarily collected by participant report or from the medical record (see Figure 3.1). However, several factors required more measurement as described below.

Nutritional intake.

Nutritional intake was measured using a subscale of the Braden Scale for pressure ulcer risk prediction (Braden & Bergstrom, 1989). The Braden Scale is comprised of six subscales developed from the aetiology of pressure ulcers (Braden & Bergstrom, 1987). The nutritional intake subscale was chosen because its underlying assumption was identical to this study: that poor nutritional intake resulted in poor wound healing.

The scale has undergone a variety of psychometric tests. Content validity was established by an expert panel and two studies of IRR were conducted in extended care facilities; $r = 0.99$, and $r = 0.83 - 0.87$ (Bergstrom, Braden, Laguzza & Holman, 1987).

The nutritional intake subscale is intended to measure a person's usual food intake pattern rather than a temporary poor or negligible intake. If a person's intake has been poor over a long period and food supplements have just been commenced, then the rating would reflect the usual poor intake. Any change in intake should be maintained for one week before it is considered usual (Braden & Bergstrom, 1989).

Personal Construct – Skin Type and Condition

Measurement of the factors in the skin type and condition section of the Personal Construct required the most development, as there was little published in this area.

Severity of skin allergies.

A scale to measure the severity of skin allergies was developed with the help of a microbiologist and clinical nurse consultant for wound care. Scale responses were structured in the following manner: (1) Mild reaction (dry and peeling), (2)

Moderate reaction (as above plus red and itchy), (3) Severe reaction (as above plus blisters/oozing).

An expert panel of four nurses as described above, reviewed the scale for content validity and the agreement achieved was r = 1.00. Study participants, who had reported skin allergy as a problem, were asked to choose a response from the scale that most closely fitted the severity of their skin to the presence of an allergen.

Family history of skin allergies was measured using a simple "yes/no" question to ascertain the presence of a family history. Participants were also asked to record the number of family members with a skin allergy problem and their relationship to the participant. Only first or second-degree blood relatives were included in any analysis.

Skin type.

After review of the electronic data bases for references to non-invasive measures of skin type, discussion with a Consultant Dermatologist revealed a well-known dermatology clinical scale for skin type in relation to reaction to the sun; the Fitzgerald scale (Harber & Bickers, 1981). The scale comprises six ordinal descriptors as shown in Table 3.3. Patients are asked to report their skin reaction to the sun following 30 to 45 minutes of unprotected sun exposure after the winter season or a long period of no sun exposure.

The Fitzgerald scale correlates with more invasive measures of skin colour. For example, the correlation between the Fitzgerald Scale and melanin density, as measured by punch biopsy, is r = 0.49 (p = .001) (Dwyer, Blizzard & Ashbolt, 1996). The scale appears to be part of the tacit knowledge of dermatology, and no record of its development or formal testing for validity and reliability was found.

Table 3.3

The Fitzgerald Scale

Skin Type	Sunburn and Tanning History
I	Always burns easily, never tans (sensitive)
II	Always burns easily, tans minimally (sensitive)
III	Burns moderately, tans gradually (normal)
IV	Burns minimally, always tans well (normal)
V	Rarely burns, tans profusely (dark brown, insensitive)
VI	Never burns, deeply pigmented (insensitive)

Exposure to ultraviolet (UV) radiation

A non-invasive measurement of the cumulative effects of UV radiation was not located. The factors involved in exposure to the sun relate to lifestyle, such as sunbathing habits and use of protective measures. These are understandably subject to a large degree of recall bias. A small qualitative study was conducted six months prior to the main data collection to identify ways in which people described their exposure to the sun. The purpose was to find a way to capture the effect of lifestyle factors as potential predictive factors. The hypothesis was that a greater cumulative exposure to the damaging effects of UV radiation was associated with the development of more severe radiation skin reactions in sun exposed areas such as the sternum.

After approval was gained from the hospital ethics committee, interviews with six patients from the Department were undertaken. A further four healthy adults were interviewed to identify if there were any additional factors not considered by patients. Data were recorded as field notes and examined for themes. Three themes emerged from the patient interviews and no new themes emerged from the additional interviews with the healthy adults.

The themes were:

1. Where free time was spent - indoors, outdoors or both
2. Where work occurred - indoors, outdoors or both
3. How often sun protection was used - almost always, often, sometimes, almost never.

The themes were further categorised by differences in their activities and behaviours as children and as adults, and differences due to geographic location, for example living in Australia versus Britain.

The developed scale was included in the content validity package sent to the original five-member panel of experts in radiation oncology. The co-efficient of expert agreement on content validity for this scale was r = 1.00. Study participants were asked to choose a response from the scale that most closely matched their history of sun exposure. The cut off point between childhood and adulthood at 15 years of age was based on the skin cancer risk factors. The complete scale is presented in the data collection form found on page 204, Appendix F.

Content Validity

The first step in developing the data collection methods was to assess the content validity of the factors identified in the conceptual framework. The content validity of the conceptual framework and tools for measuring variables was assessed using Lynn's (1986) method of determining agreement between members of an expert panel. In this method, each expert independently rates the items of the instrument and indicates, in their opinion, to which of four set categories the item belongs. The categories are: 1. Not relevant; 2. Unable to assess without item revision; 3. Relevant but needs minor alteration; 4. Very relevant and succinct.

When the responses have been collated, percent agreement among the experts is calculated. The table of correlation coefficients formulated by Lynn

(1986), indicates the number of experts from a panel who must agree to reach significant agreement when $\alpha = 0.05$. The number of experts in a panel affects the number required to achieve significant agreement. For example, to achieve significance with a panel of two requires both experts to agree, whereas a panel of five requires four experts to agree. If a particular item is rated as category 3 (relevant but needs minor alteration) or 4 (very relevant and succinct), then it is deemed to be a valid item. Lynn (1986) also suggests that an agreement coefficient of over 0.80 is required before content validity is deemed established.

The procedure for assessing content validity of the predictive factors in this study was as follows. Five expert radiotherapy practitioners, two nurses, two consultant radiation oncologists and one radiation therapist were approached by phone and all agreed to assist in the exercise. Each member of the panel was sent a letter thanking them for their assistance and instructing them in the system to check content validity. A copy of the abstract from the research proposal was also sent for their information. A table was constructed for ease of assessment where each item was alongside the categories as described above (Appendix G). All but six items achieved a content validity coefficient of greater than or equal to 0.80, which according to Lynn's (1986) criterion, is an acceptable level of agreement. Four items, age, tumour histology, recurrences, and family history of cancer attained a coefficient of 0.60. Two items had a coefficient of 0.40 (time since diagnosis and stage of disease at diagnosis). According to Lynn (1996) these six items should be modified or removed. However, panel experts offered no recommendations for modification of the items. Given the exploratory nature of the study, and the fact that the items were selected based on literature purporting relationships between these and the severity of skin reactions, all items were retained. Collection of data related to time since diagnosis and stage of disease were justified as they would be useful descriptors of the sample.

The expert panel was also asked to comment on the scoring of specific items. Minimal changes were suggested and incorporated before proceeding to the next phase of pilot testing. In addition to the expert panel's input, the consultant statistician also reviewed the instrument and commented on the scoring. The scoring system was found to be suitable for the analysis planned. Following this initial assessment of content validity, operationalisation of the factors was completed.

Reliability testing

The reliability of much of the data collection lay in the accuracy of recording. Random checks were made, comparing the medical notes of about 20% (26) of the sample and asking 5% (6) of participants to repeat the interview. No errors were detected.

The process of asking six participants to repeat the interview made it possible to assess the reliability of several of the scales used as listed below:

- The subscale of the Braden Scale used for nutritional intake
- The Cumulative UV Radiation Scale
- The Fitzgerald Skin Condition Scale
- The Skin Allergy Severity Scale

No differences in participants' responses to these scales were detected in this small group.

Scar Condition Scale

Interrater reliability for the Scar Condition Scale was conducted randomly during the data collection period between the three observers. Approximately 10% (12) of the sample was tested and reliability was found to be $r = 1.00$.

Demographic Data

In addition to the factors described, the following demographic data were collected to test for representativeness of the sample: marital status, occupation, and education level completed. In the pilot study socioeconomic status was assessed through an item on annual family income. Participants were reluctant to give this information so the item was removed and two other items replaced it, usual accommodation, and postal area code. Socioeconomic status was then assessed using the Australian Bureau of Statistics' (ABS) socioeconomic listing developed from the National Census data (1996).

Pilot Testing of Measures

The final form of the data collection form can be found in Appendix F. The instrument was piloted on the first five participants and modifications to the order of the items were made. Participants reported verbally that they could understand all items easily. No new items were added at this stage, so these participants were included in the final sample.

Training of research assistants

Two research assistants were trained during the course of the data collection period in the use of the preliminary instrument prior to commencing work on the study to ensure that the explanations and instructions given to each participant did not differ significantly. Where uncertainty arose (for example in assessing the pathology reports) the Consultant Radiation Oncologist (adviser to the project) was available to answer questions and make necessary clinical decisions.

All three observers were experienced in radiation oncology nursing and were familiar with use of the RTOG scoring system in the Department. Thus training for the measurement of the dependent variable comprised testing interrater reliability

and ensuring that a second opinion would be obtained from another observer, or the Consultant Radiation Oncologist in cases of uncertainty.

Procedures

Recruitment

Patients planned for standard protocol treatment of breast cancer were identified from the list prepared each week by the planning section of the Department. From this list the researcher/research assistant liaised with the radiation therapists working on the linear accelerator units to ensure that identified patients fitted the study criteria, and noted when treatment was to start.

Patients fitting the inclusion criteria of the study were approached to join the study during the first week of their treatment. To avoid any unnecessary stress, patients were not approached on the first day of their treatment. Prospective participants were approached in the waiting area in the following way: The researcher/research assistant introduced herself and asked if the patient had a few moments to discuss a research study in which they might participate. If willing, the patient was taken to a side room to provide the necessary privacy. The research was explained fully and questions answered. Formal consenting procedures were completed when the researcher/research assistant was sure that participants understood both what was involved and their rights as voluntary research subjects. Each participant was allocated a code number and each page of the questionnaire and follow-up schedule was numbered.

Interview - Completion of the Data Collection Form

The interview to complete the preliminary instrument was conducted at the same time as consent. An interview format was used, as the preliminary instrument was not designed for independent completion. On a very small number of

occasions the interview was completed at the first follow-up. It was essential however, that the condition of the skin was assessed and documented on the first occasion to establish a baseline.

Most items on the questionnaire were answered by patient report in the interview and no corroboration was sought. Information for items 1 - 5 on the questionnaire and the treatment details were obtained from the medical notes and the prescription for radiotherapy.

Follow-up

The follow-up procedure was facilitated by the good working relationship between the researcher/research assistants and the radiation therapists working on the linear accelerators. Once a week during the treatment period, each participant was examined immediately prior to or after the daily treatment so that they did not have to undress again for the research protocol. A list of current participants' names was given to the radiation therapists working on the linear accelerators who would then call the researcher/research assistant to the machine to see participants. Consent was verified verbally with the participant before the observation took place at each follow-up.

Participants' data were name identified on the front page only. All the research documents were kept in a lever arch file and secured along with the medical notes in the Department. Completed consent forms were kept in a locked filing cabinet in the nursing office in the Department for the duration of the data collection period and then transferred to the research office and kept in a secured place.

Closure of Study Participants

At the end of the treatment period the participant's questionnaire and follow-up schedule were removed from the lever-arch file. The section at the top of the

first page on which was the hospital label with the name of the participant was removed and placed with the consent forms in the filing cabinet. The questionnaire and follow-up schedule, now only identified by a code number, was removed from the Department, taken to the research office and secured in a locked cabinet.

Analysis Plan

The data were analysed using the Statistical Package for the Social Sciences version 7.0. Data were cleaned and data entry checked by random sample of 10% of the questionnaires. The process of data analysis was completed in the steps set out below.

1. Sample characteristics and all potential predictive factors (independent variables) were explored using descriptive statistics. Normality of continuous variables was tested graphically using a probability plot and box plot and one-sample Kolmogarov-Smirnov nonparametric test.
2. The RTOG score (dependent variable) was explored and found to have a non-normal distribution. Therefore the RTOG score was re-coded into a dichotomous variable for all eight anatomical sites and for each week thus (refer to Table 3.1 for definitions of RTOG scores):
    - RTOG score of 0 or 1, representing no reaction or a mild reaction became D-RTOG0
    - RTOG score of 2 or more, representing a less manageable reaction became D-RTOG1.
3. The independent variables were explored and collapsed where necessary to ensure the validity of chi-square testing.
4. Chi-square testing was conducted between the dependent site-specific D-RTOG score and each categorical independent variable.

5. Independent sample t-tests were conducted on the dependent site-specific D-RTOG score and each continuous independent variable.
6. Nursing interventions with creams and topical ointments were tested as possible co-variants.
7. On the basis of the univariate results, any relationship with a p-value of < 0.10 was noted for inclusion in the logistic regression analysis.
8. Stepwise logistic regression was performed on the results for week five first. This week was the last of the radiation to the whole breast area and if a more severe reaction was going to occur it would most likely have occurred by week five. The alpha level for entry of a predictor was set at 0.10 and removal at 0.15 to allow for a more complete exploration of the predictors. Categorical variables were treated as indicator (dummy) variables with the reference group being the "zero" group e.g. for smoking, the never smoked group was the reference group with which the ex-smoker and current smoker groups were compared.
9. Stepwise logistic regression was performed in the same manner on the D-RTOG scores for weeks four and three to determine what variables might predict those at risk of an early reaction.
10. The RTOG scores were described from data recording the skin reactions during the electron boost treatment in weeks six and seven.
11. Univariate level relationships were tested using chi-square analysis for categorical variables and t-tests for continuous variables for weeks six and seven.
12. Stepwise logistic regression analysis was then performed between the D-RTOG scores in week six and seven. RTOG scores for weeks six and seven record the effect of the electron boost to the lumpectomy scar and the

diminishing skin reaction effect of the remainder of the breast following completion of the whole breast protocol.

13. A prediction model for each anatomical site by week was developed providing an estimate of the relative risk for each predictive factor in the model. The Exp(B) column in the table constructed as part of the computer output is the logistic regression equivalent of the odds ratio or relative risk. The probability or likelihood that an individual may enter the more severe reaction group was calculated from the following formula:

$$\text{Probability (event)} = \frac{e^z}{1 + e^z}$$

where $z = B_0 + B_1(X_1) + B_2(X_2) \ldots B_k(X_k)$

14. The results of the Pain VAS were described and compared with the results of the RTOG and D-RTOG scores.

Ethical Considerations

Permission to conduct this study was given by Edith Cowan University Committee for the Conduct of Ethical Research on July 28, 1995 and the Institutional Ethics Committee of the study hospital on March 22, 1996 (Appendix H).

Consent

Each participant was given an information letter detailing the purpose and nature of the study and informing them of their rights as research participants. Telephone numbers were included to provide ongoing opportunity for participants to ask questions or exercise their right to withdraw (Appendix I). Fully informed, written consent was obtained from all participants before proceeding. Consent was affirmed verbally at each follow-up observation.

The research assistants were made aware of the vulnerability of patients as research participants particularly as one of the research assistants was a nurse in the Department. The issue of ensuring participants knew their rights to ask questions or to withdraw from the study was specifically targeted during training.

Confidentiality and Security of the Data

The issue of confidentiality was particularly important in this study as the data were name identified for follow-up over seven weeks and because the research office was not at the study site, necessitating transportation of confidential data. Particular care was taken in the design of the data collection forms to make it possible to facilitate follow-up by name as well as to be able to completely remove name-identification before removing forms from the Department. This was achieved by making the patient identification label removable as can be seen in Appendix F. Once in the research office the data collection forms were stored in a locked area, separate from the consent forms and master-list of participants' code numbers.

Risks and Benefits

The risks to participants in the study were minimal, as there was no change to the care given from nursing, medical or radiation therapy staff and the weekly observations were timed to coincide with treatment on the linear accelerators. The only difference was the extra time necessary to complete the consenting procedures and the interview. Only one person, approached to join the study, refused on the grounds of time.

Many participants commented that being in the study had reassured them. They felt that having their skin observed so closely meant that any adverse affect would be detected early and they would receive the help they needed straight away.

Another serendipitous benefit from participation was the opportunity for participants to talk to someone who was not directly involved with the hospital processes, but who was knowledgeable of them. Several times the interview time was extended due to the participant needing to tell the story of their diagnosis and other related events. Two women were referred, with their permission, to professional counsellors due to the distress they were suffering related to their diagnosis and other problems.

The fact that there were no withdrawals from the study suggests that any inconvenience involved in the research process were balanced by the benefits perceived by participants.

CHAPTER FOUR

RESULTS

This chapter presents the results of the two principal research objectives: Firstly, to test the theoretical relationships between factors that may impair healing and the severity of radiation skin reactions; and second, to develop a model to predict radiation skin reactions in women being treated for breast cancer.

The chapter is organised by these objectives following the description of the sample and each variable.

Descriptive Analysis

Demographic Variables

The sample comprised 126 women commencing the standard protocol of radiotherapy following surgical lumpectomy of breast cancer. The age variable was normally distributed with a mean of 53.22 years (SD = 10.64, Range = 30 – 78 years).

Sample statistics of demographic variables are shown in Table 4.1 with comparative figures for the female population in Western Australia (WA) from the 1996 census (Australian Bureau of Statistics [ABS], 1997). A typical participant in the study would be 53 years old, married (or in a long term de facto relationship), with at least a high school education although their current occupation would be classified as home duties. The participant would own or be purchasing her residence and have a weekly income of $311.

Table 4.1

Percent Distribution of Participants According to Sample Demographics for Comparison with General Population Statistics

Demographic Item	Sample (n = 126)	WA Population
Marital Status		
Never married	2.4	*8.4
Married/de facto	79.4	*67.9
Separated	0.8	4.8
Widowed	7.1	8.7
Divorced	10.3	10.1
Education/qualification		
Primary school	3.2	-
Lower secondary	31.8	42.9
Trade/secretarial	24.6	
Upper secondary	13.5	23.2
Degree/diploma	20.6	8.6
Higher degree	4.8	
Accommodation		
Own home/flat	87.3	66.7
Rent home/flat	10.3	29.0
Other e.g. Nursing home	-	4.3
Mean weekly income	$311	$307

* The ABS figures do not include de facto relationships as a separate category. Therefore, some people in de facto relationships would respond as "never married"

Occupational status was not reported in the census data in a form comparable with the study and does not appear in the table. The largest occupational group was "home duties' (34.1%) followed by clerical (19.8%), retired (16.7%) and professional (14.3%). The remaining participants classified themselves as unemployed, unskilled workers, students or skilled tradespeople.

Postal codes were used to determine the socioeconomic status of the sample using the 1996 census results (ABS, 1997). Results showed the sample had a mean weekly household income of $311. In comparing the demographic data from the sample with the population statistics from WA (ABS, 1997), the sample was reasonably representative of the general female population on most items, including income.

Radiation Construct

The organisation of the remainder of this section is based on the conceptual framework. The radiation factors: dose, doses per fraction, number of fields and treatment techniques were identical for all participants (see Chapter Three for details). It was possible for only two radiation factors to vary: overall length of time taken to complete the course of radiotherapy and the energy used for the treatment. The mean number of days taken was 38 days (SD = 2.84, range = 34 – 57 days). The mean number of days for the electron boost was 14.7 days (SD = 1.54, range = 10 - 20 days).

The other variation was the energy used for the treatment; 114 (95%) participants received their photon dose at an energy of 6MV and the remainder at 4MV. The majority received an electron boost to the scar of 9 – 16 12MeVe^- (Table 4.2).

Table 4.2

Percent Distribution of Participants According to Radiation Energy Levels Used for Electron Boost Treatment

Energy (MeVe)	Percentage of Participants
6	5.1
9	28.0
12	41.5
16	18.6
20	6.8
Total	100.0

Genetic Construct

Two items, a personal and/or a family history of cancer, represented secondary measures of genetic disposition to cancer and radiosensitivity.

Personal History of Cancer

The majority of the sample (82.5%) had not had cancer before; 15% had one previous episode of cancer and 2.5% had more than one previous episode. The types of cancer reported are summarised in Table 4.3.

Table 4.3

Frequency and Percent Distribution of Participants According to Types of Previous Cancer (N = 126).

Cancer Type	Frequency of Participants (%)
Skin cancers (including melanoma)	13 (52%)
Gynaecological (cervix, uterus)	7 (28%)
Breast cancer	3 (12%)
Other	2 (8%)
Total	25 (100%)

Overall, 21 participants reported 25 cancers. Of these, 13 participants reported having skin cancer including two cases of melanoma. A history of skin cancer was a particularly important variable on the basis that the development of skin cancers indicated significant sun damage to the skin. The criterion used to determine a history of skin cancer was a confirmed medical diagnosis and treatment. All of these had received treatment for skin cancer including liquid nitrogen, laser treatment, surgical removal and 5-Fluorouracil cream. Given the fact that medical treatment had been given, the diagnosis of skin cancer was taken as positive. There was no significant difference in age between participants with a history of skin cancer and those without a history of skin cancer as tested by an independent sample t-test.

Family History of Cancer

Overall, 69% of participants reported having one or more first or second degree relatives with a history of cancer. More than one quarter (26.4%) reported having one relative with cancer and a further 25.6% reported they had two. The remaining 10% had had between three and ten relatives with cancer.

Just over one third (39%) of participants reported a family history of breast cancer. The majority of these (67%) had one relative affected. Two participants reported four and five family members respectively.

Personal Construct – Disease-Related Factors

All participants had undergone lumpectomy for breast cancer. Histology reports revealed that the majority of tumours were Infiltrating Ductal Carcinoma (66%). The next largest group was Lobular Carcinoma (15.9%) with two participants (1.6%) having both Infiltrating Ductal and Lobular Carcinoma. The remaining tumours were classified as Adenocarcinoma (3.1%), Infiltrating Cribiform Carcinoma (1.6%), Medullary Carcinoma (0.8%) and Mucinous Carcinoma (0.8%). In 10.3% of

pathology reports specific histology typing was not reported. The recommended practice for the classification of histology type states that the tumour is ductal unless otherwise specified (Australian Cancer Network, 1997). Also, adenocarcinoma is listed as ductal meaning that a total of 79.4% of the tumours were ductal. Published figures, such as the European study of 861 describing early stage breast cancers in Kurtz et al (1989), suggest that 82% of breast cancers are ductal, suggesting that this sample was relatively typical of the breast cancer population.

Almost three-quarters (73%) of tumours were staged at surgery as Stage I, and one participant was classified as *tumour in-situ*. The next largest group was Stage II with 21.4% of participants.

Most participants (79%) began their radiotherapy within eight weeks of surgery. The remaining 21% were delayed in starting by: chemotherapy (13%); infection (1.6%); lymphocele (4.8%); one participant (0.8%) was being treated for recurrence 12 months following surgery; and one (0.8%) delayed by choice.

Personal Construct – Treatment-Related Factors

Variables in the treatment-related factors' section of the Personal Construct focused on the condition of the surgical scars, axillary lymph node clearance, the development of a lymphocele, and chemotherapy treatment.

Scar Condition Scale

The condition of the lumpectomy scars of the majority of participants (97.6%) was classified as good with the scar healing and fading. The remaining 2.4% of lumpectomy scars were still inflamed. Almost one third of participants (31%) did not have a separate scar in the axilla from clearance of axillary lymph nodes. Of the remaining 87 participants, 97.7% of the axillary scars were healing well and fading. The scar was still inflamed in one participant and there was a haemoserous discharge from the scar of another.

Axillary Lymph Node Clearance

The majority of participants (84.9%) had one or more axillary lymph node removed for pathology with a mean of 9.38 nodes (SD = 5.96 nodes, Range = 0 – 39). Of the 104 participants with nodes removed 20 (19.2%) had one or more nodes affected by cancer with a mean of 2.75 nodes affected (SD = 2.43, Range 1 – 8).

Lymphocele Drainage

Over half of the participants (55.6%) did not develop a lymphocele that required draining by needle aspiration following surgery. Table 4.4 details the frequency of needle aspirations. Seven participants required that straight drainage be re-commenced after going home due to the build-up of lymph fluid.

Table 4.4

Percent Distribution of Participants According to the Number of Needle Aspirations for Lymphocele (N = 126)

Number of Aspirations	Percentage of Participants
None	55.6
1	9.5
2	7.1
3	6.3
4	4.8
5	5.6
≥ 6 (including those recommenced on straight drainage)	11.1
Total	100.0%

Chemotherapy for Breast Cancer

Participants receiving chemotherapy were classified into two groups.

1. those who had four cycles of Etoposide and Cyclophosphamide (EC) over three months prior to radiotherapy and a further three cycles of

Cyclophosphamide, Methotrexate and 5-Fluorouracil (CMF) concurrently with radiotherapy; and

2. those who had six cycles of CMF beginning at approximately the same time as their radiotherapy.

An independent sample t-test analysis revealed that those participants receiving chemotherapy were significantly younger than those not receiving chemotherapy for breast cancer ($t(124) = 2.10$, $p = 0.038$).

Personal Construct – General Health Factors

The variables included in the general health section of the Personal Construct were those specifically relating to factors known to impair wound healing.

Chronic Illness

More than half of the participants (52.4%) reported having current chronic illness with 22% reporting two or more diagnoses. In total, 21 diagnoses were reported but none were classified as radiosensitive conditions. The most commonly occurring chronic illness was osteoarthritis (16.7%) followed by hypertension (15.2%), followed by asthma and cardiac conditions an equal third (10.6%).

An independent sample t-test analysis revealed, as expected, that participants with chronic illness were significantly older than those reporting no chronic illness ($t(124) = -4.62$, $p = 0.000$). An independent sample t-test analysis also revealed that participants with a current chronic illness were significantly higher in weight than those reporting no chronic illness ($t(123) = -2.66$, $p = 0.009$).

Prescribed drugs, Self medication and Complementary medicines

The majority of participants (62.7%) were taking prescribed medications on a regular basis. However, none of these drugs had a possible side effect of photosensitivity. Only two participants were taking drugs that could impair healing; these were steroids taken regularly for asthma. One fifth of participants were taking

Tamoxifen as part of their treatment for breast cancer. This group were significantly older than participants not taking Tamoxifen as tested by an independent sample t-test (t (124) = -4.66, p= 0.000).

Participants were asked an open-ended question to report their use of over-the-counter pharmaceuticals and complementary medicines. To assist data collection, three categories were given to determine the purpose or effect of the medicine; for general health, to aid healing, and as an anticancer treatment. Participants could nominate to which of these categories the medicine belonged or explain its use in their own words. No new categories were formed. In total, 74 (58.7%) of participants were self-medicating or taking complementary medicines prescribed by a naturopath. Of these, 58 (78.4%) were taking these medicines to improve their general health, 15 (20.3%) were taking them to aid healing and 16 (21.6%) were taking them as complementary anticancer treatments.

Participants classified the reason for taking complementary medicines differently. For example for some taking antioxidants was for their general health and for others it was an anticancer treatment. Details of the complementary medicines taken by participants can be found in Appendix J. In addition to taking complementary medicines two participants were receiving acupuncture as an anticancer treatment concurrently with radiotherapy.

The Relationship between Chronic Illness and Medication Use

Chi-square analysis revealed a significant association between the chronic illness and the use of prescribed medications, with both the dichotomous prescribed medication variable (χ^2 (1) = 142.48, p = .000) and the three level prescribed medication variable (χ^2 (2) = 184.32, p = .000). There was no association between reporting a chronic illness and taking complementary medicines, which is confirmed by the finding that the majority of participants were taking these medications to improve general health. There was, however, a significant association between

taking prescribed medications and complementary medicines (χ^2 (1) = 9.52, p = .002).

Smoking History

Just over half of the participants (52.1%) had a history of smoking. For the analysis, smoking history was collapsed into a three-level variable, with 45 (47.9%) in the never smoked group, 36 (38.3%) in the ex-smoker group, and 13 (13.8%) in the current smoker group. All the ex-smokers, except one, had quit more than 12 months prior to commencing radiotherapy. Of the current smokers nine (69.2%) smoked 15 or less cigarettes per day, two (15.4%) smoked 20 cigarettes per day, and two (15.4%) smoked 40 cigarettes per day.

Alcohol Intake

The majority of participants (64.3%) reported that they consumed alcohol. However, just over half of all participants (55.6%) indicated they had decided not to drink during treatment.

Nutritional Status

Nutritional status was indexed by body weight in kilograms, height in centimetres and by intake as assessed by the nutrition subscale of the Braden Scale (1992). The mean weight of the sample at commencement of radiotherapy was 66.9kg (SD = 13.4, range = 42 – 112kg). The weight variable was normally distributed.

Measurement of height was taken to establish the body mass index (BMI) of participants. BMI was then classified into three groups for further analysis, 9.6% of participants were underweight (BMI < 20), 69.1% were of normal weight (BMI 20 - 25), and 21.3% were overweight (BMI > 25).

Important to nutritional status is any recent change in weight. The range of reported weight change in the sample was from –13 kg to + 12kg although 57.4% had not changed their weight since diagnosis.

The majority of participants had an "excellent" intake of food (81.4%) according to the Braden Scale assessment of nutritional intake. Of the remainder, 17% reported an "adequate" intake and only 1.6% had a "probably inadequate" intake. No participants were assessed as having a "very poor" intake.

In addition to nutritional intake, participants were asked if they had changed their diet since being diagnosed with breast cancer. Only 9.6% reported a change in diet. The changes consisted of a reduced intake of fats and red meat, and an increased intake of fibre through fresh fruit and vegetables.

Breast Size

Breast size was indexed by the brassiere size and cup size. The range of brassiere size was size 10 to 22 with almost two thirds of the sample being size 12 or 14. The frequencies for cup size are shown in Table 4.5.

Table 4.5

Percent Distribution of Participants According to Brassiere Cup Size and the Dichotomous Breast Size Variable (N = 124)

Cup Size	Percentage of Participants
A	13.0
B	31.7
C	30.1
D	17.1
≥ DD	8.1
Total	100.0%

Personal Construct – Skin Condition Factors

Skin Condition and Allergies

Participants rated the skin condition in the treatment area as oily, normal or dry. The majority (78.6%) rated their skin as normal, 19% rated it as dry and the remainder (2.4%) rated their skin as oily.

Less than half the sample (42.1%) reported having skin allergies. Most avoided contact with the allergen but rated the severity of the reaction if it did occur to be mild (31%), moderate (41.1%) or severe (27.7%). Participants reported allergic reactions to a variety of substances including foods, plants, make-up, detergents and jewellery. In addition, 36.5% reported a family history of skin allergies.

Skin Reaction to UV Radiation.

Results of participants' reports of their skin reaction to UV radiation as measured by the Fitzgerald Scale are shown in Table 4.6.

Table 4.6

Percent Distribution of Participants According to Skin Reaction to UV Radiation (N = 126).

Fitzgerald Scale	Percentage of Participants
1	12.7
2	18.3
3	35.7
4	29.4
5	4.0
6	0.0
Total	100.0%

Cumulative UV Radiation Exposure

This variable was first analysed by examining frequencies for each item of the scale (see Table 4.7). Scores of the two items of the child exposure subscale (possible score range 2 – 7) and three items of the adult subscale (possible score range 3 – 10) were calculated and combined into a total score being the sum of the five items (possible score range 5 – 17). The mean of the child exposure subscale was 5.6 (SD = 1.4 range = 2 - 7). The mean of the adult exposure subscale was 5.5 (SD = 1.5 range = 3 - 9). The mean of the total UV exposure scale was 11.2 (SD = 2.4 range = 6 - 16).

Table 4.7

Percent Distribution of Participants According to Individual Items on the Cumulative UV Radiation Exposure Scale (N = 126)

Item	Percentage of Participants
Free time as a child spent in:	
1. Indoor activities	12.7
2. Indoor and outdoor activities	42.9
3. Outdoor activities	44.4
Sun protection as a child used	
1. Almost always	13.5
2. Often	4.0
3. Sometimes	16.7
4. Almost never	65.9
Work as an adult was (or is) mainly	
1. Indoors	81.7
2. Both indoors and outdoors	16.7
3. Outdoors	2.0
Free time as an adult spent in:	
1. Indoor activities	18.3
2. Indoor and outdoor activities	55.6
3. Outdoor activities	26.3
Sun protection as an adult used	
1. Almost always	36.5
2. Often	23.8
3. Sometimes	19.8
4. Almost never	19.8

The impact of the sun on the skin is dependent on the geographic location and residents of Australia are known to come from a wide range of countries. Therefore, participants were asked the predominant place they lived as a child and an adult. More than half of the participants (52.4%) had lived in Perth as a child and as an adult. The next largest group were those who lived in the UK and Europe (34.3%) as a child, but spent most of their adult life in Australia. The mean length of time lived in Australia was 41 years (SD = 18 years, range = 2 – 76 years).

Analysis of Whole Breast Radiation Treatment (Weeks One to Five)

Description of the RTOG Scores Weeks One to Five

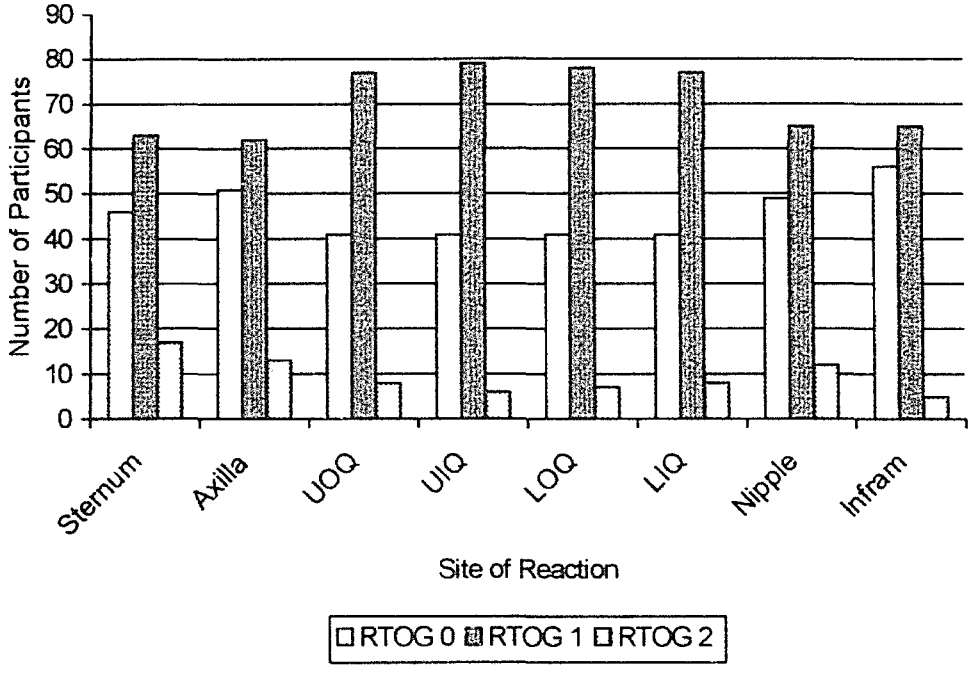
RTOG scores for the dependent variable for each anatomical area are shown in the following figures by week of treatment. One week of treatment is equivalent to five daily fractions of radiation. For the first five weeks the daily dose is 1.8 Gy. Thus, the doses for week one were 1.8 Gy to 9 Gy; week two were 10.8 Gy to 18 Gy; week three are 19.8 Gy to 27 Gy; week four are 28.8 Gy to 36 Gy; week five were 37.8 Gy to 45 Gy. Results for weeks six and seven, which are the 10 days of electron boost to the scar, are presented later in the chapter.

RTOG Scores for Weeks One and Two

In week one, no participants scored RTOG 2 or more with the vast majority scoring "0" for all anatomical sites except the nipple. One participant scored RTOG 2 in week one; this was related to inflammation of the lumpectomy scar that was located very close to the nipple. In week two, three participants scored RTOG 2 on the nipple; two participants had more severe reactions on the sternum, two in the inframammary fold; and one in the axilla, UOQ and LIQ areas.

RTOG Scores for Week Three

In week three, as expected, a number of participants showed signs of a more severe skin reaction. Figure 4. I illustrates the RTOG scores over the eight sites for the third week of treatment. The more severe reactions categorised as a RTOG 2 score or higher, were not common. The site with the most frequent severe reactions was the sternum (17 participants). The description in the comments accompanying the data collection report the sternum reactions to be follicular rashes with some blistering noted. The second most frequent site for severe reactions was the axilla with 13 participants demonstrating more severe reactions at this location.

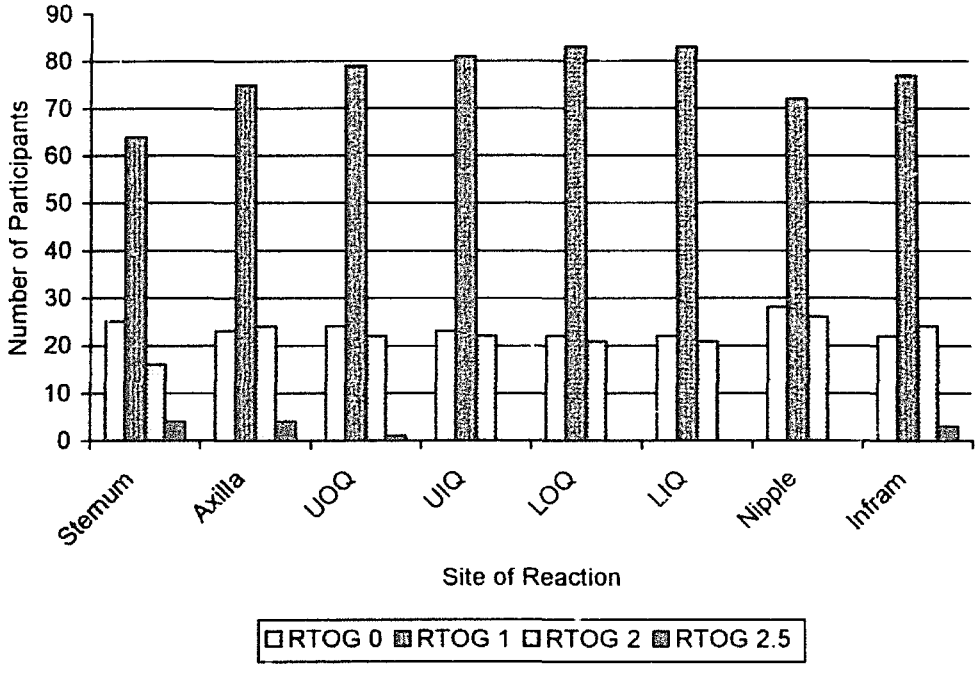


Infram = Inframammary Fold

Figure 4.1 Frequency Distribution of Participants According to RTOG Scores by Anatomical Site for Week Three of Treatment

RTOG Scores for Week Four

The frequency of more severe radiation skin reactions increased in week four as expected. Figure 4.2 illustrates the distribution of RTOG scores. Patchy moist desquamation, indicated by scores of RTOG 2.5, began to appear during week four of treatment. The areas affected were the axilla, UOQ and the inframammary fold areas. Skin loss on the sternum was different to the other areas, as the blistering reaction, noted in week three, broke down and oozed serous fluid. The reactions in the axilla, UOQ and inframammary fold were typical radiation moist desquamation reactions.



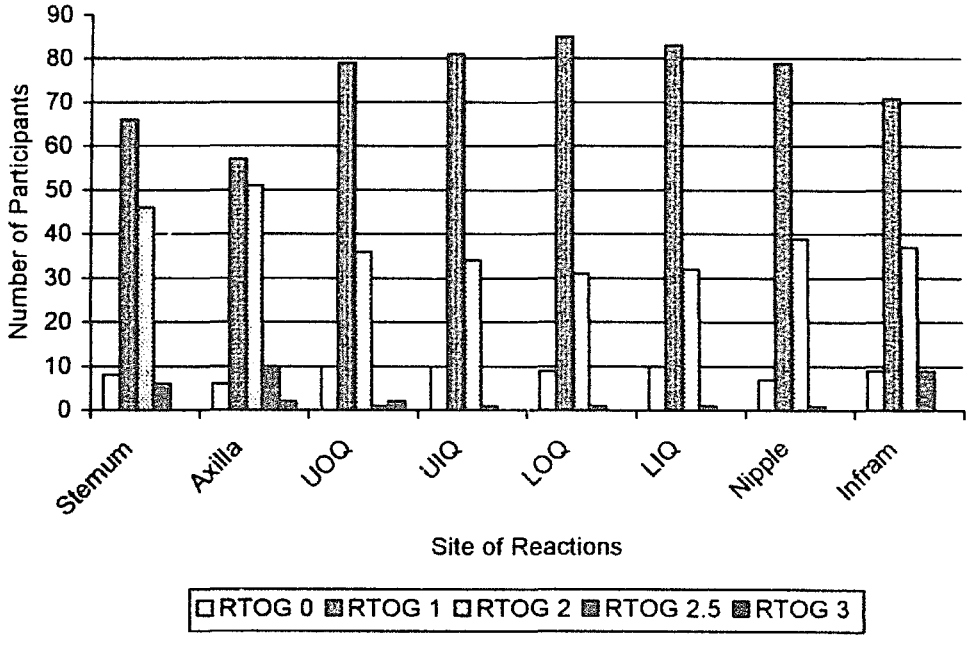
Infram = Inframammary Fold

Figure 4.2 Frequency Distribution of Participants According to RTOG Scores by Anatomical Site for Week Four of Treatment

RTOG Scores for Week Five

The frequency of patchy moist desquamation (RTOG 2.5) increased again during week five of treatment. In addition, confluent moist desquamation (RTOG 3) was recorded for the first time in the axilla and UOQ reactions. Figure 4.3 illustrates the distribution of RTOG scores for week five.

Patchy moist desquamation in the sternum area continued to be the result of the blister reaction noted in earlier weeks. The number of participants with patchy moist desquamation and confluent moist desquamation also increased in the axilla and inframammary reactions.



Infram = Inframammary Fold

Figure 4.3 Frequency Distribution of Participants According to RTOG Scores by Anatomical Site for Week Five of Treatment

Frequency of Moist Desquamation

Patchy moist desquamation (RTOG 2.5) occurred in four sites during the course of treatment: the sternum, axilla, UOQ and inframammary fold. Two of these sites, the axilla and UOQ, recorded the occurrence of confluent moist desquamation (RTOG 3). Figure 4.4 illustrates the time trends for the development of moist desquamation in this sample for the four sites. The figure includes the weeks of the electron boost to consider the pattern of moist desquamation over the full treatment time.

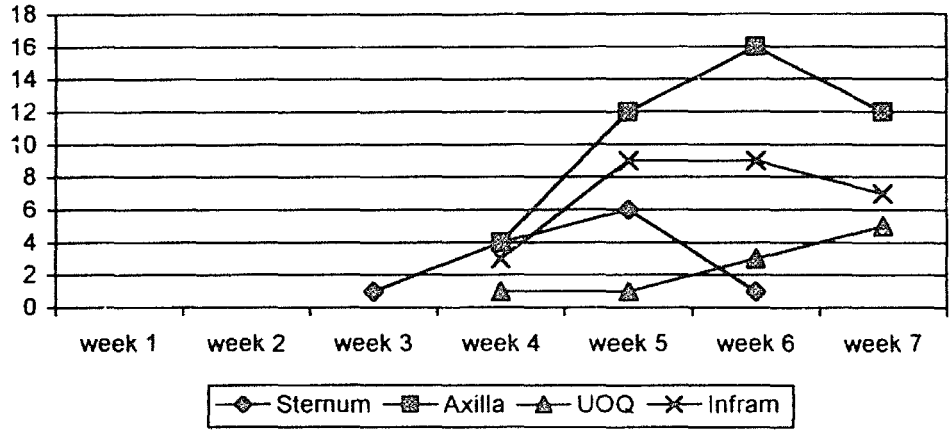


Figure 4.4 Time Trends for the Development of Patchy or Confluent Moist Desquamation in the Four Most Affected Sites

The pattern that emerged was as expected with skin loss reported in all four sites by week four. Skin loss in the sternum began in week three, but healed by week seven, an understandable pattern, as electron boosts were not administered to the sternum.

The axilla had the highest frequency of moist desquamation, peaking in week six and falling slightly in week seven. Although the axilla was a site for electron boost treatment, most participants had no treatment to this area in weeks six and

seven. The peak of the axilla reaction in week six probably indicates a carry-over effect from the end of the whole breast treatment completed in week five.

The frequency of moist desquamation in the UOQ showed a steady increase through weeks six and seven. This was expected given the fact that most of the electron boost treatments in this sample were in the UOQ.

The development of moist desquamation in the inframammary fold site followed a similar pattern to that of the axilla. Again healing was noted as the severity of the reaction decreases during week seven.

Testing the Theoretical Relationships of the Conceptual Framework in Radiation Skin Reactions during Whole Breast Treatment

To ensure the validity of univariate and multivariate testing, several predictor variables were re-coded to overcome the problem of empty cells. A standard approach was taken. First, a dichotomous variable was created with "0" indicating no and "1" indicating yes. For example if the participant did not have a history of skin cancer they would score "0", if they did, the score would be "1". Further subdivision was tested, however, in all cases this did not reveal any further significant detail. Table 4.10 details the proportion of scores in re-coded variables.

Table 4.8

Percent Distribution of Participants According to Re-coded Predictor Variables

Predictor Variable	Percentage of Participants No	Yes
History of Cancer (not skin cancer)	82.5	17.5
History of Skin Cancer	89.7	10.3
Tumour Stage ≥ II	73.8	26.2
Aspiration of Lymphocele	55.6	44.4
Chemotherapy for breast cancer (overall)	87.3	12.7
Chemotherapy commenced concurrently with radiation	89.7	10.3
Chemotherapy before radiation (part or all of chemotherapy treatment)	96.8	3.2
Breast size ≥ D cup	74.8	25.2
Skin type – Fitzgerald scale ≥ 3	31.0	69.0

Univariate Testing of Potential Predictive Factors during Whole Breast Treatment

The distributions of the RTOG scores were not normal for any of the anatomical sites in any week. The RTOG scores were re-coded into dichotomous variable values (D-RTOG). A score of "0" or "1" became D-RTOG 0, (a mild or no reaction) and a score of "2" or more became D-RTOG 1, (a severe reaction). Weeks one and two had extremely few scores in D-RTOG 1. Participants who scored D-RTOG 1 in weeks one and two were all found to have developed a breast infection. Therefore, the univariate testing focussed on weeks three to five only.

For continuous variables, independent sample t-tests were performed to test relationships between potential predictor variables and skin reactions (D-RTOG scores). Table 4.9 presents the significant t-test results ($\alpha = 0.10$) for weeks three, four and five. Each predictive factor was tested for association with the D-RTOG

scores for each anatomical site for each week of treatment. Chi-square analysis was performed on categorical variables (α = 0.10) (see Tables 4.10, 4.11 and 4.12)

Table 4.9

Significant Relationships between Site and Continuous Predictor Variables for Weeks Three, Four and Five as Measured by t-test (p-value).

Anatomical Site	Current Weight	Dose	UV child sub-score	Total UV score
Week 3 Sternum		-1.95 (.053)		
Week 3 Axilla	-3.06 (.003)			
Week 3 UOQ			1.96 (053)	
Week 3 UIQ			2.46 (.015)	
Week 3 LOQ		-1.74 (.085)	3.09 (.002)	
Week 3 Nipple		-1,92 (.057)		
Week 3 Inframammary Fold				2.52 (.013)
Week 4 Axilla	-2,93 (.004)			
Week 4 UOQ		-2.13 (.035)		
Week 5 Axilla	-4.05 (.000)			
Week 5 UOQ	-2.35 (.021)	-3.11 (.002)		
Week 5 UIQ	-1.81 (.073)	-4.07 (.000)		
Week 5 LOQ	-2.22 (.028)	-3.38 (.001)		
Week 5 LIQ	-2.22 (.028)	-3.13 (.002)		
Week 5 Nipple		-2.46 (.015)		
Week 5 Inframammary Fold	-3.93 (.000)			

Table 4.10

Significant Relationships in Dichotomous RTOG Scores for Week Three According to Site as Tested by Chi-square (p-value)

Site	Breast size	Lympho-cele	Condition of breast scar	Chemo-therapy before radiation	Concurrent chemo-therapy	Family history of cancer	Chronic illness	Smoke	Stage ≥ II	Tamoxifen	Skin-type	History of skin cancer
Sternum											4.44 (.04)	7.74 (.00)
Axilla	6.33 (.01)	3.61 (.06)				5.94 (.01)	3.50 (.06)	5.39 (.07)	2.99 (.08)	3.59 (.06)		
UOQ	2.79 (.09)	10.68 (.00)	3.76 (.05)									
UIQ	5.75 (.02)	7.88 (.00)	5.53 (.02)	3.73 (.05)	3.61 (.06)							
LOQ	4.02 (.04)	9.26 (.00)	4.52 (.03)	2.98 (.08)								
LIQ	2.79 (.09)	10.68 (.05)	3.76 (.00)									
Infra-mammary	3.35 (.07)					11.19 (.00)						

Table 4.11

Significant Relationships in Dichotomous RTOG Scores for Week Four According to Site as Tested by Chi-square (p-value)

Site	Alcohol intake	Breast size	Chemo-therapy	Concurrent chemo-therapy	Chemo-therapy before radiation	Condition of breast scar	Skin-type	Family history of skin allergies	History of skin cancer	Smoke	Tamoxifen
Sternum							3.70 (.05)		15.80 (.00)		
Axilla		15.48 (.00)	4.91 (.03)	4.80 (.03)							5 99 (01)
UOQ		8.74 (.00)			2.79 (.09)	4.83 (.03)					
UIQ	6.23 (.04)					5.16 (.02)		3.74 (05)			
LOQ	6.52 (.04)					5.53 (.02)		2.74 (.09)	4.96 (03)	6.00 (05)	
LIQ	6.52 (.04)	4.96 (.02)				5.53 (.02)		2.73 (09)	4 96 (.03)	6.00 (05)	
Nipple	5.52 (.06)	4.29 (.04)							2.81 (09)		
Infra-mammary		3.07 (.08)	5.42 (.02)	5.26 (.02)						6.32 (04)	

Table 4.12

Significant Relationships in Dichotomous RTOG Scores for Week Five According to Site as Tested by Chi-square (p-value)

Site	Breast size	Smoke	History of cancer -not skin	Lymphocele	History of skin allergies	Tamoxifen	History of skin cancer	UV protection used as an adult
Sternum							11.24 (00)	6 85 (08)
Axilla	5.46 (.02)	3.18 (.07)		3.21 (.07)				
UOQ	9.14 (.00)	4.81 (.09)		3.22 (.07)				
UIQ	5.68 (.02)			3.16 (.08)				
LOQ	7.89 (.00)	5.25 (.04)	3.30 (.07)					
LIQ	3.02 (.08)	8.95 (.01)			2 86 (.09)			
Nipple	3.02 (.08)	8.70 (.01)	4.51 (.03)					
Inframammary	17.34 (.00)	14.10 (00)	5.57 (.01)			3.67 (.06)		

Testing for Potential Covariates

A potential source of covariance was the nursing interventions used as standard practice during the course of radiation therapy. Particularly important was the use of creams and emollients. The premise for using these products was to promote patient comfort. There is no empirical evidence to date that suggests that creams used have a significant impact on reducing the severity of the skin reaction. In addition, the governing principle for deciding which cream is used and how often, is patient preference.

The null hypothesis that there was no significant association between using cream and the severity of skin reaction was tested by Chi-square analysis for weeks three, four and five at each site. No significant associations were detected for any of these tests, indicating that cream use was not associated with the severity of the skin reaction.

Development of Predictive Models for Radiation Skin Reactions during Whole Breast Treatment

Logistic regression analyses were conducted on the D-RTOG scores for each anatomical site for weeks three to five. The predictive value of all independent variables, identified from the conceptual framework, was tested by stepwise logistic regression analysis on the D-RTOG score for each site. Due to the exploratory nature of the study a variable entry level was set at $\alpha = 0.10$ and removal level was set at $\alpha = 0.15$ (Tabachnick and Fidell, 1996). This prevented the premature deletion of variables that may be clinically significant even if not reaching the usually accepted $\alpha = 0.05$ level for statistical significance. This decision increased the likelihood of Type II errors in hypothesis testing, meaning that there could be an increased chance of false positive results. This is an acceptable clinical error in the case of radiation skin reactions as it represents a cautious approach.

Results from the week five reactions are presented first as week five represents the main effect of radiation on the skin in the treatment area during whole breast irradiation. The results for the sternum reaction are used as a full example of the method of interpreting logistic regression analysis including the calculation of relative risk and the interpretation of confidence intervals.

Week Five Prediction Models

The D-RTOG scores recorded during week five represent the reactions experienced during the last five doses of whole breast treatment (Dose range = 28.8 Gy – 45 Gy). In most cases, these reactions will not become any more severe following the last dose, except for the site of the electron boost treatment. Thus, the results of the stepwise logistic regression analysis for the radiation skin reactions observed at each site in week five represents the prediction of the worst radiation skin reaction experienced during whole breast irradiation.

Week five sternum reaction results.

Data from all 126 women were available for analysis: 74 (58.7%) had a score of D-RTOG0 and 52 (41.3%) scored D-RTOG1. Of the variables tested, two entered the model: history of skin cancer and age. These two factors correctly predicted 97.3% of cases with mild or no reactions, and 26.92% of cases with severe reactions giving an overall accuracy of 68.25% for the model.

The use of a Chi-square test (Tabachnick & Fidell, 1996) determines whether the model is a significant improvement over the observed frequencies alone. This is expressed as a significantly reliable model. The model for the week five sternum reaction was significantly reliable when compared with the constant only model, $\chi^2(2) = 14.407$, $p = 0.000$, indicating that the predictors, as a set, reliably distinguished between the D-RTOG0 and D-RTOG1 scores. Table 4.13 shows details of the regression analysis for each of the two predictors.

Table 4.13

Logistic Regression Results for the Week Five Sternum Reaction

Variables	B	SE	Wald	DF	Sig	R	Exp(B)	95% CI
History of skin cancer	2.462	.808	9.272	1	.002	.206	11.723	2.404 - 57.170
Age (per year)	-.030	.018	2.713	1	.099	-.064	.970	.938 – 1.006
(Constant)	1.020	.973	1.099	1	.294			

From these results, the relative risk of developing a more severe sternum reaction in week five is 11.7 times greater in an individual with a history of skin cancer when compared with an individual with no history of skin cancer.

Relative risk calculation.

The regression equation for calculating the probability of experiencing a more severe skin reaction in the sternum is:

$$= \frac{e^z}{1 + e^z}$$

where

$$z = B_0 + B_1X_1 + B_2X_2$$

Using the week five data, estimates of model parameters give the regression equation:

$$z = 1.0202 + 2.4616(\text{skin cancer}) \ -0.0303(\text{age})$$

For example, consider an individual who has a history of skin cancer and who is 60 years of age. The calculation for the probability of developing a severe skin reaction on the sternum during week five of treatment is as follows:

As the individual has a history of cancer, the value of X_1 (where 0 = no history of cancer and 1 = history of cancer) is 1 and the value of X_2 (age in years) is 60, then:

$$z = 1.020 + 2.461(1) - 0.030(60) = 1.6638$$

The probability of a severe skin reaction is then

$$= \frac{e^z}{1 + e^z} = \frac{e^{1.6638}}{1 + e^{1.6683}} = 0.8407$$

In other words this individual has an 84% likelihood of developing a score of D-RTOG = 1, that is a standard RTOG score of $\geq$ 2, in week five of treatment.

If the probability of the individual developing a severe reaction is 0.841, then the probability of not developing a severe skin reaction is therefore:

$$1 - 0.8407 = 0.1593$$

Comparing these probabilities, the odds ratio (or risk) of developing a severe skin reaction is:

$$0.8407 : 0.1593 = 5.227 : 1$$

Therefore, this 60-year-old individual with a history of skin cancer is 5.227 times more likely to develop a severe skin reaction than not to develop a severe skin reaction.

Consider now an individual of the same age who does not have a history of skin cancer. The calculation for the probability of developing a severe skin reaction on the sternum during week five of treatment is as follows:

As the individual has no history of cancer, the value of X_1 (where 0 = no history of cancer and 1 = history of cancer) is 0 and the value of X_2 (age in years) is 60, then:

$$z = 1.020 + 2.461(0) - 0.030(60) = -.7978$$

$$= \frac{e^{z}}{1+e^{z}} = \frac{e^{-.7978}}{1+e^{-.798}} = 0.3105$$

In other words, this individual has only a 31% likelihood of developing a score of D-RTOG = 1, that is a standard RTOG score of ≥ 2, in week five of treatment.

The probability of the individual not developing a severe skin reaction is, therefore:

$$1 - 0.3105 = 0.6895$$

Comparing these probabilities, the odds ratio of the individual developing a severe skin reaction, or not developing a severe reaction, is:

$$0.3105 : 0.6895 = 0.4503 : 1$$

Therefore, a 60-year-old individual who does not have a history of skin cancer is only 0.4503 times more likely (meaning the individual is less than half as likely) to develop a severe skin reaction, than not to develop a severe skin reaction.

The effect of the history of skin cancer is to increase the odds, or risk, of a severe skin reaction from 0.4503 : 1, to 5.227 : 1

thus:

$$5.227 / 0.4503 = 11.7233$$

$$= \exp(2.4616)$$

The relative risk of a severe skin reaction, therefore, is 11.7233 times greater for an individual with a history of skin cancer. The relative risk is calculated automatically by the computer and can be found in the Exp(B) column of Table 4.13.

As the stepwise logistic regression resulted in a regression equation with no significant interaction term, the relative risk of a history of skin cancer on developing a severe reaction is constant for all ages. Thus, the relative risk of 11.7233 applies for individuals of all ages, not just a 60-year-old.

The process is the same for calculating the impact of age on the severity of the skin reaction. In this case, the inverse relationship between age and the sternum reaction, shown by the negative B result, means that as age increases the relative risk of a severe skin reaction reduces.

For example, consider an individual with no history of skin cancer who is 30 years of age. The calculation for the probability of developing a severe skin reaction on the sternum during week five of whole breast treatment is as follows:

As the individual has no history of cancer, the value X_1 (History of skin cancer) = 0 and the value of X_2 (age) = 30,

then:

$$z = 1.0202 + 2.4616(0) - 0.0303(30) = 0.1112$$

The probability of a severe skin reaction is:

$$\frac{e^z}{1+e^z} = \frac{e^{0.1112}}{1+e^{0.1112}} = 0.5277$$

In other words this individual has a 52.7% likelihood of developing a severe skin reaction.

If the probability of the individual developing a severe reaction is 0.5277, then the probability of not developing a severe reaction is:

$$1 - 0.5277 = 0.4723$$

Comparing these probabilities, the odds ratio or risk of developing a severe skin reaction is:

$$0.5277 : 0.4723 = 1.1173 : 1$$

Consider then the individual in the previous example who was 60 years of age and had no history of skin cancer. Recall that the risk of developing a severe reaction for this individual was 0.4503 : 1.

To compare the effect of age between a 60-year-old and a 30-year-old the odds ratio, or risk, of a severe skin reaction is:

$$0.4503 / 1.1173 = 0.4030$$

In the example calculating the relative risk of a severe skin reaction due to having a history of skin cancer, this final result would represent the relative risk, or Exp(B), as listed on the table (11.723). However, the calculation of the relative risk with a continuous variable differs from the calculation of an indicator (dummy) variable in that the relative risk accounts for the effect of one year only. This means that the relative risk for a specific age difference is the relative risk per year raised to the appropriate power. Thus to calculate the relative risk of an age difference of 30 years (60 – 30 years) the Exp(B) must be raised to the power of 30.

then,

$$0.9701^{30} = 0.4030$$

This means that when no history of skin cancer is reported, the 60 year old individual is less than half as likely to develop a severe skin reaction in week five than a 30-year-old individual.

In a similar way, each logistic regression table lists the estimates of model parameters specifying the regression equation enabling the calculation of the probability of a severe skin reaction for any individual. In addition, each listed value of the relative risk (Exp(B)) enables us to summarise the effect of each factor on the likelihood of developing a severe skin reaction.

Confidence intervals.

Confidence intervals for logistic regression analysis are calculated for the estimated exponential B values (Exp(B)) or relative risk. It must be remembered that Exp(B) values and the limits of confidence intervals are in an exponential scale therefore the Exp(B) value does not fall in the middle of the interval but closer to the

lower limit. Also, when the estimated Exp(B) value is large, then consequently the confidence interval will be large. In the sternum reaction model for week five, history of skin cancer has a large estimated Exp(B) value and this is reflected in the wide range for the confidence interval.

Other than these points, the usual rules for interpretation stand. The confidence interval is testing that:

$$B \neq 1$$

Therefore, the confidence interval should not include "1". Occasionally the lower limit of the confidence interval is less than 1.00 as in the case of "age" in the week five sternum reaction model. There are three potential explanations for this finding. A lower confidence interval limit of < 1.00 can result from:

1. A small estimated Exp(B) value (< 1.00).
2. Accepting a significance level of 0.10 for entry of predictors to the model has weakened the statistical power for testing that predictor.
3. The predictive factor being represented by a small number of participants resulting in a loss of statistical power to detect the effect of the predictor.

The first two of these explanations apply to "age" in the sternum reaction model; the Exp(B) value is less than 1.00 and the significance level for age is 0.099.

Week five axilla reaction results.

After deletion of one case due to missing values, data from 125 women were available for analysis: 63 (50.4%) had a score of D-RTOG0 and 62 (49.6%) scored D-RTOG1. Two variables entered the model: lymphocele aspirated and current weight. These two variables correctly predicted 76.19% of cases with mild or no skin reactions and 69.35% of severe reactions, giving an overall accuracy of 72.80% of cases overall. The model was significantly reliable when compared with the constant only model, $\chi^2(2) = 19.872$, $p = 0.0000$, indicating that the predictors, as a set,

reliably distinguished between the D-RTOG0 and D-RTOG1 scores. Table 4.14 shows details of the regression analysis for each of the two predictors.

Table 4.14

Logistic Regression Results for the Week Five Axilla Reaction

Variables	B	SE	Wald	DF	Sig	R	Exp(B)	95% CI
Lymphocele aspirated	.788	.395	3.984	1	.046	.107	2.199	932 – 4.322
Weight (per kilogram)	063	.017	13.189	1	.000	.254	1.065	1.028 – 1.098
(Constant)	-4.530	1.194	14.384	1	.000			

Those participants who had developed a lymphocele requiring drainage had a relative risk of developing a more severe skin reaction 2.2 times greater than those who did not. The relative risk is based on the weight of the participant in kilograms, therefore the relative risk of developing a more severe reaction increases 1.065 times per kilogram increase in weight. Thus the magnitude of the impact of weight on severity of skin reaction becomes more apparent.

The equation for calculating the probability of experiencing a more severe skin reaction in the axilla then, is:

$$\frac{e^{-4.5301 + .7882(\text{lymphocele}) + 0.0626(\text{weight})}}{1 + e^{-4.5301 + .7882(\text{lymphocele}) + 0.0626(\text{weight})}}$$

It is possible to compare the impact of these two predictors despite one being an indicator variable (lymphocele aspiration) and the other being continuous (weight in kgs), to answer the question: what weight difference corresponds with the risk associated with having had a lymphocele aspirated?

The process illustrated in the calculation of relative risk for an age difference is also used in this example. The relative risk of a severe skin reaction is ExpB = 1.0646 which means that the relative risk of severe skin reaction for a weight

difference of dkg (where d = difference in weight) is 1.0646^d. To calculate the impact of weight compared with the impact of lymph drainage, then the value of d must be calculated when

$$1.0646^d = 2.1995$$

That is when

$$d = {}^*\ln 2.1995 / \ln 1.0464 = 12.6$$

*ln = natural log

The effect of an increase in weight of 12.6 kg is equivalent, in risk, to an individual who has had a lymphocele aspirated. That is an individual who is 72.6 kg in weight, but has not had a lymphocele aspirated, has the same risk of developing a severe skin reaction as an individual who is 60 kg in weight but has had a lymphocele aspirated. This calculation illustrates the magnitude of the weight variable on the development of severe skin reactions.

Week five upper outer quadrant (UOQ) reaction results.

After deletion of three cases due to missing values, data from 126 women were available for analysis: 86 (68.2%) had a score of D-RTOG0 and 37 (31.8%) scored D-RTOG1. Five variables entered the model: breast size, dose group, lymphocele aspirated, smoking and stage. Dose was re-coded (dose group) into dichotomous variable values with 37.8 Gy to 43.2 Gy (fractions 1-4 in the 5th week of treatment) = 0, and 45 Gy (5th fraction in the 5th week of treatment) = 1. This was done to account for a non-normal frequency distribution for dose and the need to estimate risk for the highest dose received in the whole breast treatment.

These five variables correctly predicted 88.24% of mild or no skin reactions and 42.11% of severe skin reactions giving an accuracy of 73.98% overall. The model was significantly reliable when compared with the constant only model, $\chi^2(6) = 24.463$, $p = 0.0004$, indicating that the predictors, as a set, reliably distinguished

between the D-RTOG0 and D-RTOG1 scores. Table 4.15 shows details of the regression analysis for each of the five predictors.

Table 4.15

Logistic Regression Results for the Week Five UOQ Reaction

Variables	B	SE	Wald	DF	Sig	R	Exp(B)	95% CI
Breast size	1.025	.478	4.610	1	.032	131	2.788	1.093 – 7.112
Dose group	1.050	.528	3.949	1	.047	.113	2.856	1.015 – 8.042
Lymphocele aspirated	1.044	.468	4.974	1	.026	.140	2.840	1.135 – 7.105
Stage group	.852	.492	3.000	1	.083	.081	2.343	.894 – 6.150
*Smoking			6.670	2	.036	.133		
Ex-smoker	0.480	.481	0.994	1	.320	.000	1.620	.630 – 4.150
Current smoker	1.780	.692	6.615	1	.010	.174	5.930	1.530 – 23.019
(Constant)	-2.491	.500	25.122	1	.0000			

*Reference group for smoking is the "never smoked" group

For breast size, where the cup size is "D" or more, the risk of having a more severe reaction is almost three times greater than if the cup size is "A, B or C". The last fraction of the whole breast treatment (45 Gy), increases the risk of severity by almost three times. For women who have had a lymphocele aspirated one or more times, the relative risk of a more severe reaction is almost three times greater than if no drainage was performed. For those participants whose tumour was stage II or greater at surgery, the relative risk of developing a more severe reaction in week five is over twice as great than for participants who were stage I or tumour in situ. This result must be considered with cautioun as the confidence includes 1. The smoking predictor reveals a slight increase in risk for ex-smokers but a high relative

risk six times greater for those smoking through treatment than for those who have never smoked. The confidence interval includes 1 for the ex-smokers, however the ex-smoker group was not at significant risk.

The lower limits of the confidence intervals for stage group and ex-smokers are both less than 1.00. In the case of these two predictors the explanation lies in the significance level being > 0.05 for entry into the model. In the case of ex-smokers the significance level is 0.320 and is included in the model only as a level of the smoking variable.

The equation for calculating the probability of experiencing a more severe skin reaction in the UOQ is:

$$\frac{e^{-2.491 + 1.025(\text{Breast size}) + 1.050(\text{Dose group}) + 1.044(\text{Lymphocele}) + 0.480(\text{Ex-smoker}) + 1.780(\text{Current smoker}) + 0.052(\text{Stage})}}{1 + e^{-2.491 + 1.025(\text{Breast size}) + 1.050(\text{Dose group}) + 1.044(\text{Lymphocele}) + 0.480(\text{Ex-smoker}) + 1.780(\text{Current smoker}) + 0.052(\text{Stage})}}$$

Week five upper inner quadrant (UIQ) reaction results.

After deleting three cases due to missing values, data from 123 women were available for analysis: 86 (68.2%) had a score of D-RTOG0 and 37 (31.8%) scored D-RTOG1. Three variables entered the model: breast size, dose group, and lymphocele aspirated. These variables correctly predicted 97.70% of mild or no reactions, and 25.00% of severe reactions giving an accuracy of 76.42% of cases overall. The model was significantly reliable when compared with the constant only model, $\chi^2(4) = 13.100$, $p = 0.0108$ indicating that the predictors, as a set, reliably distinguished between the D-RTOG0 and D-RTOG1 scores. Table 4.16 shows details of the regression analysis for each of the three predictors.

The prediction model for the radiation skin reaction in the UIQ is similar to that of the UOQ except the factors smoking and stage did not enter the model. The relative risks indicate that the larger breast size is over twice as likely to have a more severe reaction; receiving the last fraction of treatment (45 Gy) has a relative

risk two times greater than the fractions given on the other four days of week five (i.e. 37.8 – 43.2 Gy). Lymphocele aspiration increases the relative risk for this site by two times. The confidence intervals for all three variables include 1, and therefore, must be viewed with caution. The significance level for all three variables was > 0.05 and this probably explains the lower limit of the confidence levels.

Table 4.16

Logistic Regression Results for the Week Five UIQ Reaction

Variables	B	SE	Wald	DF	Sig	R	Exp(B)	95% CI
Breast size	.837	.457	3.357	1	.067	.096	2.310	.943 – 5.655
Dose group	.875	.501	3.050	1	.081	.084	2.398	.899 – 6.399
Lymphocele aspirated	.772	.421	3.367	1	.067	.096	2.166	.949 – 4.944
(Constant)	-1.853	.379	23.888	1	.000			

The equation for calculating the probability of experiencing a more severe skin reaction in the UIQ is:

$$\frac{e^{-1.850 + 0.837(\text{Breast size}) + 0.875(\text{Dose group}) + 0.772(\text{Lymphocele})}}{1 + e^{-1.650 + 0.837(\text{Breast size}) + 0.875(\text{Dose group}) + 0.772(\text{Lymphocele})}}$$

Week five lower outer quadrant (LOQ) reaction results.

Three cases were deleted due to missing values, therefore data from 123 women were available for analysis: 91 (73.9%) had a score of D-RTOG0 and 32 (27.1%) scored D-RTOG1. Two variables entered the model: breast size and smoking. These variables correctly predicted 96.67% of mild or no reactions and 6.06% of severe reactions, giving an accuracy of 72.36% overall. The model was significantly reliable when compared with the constant only model, $\chi^2(3) = 11.942$, $p = 0.0076$, indicating that the predictors, as a set, reliably distinguished between the

D-RTOG0 and D-RTOG1 scores. Table 4.17 shows details of the regression analysis for each of the two predictors

The relative risk associated with a large breast size is similar to that seen in both UOQ and UIQ reactions. The results for smoke group indicate that there is little additional risk of severe reaction for ex-smokers but over four times the risk for current smokers. The lower limit of the confidence interval for ex-smokers is < 1 probably because the ex-smoker group did not have a significant level of risk.

Table 4.17

Logistic Regression Results for the Week Five LOQ Reaction

Variables	B	SE	Wald	DF	Sig	R	Exp(B)	95% CI
Breast size	1.092	.460	5.642	1	.018	.160	2.981	1.210 – 7.343
*Smoking			5.327	2	.070	.097		
Ex-smoker	.282	.477	.350	1	.554	.000	1.325	.551 – 3.372
Current smoker	1.427	.621	5.286	1	.022	.152	4.165	1.234 – 14.058
(Constant)	-1.641	.341	23.107	1	.000			

*Reference group for smoking is the "never smoked" group

The equation for calculating the probability of experiencing a more severe skin reaction in the LOQ is:

$$\frac{e^{-1.641 + 1.092(\text{Breast size}) + 0.282(\text{Ex-smoker}) + 1.427(\text{Current smoker})}}{1 + e^{-1.641 + 1.092(\text{Breast size}) + 0.282(\text{Ex-smoker}) + 1.427(\text{Current smoker})}}$$

Week five lower inner quadrant (LIQ) reaction results

Three cases were deleted due to missing values therefore data from 123 women were available for analysis: 90 (73.2%) had a score of D-RTOG0 and 33 (27.8%) scored D-RTOG1. Three variables entered the model: breast size,

lymphocele aspirated and smoking. These variables correctly predicted 93.26% of mild or no reactions, and 20.59% of severe reactions, giving an accuracy of 73.17% overall. The model was significantly reliable when compared with the constant only model, $\chi^2(4) = 19.667$, $p = 0.0006$, indicating that the predictors, as a set, reliably distinguished between the D-RTOG1 and D-RTOG2 scores. Table 4.18 shows details of the regression analysis for each of the three predictors.

Table 4.18

Logistic Regression Results for the Week Five LIQ Reaction

Variables	B	SE	Wald	DF	Sig	R	Exp(B)	95% CI
Breast size	1.191	.471	6.389	1	.012	.174	3.289	1.307 – 8.278
Lymphocele aspirated	.886	.476	3.468	1	.063	.101	2.426	.955 – 6.168
*Smoking			9.569	2	.008	.196		
Ex-smoker	.192	.487	.155	1	.694	.000	1.211	.466 – 3.146
Current smoker	2.067	.679	9.284	1	.002	.224	7.904	2.091 – 29.881
(Constant)	-2.117	.445	22.693	1	.000			

*Reference group for smoking is the "never smoked" group

The model is similar to the LOQ reaction, with a relative risk over three times greater for those with a larger breast size. The lymphocele group had a relative risk of over twice that of the no lymphocele group. It should be noted that the lower limit of the confidence interval < 1. Again, the ex-smokers have a small but non-significant increase in risk of severe skin reaction, but the current smoker's risk is eight times that of the never smoked group.

The regression equation for calculating the probability of experiencing a more severe skin reaction in the LIQ is

$$\frac{e^{-2.117 + 1.191(\text{Breast size}) + 0.886(\text{Lymphocele}) + 0.192(\text{Ex-smoker}) + 2.067(\text{Current smoker})}}{1 + e^{-2.117 + 1.191(\text{Breast size}) + 0.886(\text{Lymphocele}) + 0.192(\text{Ex-smoker}) + 2.067(\text{Current smoker})}}$$

Week five nipple reaction results.

Data from 126 women were available for analysis: 86 (68.2%) had a score of D-RTOG0 and 40 (32.8%) scored D-RTOG1. Only one variable entered the model: smoking. This model correctly predicted 92.86% of mild or no reactions and 23.81% of severe reactions, giving an accuracy of 69.84% overall. The model was significantly reliable when compared with the constant only model, $\chi^2(2) = 7.461$, $p = 0.0240$, indicating that the predictor reliably distinguished between the D-RTOG0 and D-RTOG1 scores. Table 4.19 shows details of the regression analysis for the single predictor.

Table 4.19

Logistic Regression Results for the Week Five Nipple Reaction

Variables	B	SE	Wald	DF	Sig	R	Exp(B)	95% CI
*Smoking			7.131	2	.028	.140		
Ex-smoker	.399	.425	.884	1	.347	.000	1.491	.649 – 3.427
Current smoker	1.569	.588	7.121	1	.008	.179	4.804	1.517 – 15.213
(Constant)	-1.059	.282	14.144	1	.000			

*Reference group for smoking is the "never smoked" group

The model for predicting the nipple reaction differs from the reactions of the four quadrants of the breast, in particular, in that the size of the breast did not predict the severity of the reaction. The ex-smokers had a slightly increased relative risk although again, not significant, of one and a half times that of never smokers.

The confidence interval reflects this, as the lower limit is <1 The risk is significantly increased for current smokers who had an almost five times greater risk of a more severe reaction.

The regression equation for calculating the probability of experiencing a more severe skin reaction in the nipple is:

$$\frac{e^{-1.059 + 0.399(\text{Ex-smoker}) + 1.569(\text{Current smoker})}}{1 + e^{-1.059 + 0.399(\text{Ex-smoker}) + 1.569(\text{Current smoker})}}$$

Week five inframammary fold reaction results.

Three cases were removed due to missing values therefore data from 123 women were available for analysis: 78 (63.4%) had a score of D-RTOG0 and 45 (36.6%) scored D-RTOG1. Two variables entered the model: breast size and smoking. This model correctly predicted 90.91% of mild or no reactions and 47.83% of severe reactions giving an accuracy of 74.80% overall. The model was significantly reliable when compared with the constant only model, $\chi^2(3) = 31.080$, $p = 0.0000$, indicating that the predictors, as a set, reliably distinguished between the D-RTOG0 and D-RTOG1 scores. Table 4.20 shows details of the regression analysis for each of the two predictors.

The relative risk of developing a more severe skin reaction in the inframammary fold was increased over five times with a large breast size. It is notable that for skin reactions in the inframammary fold, ex-smokers showed a significantly increased risk of severe reaction of three times over the never smoked group. Those participants smoking through treatment had over ten times the risk of the never smokers.

Table 4.20

Logistic Regression Results for the Week Five Inframammary Fold Reaction

Variables	B	SE	Wald	DF	Sig	R	Exp(B)	95% CI
Breast size	1.687	.482	12.282	1	.001	.252	5.406	2.104 – 13.890
Smoke group			13.479	2	.001	.241		
Ex-smoker	1.142	.458	6.233	1	.013	.161	3.134	1.278 – 7.681
Current smoker	2.316	.690	11.261	1	.001	.239	10.139	2.621 – 39.223
(Constant)	-1.715	.351	23.907	1	.000			

*Reference group for smoking is the "never smoked" group

The equation for calculating the probability of experiencing a more severe skin reaction in the inframammary fold in week five is:

$$\frac{e^{-1.715 + 1.687(\text{Breast size}) + 1.142(\text{Ex-smoker}) + 2.316(\text{Current smoker})}}{1 + e^{-1.715 + 1.687(\text{Breast size}) + 1.142(\text{Ex-smoker}) + 2.316(\text{Current smoker})}}$$

Week Four Prediction Models

The reactions recorded for week four represent the dose range of 28.8 Gy – 36 Gy. A score of D-RTOG 1 (standard RTOG > 2) during week four represents an early severe reaction. Thus the prediction models developed by stepwise logistic regression produce factors that indicate the likelihood of an earlier reaction occurring in an individual. Dose group was categorised in a similar way as week five with 28.8 Gy – 34.2 Gy as the reference group (0) and the last dose of the week, 36 Gy being grouped as 1.

Week four sternum reaction results.

Data from 126 women were available for analysis: 89 (70.6%) had a score of D-RTOG0 and 37 (29.4%) scored D-RTOG1. Two variables entered the model dose group and history of skin cancer. These variables correctly predicted 96.63% of mild or no reactions and 27.03% of severe reactions, giving an accuracy of 76.19% overall. Dose group in week four represents the last fraction of week four of the whole breast treatment (36 Gy). The model was significantly reliable when compared with the constant only model, $\chi^2(2) = 18.212$, $p = 0.0001$, indicating that the predictors, as a set, reliably distinguished between the D-RTOG0 and D-RTOG1 scores. Table 4.21 shows details of the regression analysis for each of the two predictors.

Table 4.21

Logistic Regression Results for the Week Four Sternum Reaction

Variables	B	SE	Wald	DF	Sig	R	Exp(B)	95% CI
Dose group	.994	.493	4.068	1	.044	.116	2.701	1.028 – 7.092
History of skin cancer	2.334	.705	10.960	1	.001	.242	10.322	2.592 – 41.110
(Constant)	-1.379	.257	28.750	1	.000			

A history of skin cancer is an important predictor in the model for week four sternum reactions. The relative risk for a history of skin cancer is 10.3, which is very similar to the week five model. The difference seen here is that the dose factor, rather than age, entered the model in week four. The last fraction of treatment in week four more than doubles the relative risk of a severe skin reaction.

The equation for calculating the probability of experiencing a severe skin reaction in the sternum in week four is:

$$\frac{e^{-1.4656 + 0.8410(\text{Dose group}) + 2.4514(\text{Skin cancer})}}{1 + e^{-1.4656 + 0.8410(\text{Dose group}) + 2.4514(\text{Skin cancer})}}$$

Week four axilla reaction results.

Three cases were deleted due to missing values, therefore data from 123 women were available for analysis: 95 (77.2%) had a score of D-RTOG0 and 28 (22.8%) scored D-RTOG1. Three variables entered the model: breast size, chemotherapy, and lymphocele aspirated. These variables correctly predicted 92.55% of mild or no reactions and 41.38% of severe reactions, giving an accuracy of 80.49% overall. The model was significantly reliable when compared with the constant only model, $\chi^2(3) = 18.726$, $p = 0.0003$, indicating that the predictors, as a set, reliably distinguished between the D-RTOG0 and D-RTOG1 scores. Table 4.22 shows details of the regression analysis for each of the three predictors.

Table 4.22

Logistic Regression Results for the Week Four Axilla Reaction

Variables	B	SE	Wald	DF	Sig	R	Exp(B)	95% CI
Breast size	1.553	.477	10.614	1	.001	.253	4.726	1.857 – 12.032
Chemo-therapy	1.101	.619	3.160	1	.075	.093	3.008	.893 – 10.125
Lymphocele aspirated	.766	.466	2.702	1	.100	.072	2.150	.863 – 5.356
(Constant)	-2.222	.402	30.482	1	.000			

The model differs slightly from the week five model in that breast size has replaced weight: a larger breast size increases the relative risk of a more severe

skin reaction by three times. Chemotherapy also entered the model, indicating that when having chemotherapy for breast cancer the relative risk of having a severe radiation skin reaction is three times as great. This result must be viewed with caution, as the lower limit of the confidence interval is <1. The impact of lymphocele aspiration is very similar to that in the week five model at just over two times the relative risk. Again, it should be noted that the lower limit of the confidence interval is < 1.

The equation for calculating the probability of experiencing a more severe skin reaction in the axilla in week four is:

$$\frac{e^{-2.222 + 1.553(\text{Breast size}) + 1.101(\text{Chemotherapy}) + .706(\text{Lymphocele})}}{1 + e^{-2.222 + 1.553(\text{Breast size}) + 1.101(\text{Chemotherapy}) + .706(\text{Lymphocele})}}$$

Week four UOQ reaction results.

Three cases were deleted due to missing values therefore data from 123 women were available for analysis: 100 (81.3%) had a score of D-RTOG0 and 23 (18.7%) scored D-RTOG1. Two variables entered the model: breast size, condition of the breast scar. These variables correctly predicted 99.00% of mild or no reactions and 8.70% of severe reaction, giving an accuracy of 82.11% overall. The model was significantly reliable when compared with the constant only model, $\chi^2(2) = 10.315$, $p = 0.0058$, indicating that the predictors, as a set, reliably distinguished between the D-RTOG0 and D-RTOG1 scores. Table 4.23 shows details of the regression analysis for each of the two predictors.

The model is quite different for UOQ reactions in week four compared with week five. Breast size is the only predictor that is the same; interestingly the relative risk also remains similar. The condition of the breast scar as a predictor indicates that if the lumpectomy scar is inflamed or discharging at the commencement of treatment, then the risk of a severe skin reaction in week four is over 10 times greater.

The lower limit of the confidence interval for "Condition of the breast scar" is less than 1.00 and is probably due to there being only three participants with inflammation or infection in the scar at the commencement of radiation. The high upper limit of the confidence interval for this predictor reflects the high relative risk

Table 4.23

Logistic Regression Results for the Week Four UOQ Reaction

Variables	B	SE	Wald	DF	Sig	R	Exp(B)	95% CI
Breast size	1.319	.497	7.046	1	.008	.206	3.741	1.412 – 9.911
Condition of breast scar	2.315	1.295	3.194	1	.074	.100	10.122	.799 – 128.144
(Constant)	-1.988	.322	38.104	1	.000			

The equation for calculating the probability of experiencing a more severe skin reaction in the UOQ in week four is:

$$\frac{e^{-1.988 + 1.319(\text{Breast size}) + 2.315(\text{Condition of breast scar})}}{1 + e^{-1.988 + 1.319(\text{Breast size}) + 2.315(\text{Condition of breast scar})}}$$

Week four UIQ reaction results.

Three cases were deleted due to missing values therefore data from 123 women were available for analysis: 101 (82.1%) had a score of D-RTOG0 and 22 (17.9%) scored D-RTOG1. Two variables entered the model: breast size and condition of the breast scar. These variables correctly predicted 99.01% of mild or no reactions and 9.09% of severe reactions, giving an accuracy of 82.93% overall. The model was significantly reliable when compared with the constant only model, $\chi^2(2) = 8.809$, $p = 0.012$, indicating that the predictors, as a set, reliably distinguished between the D-RTOG0 and D-RTOG1 scores. Table 4.24 shows details of the regression analysis for each of the four predictors.

Table 4.24

Logistic Regression Results for the Week Four UIQ Reaction

Variables	B	SE	Wald	DF	Sig	R	Exp(B)	95% CI
Breast size	1.171	.504	5.386	1	.020	.171	3.225	1.200 – 8.669
Condition of breast scar	3.350	1.287	3.333	1	.068	.107	10.483	.841 – 130.615
(Constant)	-1.990	.322	38.144	1	.000			

The predictors entering the model for the UIQ: breast size and condition of the breast scar, are the same as for the UOQ in week four. The levels of relative risk associated with the predictors are also very similar. Again, the confidence interval includes 1 for "condition of the breast scar".

The regression equation for calculating the probability of experiencing a severe skin reaction in the UIQ in week four is:

$$\frac{e^{-1.990 + 1.171(\text{Breast size}) + 3.350(\text{Condition of breast scar})}}{1 + e^{-1.990 + 1.171(\text{Breast size}) + 3.350(\text{Condition of breast scar})}}$$

Week four LOQ and LIQ reaction results.

Please note that the results for LOQ and LIQ reactions are identical. They are therefore presented together. Three cases were deleted due to missing values, therefore data from 123 women were available for analysis: 103 (83.7%) had a score of D-RTOG0 and 20 (16.3%) scored D-RTOG1. Three variables included in the model: breast size, condition of the breast scar, and smoking. These variables correctly predicted 96.08% of mild or no reactions and 14.29% of severe reactions, giving an accuracy of 82.11% overall. The model was significantly reliable when compared with the constant only model, $\chi^2(4) = 12.874$, $p = 0.012$, indicating that the predictors, as a set, reliably distinguished between the D-RTOG0 and D-RTOG1

scores. Table 4.25 shows details of the regression analysis for each of the three predictors.

Table 4.25

Logistic Regression Results for Week Four LOQ and LIQ Reactions

Variables	B	SE	Wald	DF	Sig	R	Exp(B)	95% CI
Breast size	.900	.5390	2.709	1	.095	.084	2.460	.856 – 7.077
Condition of breast scar	2.619	1.399	3.506	1	.0611	.115	13.727	.885 – 212.962
Smoking			5.457	2	.065	.114		
Ex-smoker	.665	.593	1.258	1	.262	.000	1.944	.609 – 6.214
Current smoker	1.490	.706	5.447	1	.019	.175	5.190	1.302 – 20.691
(Constant)	-2.490	.464	28.869	1	.000			

The equation for calculating the probability of experiencing a more severe skin reaction in the LOQ and the LIQ in week four is:

$$\frac{e^{-2.490 + .900(\text{breast size}) + 2.619(\text{condition of breast scar}) + .665(\text{ex-smoker}) + 1.490(\text{current smoker})}}{1 + e^{-2.490 + .900(\text{breast size}) + 2.619(\text{condition of breast scar}) + .665(\text{ex-smoker}) + 1.490(\text{current smoker})}}$$

Week four nipple reaction results.

Data from 126 women were available for analysis: 98 (79.7%) had a score of D-RTOG0 and 25 (20.3%) scored D-RTOG1. With the standardised approach to the logistic regression, a model that significantly improved the prediction of severe skin reactions to the nipple was not found.

Week four inframammary fold reaction results.

Data from 126 women were available for analysis: 98 (77.7%) had a score of D-RTOG0 and 28 (22.3%) scored D-RTOG1. Two variables entered the model, chemotherapy and smoking. These variables correctly predicted 96.94% of mild or no reactions and 14.29% of severe reactions, giving an accuracy of 7. .57% overall. The model was significantly reliable when compared with the constant only model, $\chi^2(3) = 10.709$, $p = 0.0134$, indicating that the predictors, as a set, reliably distinguished between the D-RTOG0 and D-RTOG1 scores. Table 4.26 shows details of the regression analysis for each of the two predictors.

Table 4.26

Logistic Regression Results for the Week Four Inframammary Fold Reaction

Variables	B	SE	Wald	DF	Sig	R	Exp(B)	95% CI
Chemo-therapy	1.306	.584	5.006	1	.025	.150	3.692	1.176 – 11.593
Smoking			6.349	2	.042	.133		
Ex-smoker	.692	.503	1.885	1	.169	.000	1.998	.746 – 5.323
Current smoker	1.563	.629	6.182	1	.013	.177	4.773	1.392 – 16.363
(Constant)	-1.974	.380	27.033	1	.000			

The regression equation for calculating the probability of experiencing a more severe skin reaction in the Inframammary Fold in week four is:

$$\frac{e^{-1.974 + 1.306(\text{Chemotherapy}) + 0.692(\text{Ex-smoker}) + 1.563(\text{Current smoker})}}{1 + e^{-1.974 + 1.306(\text{Chemotherapy}) + 0.692(\text{Ex-smoker}) + 1.563(\text{Current smoker})}}$$

Week Three Prediction Models

Although very few participants scored D-RTOG 1 during week three, a logistic regression analysis was attempted in order to determine if any predictors could be proposed to identify very early reactions. The reactions recorded for week three represent the dose range of 19.8 Gy – 27 Gy.

Week three sternum reaction results.

Data from 126 women were available for analysis: 109 (86.5%) had a score of D-RTOG0 and 17 (22.4%) scored D-RTOG1. One variable was included in the model: history of skin cancer, and correctly predicted 100.00% of mild or no reactions and 0.00% of severe reactions predicted 86.51% of cases overall. The model was significantly reliable when compared with the constant only model, $\chi^2(1) = 5.879$, $p = 0.0153$, indicating that this predictor reliably distinguished between the D-RTOG0 and D-RTOG1 scores. Table 4.27 shows details of the regression analysis.

Table 4.27

Logistic Regression Results for the Week Three Sternum Reaction

Variables	B	SE	Wald	DF	Sig	R	Exp(B)	95% CI
History of skin cancer	1.660	.647	6.590	1	.010	.215	5.260	1.481 – 18.685
(Constant)	-2.130	.305	48.671	1	.000			

A history of skin cancer entered the model as it did in the models of both weeks four and five. The relative risk is noticeably lower in this model, indicating that the relative risk of a severe reaction is just over six times greater in those with a history of skin cancer. The relative risk was calculated at 10 and 11 times greater in the models for weeks four and five respectively.

The equation for calculating the probability of experiencing a more severe skin reaction in the sternum in week three is:

$$\frac{e^{-2.130 + 1.660(\text{History of skin cancer})}}{1 + e^{-2.130 + 1.660(\text{History of skin cancer})}}$$

Week Three Results for the Remainder of the Sites

The frequency of D-RTOG 1 scores were small in week three, therefore the predictive models produced through logistic regression were not significantly reliable when compared with the constant only model for each site.

One variable, lymphocele group, consistently appeared in the models as significantly related to the severity of skin reactions in week three, as determined by the Wald statistic. The lymphocele group appeared in the model for reactions in the axilla, and all four quadrants of the breast. The size of the breast variable was also significantly related to the severity of the skin reaction in the UIQ and LOQ sites.

Analysis of Electron Boost Treatment

Description of RTOG Scores in Weeks during Electron Boost Treatment

The results of the RTOG scores for weeks six and seven are displayed in Figures 4.5 and 4.6 respectively.

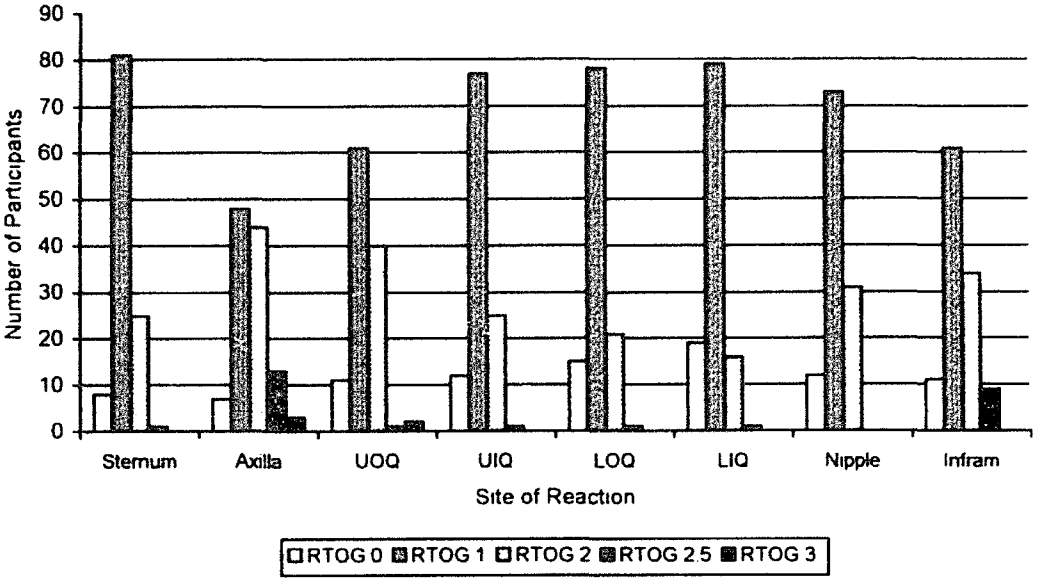


Figure 4.5 Frequency Distribution of Participants According to RTOG Scores for Week Six

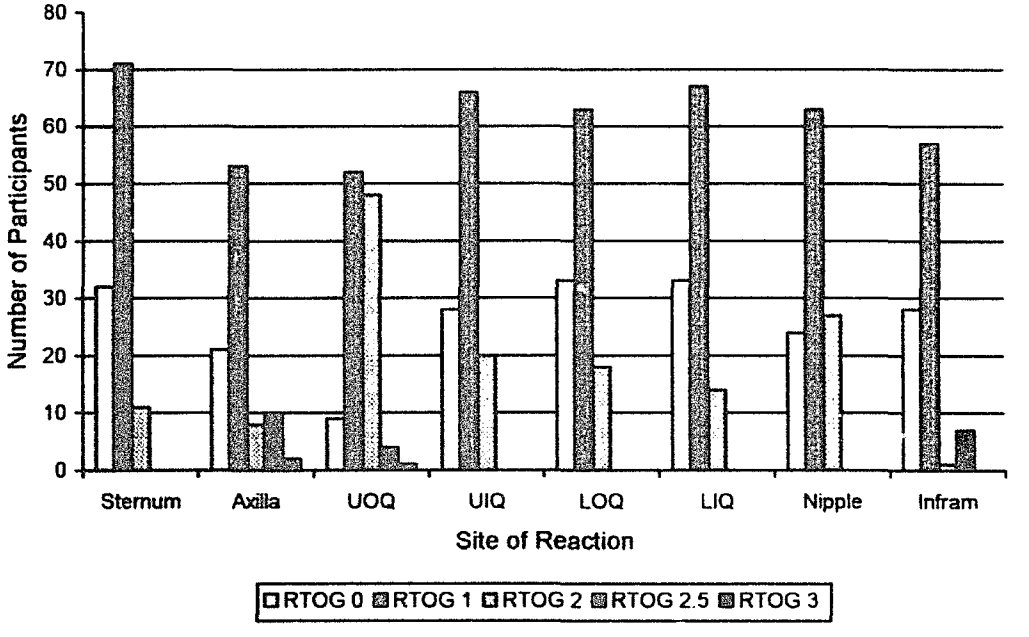


Figure 4.6 Frequency Distribution of RTOG score for Week Seven

The highest frequency of moist desquamation (RTOG ≥ 2) occurred in week six. When comparing Figure 4.4 and 4.5, it can be seen that the frequency of RTOG 0 scores increase and the frequency of RTOG 1 scores decrease concurrently in week seven indicating that overall there was healing and recovery during the last week of the boost treatment.

Over half of the participants (55.6%) had their lumpectomy scar, and thus their boost, in the UOQ of the breast. The frequency distribution for lumpectomy scars is detailed in Table 4.28.

Table 4.28

Frequency and Percent Distribution of Participants According to the Site of Lumpectomy Scar

Site of Lumpectomy Scar	Frequency (%) of Participants
UOQ	70 (55.6%)
UIQ	19 (15.1%)
LOQ	10 (7.9%)
Central scars (including the nipple)	10 (7.9%)
Across both UOQ & axilla	9 (7.1%)
LIQ	6 (4.8%)
Axilla	3 (2.4%)
Inframammary Fold	1 (0.8%)

The severity of the reaction only continues to increase at the site of the lumpectomy scar, where the electron boost is delivered. At the remainder of sites the reaction diminishes as healing progresses. Given this fact, it was not logical to include all sites in the analysis, as the diminishing reactions in most cases would confound the results. Therefore, for the purposes of analysis, only participants whose lumpectomy site was located in the UOQ, the UOQ and axilla, or the axilla were included (N = 82, 65.1% of total sample).

Univariate Testing of Potential Predictive Factors Related to Severe Skin Reactions during the Boost Treatment

Chi-square analysis was performed on dichotomous and categorical predictor variables and the D-RTOG scores for week six and seven. The analysis was confined to those participants with the boost treatment in the axilla and/or the UOQ of the breast. Tables 4.29 and 4.30 present the results of the Chi-square analysis for weeks six and seven respectively.

For continuous variables, t-tests were performed to test relationships between potential predictor variables and skin reactions (D-RTOG scores). In week six, participants with a more severe axilla reaction had a significantly higher mean weight ($t(72) = -3.96$, $p = .000$), as did participants with a more severe UOQ reaction ($t(72) = -2.17$, $p = .033$).

In week seven, participants with a more severe axilla reaction had a significantly higher mean weight ($t(75) = -2.64$, $p = .010$). Participants with a more severe UOQ reaction had both a significantly higher mean weight ($t(74.91) = -3.22$, $p = .002$), and a significantly higher mean age ($t(75) = -2.40$, $p = .019$) than their counterparts with a mild skin reaction.

Table 4.29

Significant Relationships in Dichotomous RTOG Scores for Week Six According to Site as Tested by Chi-square (p-value)

Site	Alcohol intake (p-value)	Breast Size (p-value)	Boost energy (p-value)	Family history of breast cancer (p-value)	Family history of cancer (p-value)	Lympho-cele group (p-value)	History of previous cancer (p-value)	Smoker current or ex- (p-value)	Smoke group (p-value)	D-RTOG Axilla week 5 (p-value)	D-RTOG UOQ week 5 (p-value)
Week 6											
Axilla		11.17 (.001)		6.86 (.009)	5.11 (.024)	4.49 (.034)	3.13 (.077)	3.46 (.063)		10.66) (.001)	
UOQ	6.81 (.033)	4.09 (.043)	12.68 (.013)			2.71 (.099)		9.76 (.002)	11.51 (.003)		20.83 (.000)

Table 4.30

Significant Relationships in Dichotomous RTOG Scores for Week Seven According to Site as Tested by Chi-square (p-value)

	Age group	Breast size	Boost energy	Chronic Illness	Alcohol intake	Hyper-tension	Smoker current or ex- (p-value)	Smoke group (p-value)	Skin condi-tion	D-RTOG Axilla week 6	D-RTOG UOQ week 6
Axilla		3.35 (.067)		4.10 (.043)						14.01 (.000)	
UOQ	7.164 (.028)		9.27 (.056)		5.55 (.062)	3.36 (.067)	6.93 (.008)	7.69 (.021)	5.63 (.060)		5.64 (.018)

Development of Prediction Models for Radiation Skin Reactions during Electron Boost Treatment

Week Six Prediction Models

Week six represents the first week of electron boost treatment following the completion of 45 Gy to the whole breast. The electron boost is delivered to the tumour bed located under the lumpectomy scar plus a small margin of tissue surrounding the area. As can be seen from the description of the RTOG scores, those areas not included in the boost site begin to heal.

Week six axilla reaction.

Following the deletion of eight cases due to missing values, data from 74 women were available for analysis: 37 (50%) had a score of D-RTOG0 and 37 (50%) scored D-RTOG1. Two variables were included in the model: lymphocele aspirated and current weight. These variables correctly predicted 83.78% of mild or no reactions and 75.68% of severe reactions, giving an accuracy of 79.73% overall. The model was significantly reliable when compared with the constant only model, $\chi^2(2) = 22.066$, $p = 0.0000$, indicating that the predictors, as a set, reliably distinguished between the D-RTOG0 and D-RTOG1 scores. Table 4.31 shows details of the regression analysis for each of the two predictors.

Table 4.31

Logistic Regression Results for the Week Six Axilla Reaction

Variables	B	SE	Wald	DF	Sig	R	Exp(B)	95% CI
Lymphocele aspirated	1.531	.584	6.885	1	.009	.218	4.623	1.473 – 14.506
Current weight	.105	.029	12.906	1	.000	.326	1.111	1.049 – 1.176
(Constant)	-7.487	2.010	13.880	1	.000			

Those participants who had developed a lymphocele requiring drainage had a relative risk of developing a more severe skin reaction 4.6 times greater than those who did not. The relative risk is based on the weight of the participant in kilograms. The relative risk value appears small but it represents an increase per kilogram increase. Thus the magnitude of the relative risk is quite large.

The equation for calculating the probability of experiencing a more severe skin reaction in the axilla is:

$$\frac{e^{-7.4873 + 1.5130(\text{lymphocele}) + 0.1050(\text{weight})}}{1 + e^{-7.4873 + 1.5130(\text{lymphocele}) + 0.1050(\text{weight})}}$$

Week six UOQ reaction.

Following the deletion of 8 cases due to missing values, data from 74 women were available for analysis: 41 (59.4%) had a score of D-RTOG0 and 28 (40.6%) scored D-RTOG1. Two variables entered the model: boost energy and skin-type. This model correctly predicted 90.91% of mild or no reactions and 43.33% of severe reactions, giving an accuracy of 71.62% overall. The model was significantly reliable when compared with the constant only model, $\chi^2(2) = 19.008$, $p = 0.0001$, indicating that the predictors, as a set, reliably distinguished between the D-RTOG0 and D-RTOG1 scores. The lower energy levels of the electron boost treatment (6 – 12 $MeVe^-$) were not associated with a severe reaction so "boost energy" was re-coded into a dichotomous variable where 6 – 12 $MeVe^-$ = 0 and 16 – 20 $MeVe^-$ = 1. Table 4.34 shows details of the regression analysis for each of the two predictors.

Table 4.32

Logistic Regression Results for the Week Six UOQ Reaction

Variables	B	SE	Wald	DF	Sig	R	Exp(B)	95% CI
Boost energy	2.822	.848	11.059	1	.001	.301	16.802	3.186 – 88.621
*Skin-type	1.858	.814	5.209	1	.023	.179	6.414	1.300 – 31.645
Constant	-2.398	.795	9.108	1	.003			

*Reference group was sensitive response to the sun

The relative risk of a severe reactions was over 16 times greater if the boost was at the higher energy levels. The skin-type variable predicted that those with a normal or insensitive response to UV (Fitzgerald scale = 4 – 6) had a relative risk of almost six times greater than participants with sun-sensitive skin (Fitzgerald scale = 1 – 2).

The equation for calculating the probability of experiencing a more severe skin reaction in the axilla is:

$$\frac{e^{-2.398 + 2.822(\text{boost energy}) + 1.858(\text{skin-type})}}{1 + e^{-2.398 + 2.822(\text{boost energy}) + 1.858(\text{skin-type})}}$$

Week Seven Prediction Models

Week seven axilla reaction.

Following the deletion of five cases due to missing values, data from 77 women were available for analysis: 45 (58.4%) had a score of D-RTOG0 and 32 (41.6%) scored D-RTOG1. Two variables were included in the model: lymphocele group and current weight. This model correctly predicted 77.78% of mild or no reactions and 50.00% of severe reactions, giving an accuracy of 66.23% overall. The model was significantly reliable when compared with the constant only model, $\chi^2(2) = 9.455$, $p = 0.0088$, indicating that the predictors, as a set, reliably

distinguished between the D-RTOG0 and D-RTOG1 scores. Table 4.33 shows details of the regression analysis for each of the two predictors.

Table 4.33

Logistic Regression Results for the Week Seven Axilla Reaction

Variables	B	SE	Wald	DF	Sig	R	Exp(B)	95% CI
Lymphocele aspirated	.832	.510	2.668	1	.102	.080	2.298	.847 – 6.239
Current weight	.061	.023	6.941	1	.008	.217	1.063	1.016 – 1.112
(Constant)	-4.685	1.608	8.487	1	.004			

Those participants who had developed a lymphocele requiring drainage had a relative risk of developing a more severe skin reaction over two times greater than those who did not. It should be noted that the confidence interval includes 1 for this predictor. The relative risk is based on the weight of the participant in kilograms, therefore the relative risk of developing a more severe reaction increases slightly per kilogram increase in weight.

The equation for calculating the probability of experiencing a more severe skin reaction in the axilla is:

$$\frac{e^{-4.6850 + .8322(\text{lymphocele aspirated}) + 0.0608(\text{weight})}}{1 + e^{-4.6850 + .8322(\text{lymphocele aspirated}) + 0.0608(\text{weight})}}$$

Week seven UOQ reaction.

Following the deletion of five cases due to missing values, data from 77 women were available for analysis: 33 (42.8%) had a score of D-RTOG0 and 44 (57.2%) scored D-RTOG1. Only one variable was included in the model: current weight. This model correctly predicted 51.52% of mild or no reactions and 72.73% of

severe reactions, giving an accuracy of 63.64% overall. The model was significantly reliable when compared with the constant only model, $\chi^2(1) = 9.378$, $p = 0.0022$, indicating that the predictor reliably distinguished between the D-RTOG0 and D-RTOG1 scores. Table 4.37 shows details of the regression analysis for the single predictor.

Table 4.34

Logistic Regression Results for the Week Seven UOQ Reaction

Variables	B	SE	Wald	DF	Sig	R	Exp(B)	95% CI
Current Weight	.067	.024	7.876	1	.005	.236	1.070	1.021 – 1.121
Constant	-4.042	1.543	6.862	1	.009			

The relative risk is based on the weight of the participant in kilograms. Therefore, the relative risk for developing a severe skin reaction in the UOQ during the boost treatment in week seven increases 1.070 times per kilogram increase in weight.

The equation for calculating the probability of experiencing a more severe skin reaction in the axilla is:

$$\frac{e^{-4.042 + 0.067(\text{weight})}}{1 + e^{-4.042 + 0.067(\text{weight})}}$$

Pain and Discomfort with Radiation Skin Reactions: Results of the VAS Pain Scale

Pain was not as great a problem as anticipated during the course of the radiotherapy. Many participants said that what they felt was discomfort and not real

pain and chose to report zero on the VAS scale. Table 4 35 details the frequencies of scores on the VAS over the seven weeks of treatment.

Table 4.35

Percent Distribution of Participants According to VAS Pain Scores over Seven Weeks of Treatment

	Pain VAS								
Week	0	1	2	3	4	5	6	8	9
1	99.2%	0.8%							
2	98.4%	0.8%	0.8%						
3	96.8%		2.4%	0.8%					
4	92.8%	0.8%	0.8%	1.6%	3.2%			0.8%	
5	87.3%	1.6%	2.4%	3.2%	1.6%	2.4%	0.8%	0.8%	
6*	83.2%	2.7%	6.0%	0.9%	1.8%	1.8%	2.7%		0.9%
7**	88.6%		4.4%	0.9%	1.8%	1.8%	2.7%		

* N = 115 ** N = 114

Moderate to severe pain (VAS = 4 – 10) appeared in week four with one participant reporting a score of eight. Week six represents the highest number of participants reporting pain with 16.5% (19) scoring between one and nine on the VAS. Figure 4.6 illustrates the similarity in pattern between the pain score over the weeks of treatment, and the development of radiation skin reaction and moist desquamation in the axilla.

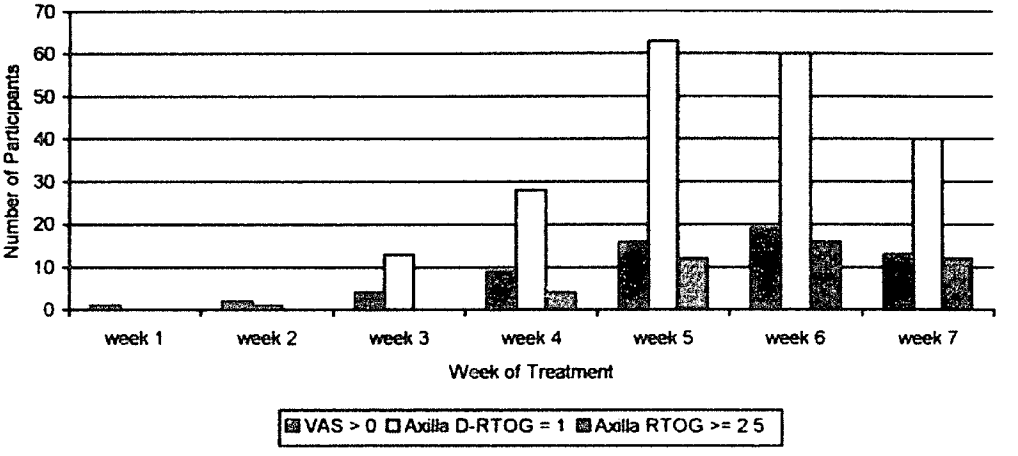


Figure 4.7 Comparison of Pain Scores with Axilla D-RTOG Reactions and Moist Desquamation over the Seven Weeks of Treatment.

Cross Validation of Predictive Models

To test the validity of the predictive models two random samples of about 40% of the sample were taken and stepwise logistic regression performed using the same criteria as in the main analysis. A sample of cases was selected randomly by SPSS using the select cases facility. Random sample 1 had 54 cases and random sample 2 had 50 cases. The details of the logistic regression analysis for predicting the severity of radiation reactions in weeks four and five, for these samples, can be found in Appendix K. Table 4.36 lists the significant predictors from the analysis of the full sample and the two random samples by site for reactions in week five. Only week five prediction models were cross validated because with the small numbers in the random samples, the proportion of severe reactions would be too small to interpret the predictive models in a meaningful way.

The models developed for cross validation were very similar in the predictor variables to enter the models for each site. This provides an indication of the trustworthiness of the predictive models developed with the full sample.

Table 4.36

Comparison of Significant Factors between Analysis of Full Sample and Two Random Samples for Week Five Reactions

Full Sample (N = 126)	Random Sample 1 (N = 54)	Random Sample 2 (N = 50)
Sternum	Sternum	Sternum
History of skin cancer	History of skin cancer	History of skin cancer
Age	Age	
Axilla	Axilla	Axilla
Lymphocele aspirated	Lymphocele aspirated	Lymphocele aspirated
Weight		
UOQ	UOQ	UOQ
Breast size	Breast size	
Dose		
Lymphocele aspirated	Lymphocele aspirated	Lymphocele aspirated
Stage of tumour		Stage of tumour
Smoking	Smoking	
UIQ	UIQ	UIQ
Breast size		
Dose		
Lymphocele aspirated		Lymphocele aspirated
		Stage of tumour
LOQ	LOQ	LOQ
Breast size		
Lymphocele aspirated		
Smoking	Smoking	Smoking
LIQ	LIQ	LIQ
Breast size	Breast size	Breast size
Lymphocele aspirated		
Smoking	Smoking	Smoking
Nipple	Nipple	Nipple
Smoking	Smoking	Smoking
Inframammary Fold	Inframammary Fold	Inframammary Fold
Breast size		
Smoking		Smoking

Summary of Chapter

This chapter has documented the analysis and findings of data collected on the development of skin reactions in 126 women being treated for breast cancer with a standard protocol of post lumpectomy radiation. The results show that the theoretical relationships posed in the conceptual model could be demonstrated empirically on univariate and multivariate levels. Prediction models for each of eight anatomical areas of the breast exposed to radiation were constructed for skin reactions during the weeks of treatment to the whole breast area supporting the proposition that it is possible to estimate the risk of skin reactions for individual women facing radiotherapy. Prediction models were also constructed for the electron boost treatment phase for the UOQ and axilla sites.

The validity of the prediction models for week five reactions was tested by cross validation with two random samples. Comparison between the predictive models from the full sample and the two random samples indicated a satisfactory level of validity.

Pain associated with radiation skin reactions was not as severe as expected with many participants preferring to describe the reaction as discomfort. When pain was reported it followed a very similar pattern to that of moist desquamation. That is, when skin loss had occurred, then pain, rather than discomfort, is reported.

The findings reveal that radiation factors alone cannot predict the severity of radiation skin reactions. The addition of factors from the Personal Construct of the Conceptual Framework, particularly the impact of smoking, breast size and lymphocele aspiration, make the prediction model more complete.

CHAPTER FIVE

DISCUSSION AND CONCLUSION

The principle hypothesis developed and tested in this study is that knowledge of factors that impair wound healing will contribute to creating a more complete understanding of radiation skin reactions and make the prediction of individual risk possible. The ultimate purpose of this study was to develop an instrument for clinical and research use that would enable nurses to predict the severity of radiation skin reactions on an individual basis. The research focussed on women with breast cancer as they represented a reasonably homogenous group for studying such a complex and multifactorial issue.

The development of the prediction instrument was reported in detail in this thesis, as follows. Chapter One presented an argument for obtaining empirically based knowledge about the importance of radiation skin reactions in relation to the preparation of women for treatment. Chapter Two traced the theoretical relationships between the effects of ionizing radiation on normal skin and the impact of factors that impair the processes of tissue healing. A model supporting the following hypothesis was offered: that the severity of radiation skin reactions is a function of radiation, genetic and personal factors. Chapter Three detailed the methods and procedures developed to test the hypothesis and Chapter Four detailed the findings of the research process.

This chapter discussed the study findings in relation to the conceptual framework and identifies practice implications through the development of a method of risk prediction for women commencing standard radiotherapy post lumpectomy. In addition, the chapter includes a critical reflection on measurement

issues arising from the study and study limitations. A summary of the findings is presented first.

Summary of Findings

Data from a sample of 126 women commencing standard post-lumpectomy radiation protocol were collected on factors that were potentially predictive of radiation skin reaction severity. Skin reactions of these women were documented over the seven weeks of treatment to determine the relationship between the predictive factors and the severity of the skin reaction that developed. The sample was representative of the general population of women in Western Australia on a range of socio-demographic items. The sample was also similar to the breast cancer population in disease related factors such as histology of the tumour when compared with published figures (Kurtz et al., 1989).

Predictive Factors

A review of treatment-related factors revealed that at the time radiation therapy commenced, the women's surgical incisions at the lumpectomy and axillary clearance sites were in good condition with less than 3% having any inflammation or haemoserous discharge. Almost half of the sample had required the aspiration of a lymphocele on one or more occasions post axillary clearance. Indications for aspiration were: discomfort due to the collection of lymph fluid, and/or a change in contour of the lateral chest wall due to the accumulation of fluid thus changing the measurements for accurate administration of ionizing radiation. Only 16 participants were receiving or had received chemotherapy for their breast cancer.

In terms of general health, over half of the sample had one or more concurrent diagnoses of chronic illness. None of these illnesses were radiosensitive and the majority were not identified as illnesses that would impair healing. Almost two-thirds of the sample were taking prescribed medications, this

being significantly related to the presence of a chronic illness. In addition, over half of the sample were self-medicating or taking medicines prescribed by a naturopath. Over three-quarters of these self-medications were vitamin and mineral supplements and just over one fifth of the sample were taking alternative medicines for their anticancer properties.

Just over half of the sample had smoked at some time, but only 13 reported smoking throughout treatment. Alcohol consumption during treatment was reported by just over half of the sample.

The nutritional status of the participants, as assessed by the nutrition subscale of the Braden Scale, showed that intake was adequate or excellent in 98% of cases. There was a considerable range in the weight of participants from 42 to 112kg, but the majority had a body mass index in the normal range. The size of the breast was significantly related to weight as would be expected. The majority of participants had smaller breast size as defined by brassiere "C" cup or smaller.

The condition of the skin was normal in almost 80% of cases and less than half reported problems with skin allergies. In relation to participants' skin responses to UV radiation, as measured by the Fitzgerald Scale, almost 70% reported a normal or insensitive response. The mid to high level scores on the Cumulative UV Scale showed that the sample as a whole had spent their time in the sun unprotected with a hat, clothing or sunscreen in both childhood and adulthood. The majority of participants had lived in Perth thus being exposed to the high-intensity UV radiation for which this area is known.

RTOG Scores

The patterns of skin reaction development followed the expected course, as described in Chapter Two, with dull erythema with or without dry desquamation (RTOG = 1) appearing about two weeks after the commencement of radiation. This was followed by a steady increase with the intensity of erythema becoming bright

and/or tender with or without moist desquamation (RTOG ≥ 2). The reactions during electron boost treatment reflected the anticipated change in protocol, with reactions remaining high or increasing at the boost site and receding elsewhere.

Also as anticipated, the three sites with the most severe skin reactions (RTOG ≥ 2) were the axilla, the upper outer quadrant and the inframammary fold. The severity of the sternum reaction with the blister reaction was not unexpected, but required less nursing intervention with creams and/or dressings. The blister reaction is not uncommon with patients treated in the Department, but has not been reported in the literature. It is this type of variance to the usually reported reactions that suggests that the chronic sun-exposure of the sternum is responsible. This phenomenon requires comparison with other geographic areas.

Also as expected, the most severe reactions were recorded during week five of treatment with confluent moist desquamation being noted in the axilla and upper outer quadrants. During the two weeks of boost treatment, the reactions generally began to heal in the areas that were not in the vicinity of the boost. RTOG scores of two or more were recorded most frequently in week six. Unless actual skin loss had occurred, skin reactions were not reported to be painful, but rather there was a heightened awareness of the breast and some discomfort.

Similarities between Prediction Models.

Some clear patterns emerge in the prediction models between the sites of the breast. Table 5.1 summarises the predictors. Most notable is the similarity between the breast quadrants. The two lower quadrants had identical prediction models in week four and the same predictors with only slight variation in relative risk values in week five. In the two upper quadrants, the predictors that entered the models in week five were similar with the exception of smoking and tumour stage, which were not predictive in the UIQ. The small number of smokers may explain the anomaly of smoking not being a predictor in only one quadrant in week five.

Table 5.1

Patterns of Predictors between Sites and Over Time

Site	Week Three	Week Four	Week Five	Week six	Week Seven
Sternum	History of skin cancer	History of skin cancer	History of skin cancer		
		Dose	Age*		
Axilla		Lymphocele aspirated*	Lymphocele aspirated*	Lymphocele aspirated	Lymphocele aspirated*
		Breast size	Weight	Weight	Weight
		Chemotherapy*			
UOQ		Breast size	Breast size	Boost energy	Weight
		Condition of breast scar*	Current smoker	Skin type	
			Lymphocele aspirated		
			Stage*		
			Dose		
UIQ		Breast size	Breast size*		
		Condition of breast scar*	Lymphocele aspirated*		
			Dose*		
LOQ		Breast size*	Breast size		
		Current smoker	Current smoker		
		Condition of breast scar*	Lymphocele aspirated		
LIQ		Breast size*	Breast size		
		Current smoker	Current smoker		
		Condition of breast scar*	Lymphocele aspirated*		
Nipple			Current smoker		
Inframammary Fold		Chemotherapy	Breast size		
		Current smoker	Ex-smoker		
			Current smoker		

* indicates that the confidence interval included "1".

In week five, predictive factors included in the models for all breast quadrants were: a larger breast size; receiving the last fraction of whole breast treatment; and having had a lymphocele aspirated. In week four, breast size and the condition of the breast scar were predictors in all quadrants. This is of interest given that the majority of scars were in the upper quadrants suggesting that the impact of increased inflammatory response along the scar line affects the overall healing of the whole breast. However, this finding must be viewed with caution as the confidence interval included 1.

The similarities between the models suggest that with further development, it may be possible to group the sites, thus making the assessment simpler for daily clinical practice and more practical for educational purposes.

Mechanisms Underlying the Relationships between Predictors and the Severity of Radiation Skin Reactions

The development of models to predict the severity of radiation skin reactions in women with breast cancer was undertaken systematically and rigorously to ensure the final product would be statistically sound and clinically useful. Selection of potential predictors for entry into the stepwise logistic regression was based on the conceptual model and results of the univariate testing. In interpreting the findings in terms of the theoretical basis for the predictive relationships, it was clear that the conceptual framework could be modified to represent the findings more closely. The discussion that follows develops hypotheses for each predictive factor suggesting possible mechanisms underlying the predictive relationships. Factors are presented in order of frequency of occurrence in the prediction models.

Breast Size and Weight

Breast size was a significant predictor of severe radiation skin reactions in all quadrants of the breast and the inframammary fold in week five, and the axilla, all

quadrants of the breast and the nipple, in week four. The participant's weight was a significant predictor in the axilla reaction models in weeks five, six and seven. Breast size and weight were closely related variables as indicated by the finding of a significant moderate correlation between the two measures and a significantly higher mean weight for participants in the larger breast size group. The hypotheses presented to support these two factors are the same; thus the discussion is combined.

There are two possible hypotheses that probably combine to explain the influence of the participant's breast size/weight on the severity of the radiation skin reaction. From a wound management perspective, increasing breast size/weight is an indicator of several mechanisms that may impair healing. The negative impact on the efficiency of healing caused by excess layers of adipose tissue or obesity was discussed in Chapter Two. One mechanism suggested was that the poor vascularity of adipose tissue compromises healing (Carville, 1995; Dealey, 1994). Obesity can also cause excessive wear and tear on skin through increased friction on movement, causing abrasion. In surgical patients, obesity is also a factor in increased risk of postoperative infection. A larger breast size, even when a woman is not obese, can increase the risk of friction particularly if a brassiere is always needed for support.

Areas such as the axilla where there is appositional skin are also more prone to severe skin reactions due to the increased moisture, warmth and friction along with poor aeration. It is well recognised that these elements can contribute to a more severe radiation skin reaction through increasing the rate at which the stratum corneum sloughs (Sitton, 1992). A mainstay of radiation skin care protocols has been to artificially maintain the stratum corneum through actions aimed at reducing possible friction for example by patting the skin dry rather than rubbing; wearing loose cotton clothing; and moisturising the skin.

From a radiation therapy perspective, weight can be viewed as an indication of increasing size of the chest area, i.e. as weight increases the area included in the treatment field increases. A skin-sparing effect occurs as the higher energies produced by megavoltage linear accelerators result in the accumulation of the dose deeper in the tissues. A larger (heavier) person would, therefore, require a higher dose of radiation to the skin surface to ensure that the tumour receives the full dose required for eradication. Based on the hypothesis that the heavier the person, or the larger the breast size, the higher is the dose required relative to the skin surface, then a better measure of size might be a caliper reading between the sternum to the lateral aspect of the torso taken for treatment planning. Another alternative would be to develop a method of calculating skin dose for each of the observations sites that could be used on a practical level by nurses. In addition, a larger breast size is an indication of increased tissue volume being treated. A larger treatment volume has been implicated as increasing the severity of reactions (Maciejewski et al., 1990; Perez & Brady, 1992).

Smoking

Smoking during treatment was a significant predictor in all models in week five except for the sternum and upper inner quadrant. It was also a significant predictor in the two lower quadrants, nipple and inframammary fold reactions in week four. The impact of smoking on the development of more severe skin reactions was an extremely interesting finding. Wound healing literature suggests that smoking, and nicotine in particular, delays or impairs healing through a number of mechanisms. These mechanisms, as presented in Chapter Two, are:

- Cutaneous vasoconstriction as a result of one or more of the constituents of cigarette smoke (Cohen, et al., 1992)
- The negative impact on the nutritional status of the patient, in particular vitamin and mineral depletion (Cohen, et al., 1992; Dealey, 1994)

- Changes to the endothelium, increased platelet stickiness, high levels of carbon monoxide in the blood of smokers limiting the oxygen-carrying capacity of haemoglobin (Cohen, et al., 1992)
- Reduction in macrophage activity and epithelialisation (Siana, Frankild & Gottrup, 1992)

The effects of smoking on mucosal reactions in the mouth and throat have been described on several occasions in the radiation therapy literature. The mechanism hypothesised to explain the increased severity in mucosal reactions has been the direct contact of an irritant (cigarette smoke) with the mucosa (Bentzen & Overgaard, 1994b; Browman et. al., 1993; Des-Rochers, Dische & Saunders, 1998; Rugg, Saunders & Dische, 1990). These findings suggest that adverse effects result not only in relation to direct contact, but also from the systemic effects of smoking that have been described and tested in the wound management literature.

The relative risk of the ex-smoker group was not significantly higher than the group who had never smoked, suggesting the possibility that encouraging patients to quit smoking may positively impact on the severity of the skin reaction. This suggestion must be tempered by the knowledge that all except one of the ex-smokers had quit more that one year prior to diagnosis. The efficacy of a quit smoking intervention on reducing the severity of skin reaction would require further testing.

The significant impact on the severity of the skin reaction by smoking whilst on treatment cannot be ignored and may help identify new patients who may be at particular risk for severe skin reaction. The finding also underscores the importance of health promotion activities, such as smoking cessation, in cancer nursing practice. From the findings presented here it is clear that encouraging patients to quit smoking during treatment is an area of research that requires further attention.

Aspiration of a Lymphocele

Having had a lymphocele aspirated was predictive of a more severe skin reaction in the axilla and all quadrants of the breast in week five and in the axilla reaction in week four. Entry into the models occurred in some instances because of the broader entry criteria of p = .10; where the significance level was greater that .50 but less than .10, then the confidence interval included 1. Despite these qualifications on the interpretation of lymphocele aspiration as a predictor, there are significant clinical implications which support the inclusion of the variable in the prediction models.

The theoretical explanation for lymphocele aspiration exacerbating the skin reaction is related to the role the lymphatic system plays in the physiology of healing. It is logical to assume that participants who required aspiration of a lymphocele experienced more damage to the lymphatic system in the axilla due to clearance of axillary lymph nodes. The mean number of lymph nodes removed was not significantly different between participants who had a lymphocele aspirated and those who did not.

As lymph oedema of the breast increases due to an inflammatory response to the ionizing radiation, the congestion resulting from axillary clearance increases, exacerbating the skin reaction and compromising the normal healing processes. Those women, who have demonstrated more damage to the lymph drainage channels by requiring aspiration of a lymphocele, are therefore at greater risk of breast lymph oedema and of compromised healing.

It is possible that as a result of having the additional trauma to the axillary tissue from needle aspiration, a more marked inflammatory response would follow, further compromising the already weakened lymphatic system in the axilla. In addition, the possibility that the normal flora of the skin could be introduced into

tissue during the procedure would suggest further heightening of the inflammatory response or even a low-grade infection.

The usual channel for drainage of lymph fluid for the breast is via the axillary nodes. The fact that aspiration of a lymphocele was not predictive in the inframammary fold reaction in either week four or five supports the hypothesis of increased tissue damage due to impaired lymphatic drainage in the upper breast, as there are alternative lymph node stations to channel lymph fluid from the lower aspect of the breast.

Condition of the Breast Scar

Less than 3% of lumpectomy scars were inflamed or discharging haemoserous fluids. The condition of the breast scar was predictive of severe skin reactions in three of the breast quadrants (not upper outer quadrant) in week four. Although the effects of scar condition are no longer predictive in week five reactions, it does appear to be an important indicator of risk for early onset reactions. The confidence intervals indicate that these findings should be viewed with caution and therefore further research is required before accepting the condition of the breast scar as a predictor in clinical assessment.

The theoretical explanation for the predictive influence of scar condition lies in the delay in the healing processes due to inflammation and/or infection. The presence of infection or immunosuppression may affect the normal tissue response to radiation as described by Bentzen and Overgaard (1994b) and Chak et al., (1988). As discussed in Chapter Two, immunosuppression may well be part of the causal chain in the development of infection in radiation reactions where the integrity of the skin has been compromised.

Clinical infection delays healing by prolonging the inflammatory phase and inhibiting the ability of fibroblasts to produce collagen (Senter & Pringle, 1985). In addition, there is competition for white cells and nutrients; therefore, healing may

be delayed until the body has overcome the infection. Furthermore, systemic infection causes fever, raising the metabolic rate, thus increasing catabolism and tissue breakdown. Pain, also produced by infection, may further increase the metabolic rate.

The small group size and the interpretation of confidence intervals indicate that this finding must be viewed with caution.

History of Skin Cancer and Skin Type

Having a history of skin cancer was significantly related to a more severe skin reaction to the sternum on a univariate level and as a significant predictor in weeks three, four and five. Skin type (as measured by the Fitzgerald scale) was significantly related to the severity of the sternum reaction in weeks three and four, and entered the prediction model for the UOQ in week six, during the first week of electron boost treatment.

History of Skin Cancer

The most likely explanation for a history of skin cancer being a significant predictor is that skin cancer is a measure of skin damage from chronic UV radiation exposure. The effects of chronic exposure to the sun were described in Chapter Two. It is interesting to note that other variables indicative of sun damage were significantly related to the severity of the skin reaction on a univariate level. These were skin-type in weeks three and four and the level of protection from UV radiation used as an adult (as measured by the Cumulative UV Radiation Scale) in week five.

Of the variables associated with sun damage, only a history of skin cancer remained in the predictive model for the sternum. Given that only participants with a confirmed medical diagnosis of skin cancer were included in the analysis, this factor was a very conservative measurement of damage due to UV radiation. It also may suggest that a more discriminating measure of cumulative sun damage

could provide a better understanding of the impact of sun damage to areas of chronic exposure.

Another interpretation of the theoretical basis for a history of skin cancer predicting the severity of the skin reaction would be that an individual who demonstrated sensitivity to the carcinogenic effects of UV radiation may also have a propensity to be generally more radiosensitive. In addition, the general immune depletion effects of chronic exposure to UV radiation as described by Santucci (1996), may have resulted in some impairment of the inflammatory phase of the normal process of wound healing. Although logical, these two hypotheses would be more credible if a history of skin cancer had featured in the prediction models in the reactions in other areas of the breast. It should be noted however, that on a univariate level, a history of skin cancer was significantly related to more severe reactions in the two lower quadrants and the nipple in week four. Thus, it would be premature to disregard the alternative hypotheses of radiosensitivity or immune depletion.

Skin type

The Fitzgerald scale, used to measure skin-type, incorporates sunburn and tanning history in a six point ordinal scale, to indicate the individual's sensitivity to the effects of UV radiation from the sun. Due to missing values, the variable was re-coded to two levels representing participants who were sensitive to the sun and those who had a normal or insensitive reaction to the sun. The finding that a high risk was associated with participants who had a normal or insensitive reaction to the sun would seem initially illogical. However, experience in the sun would lead those with sun-sensitive skin to prevent sunburn by using a hat, clothing and/or sunscreen. Those with skin that tans and is classed as either normal or insensitive to the sun, would be more likely to spend time in the sun unprotected, thus leading to a greater risk for chronic UV radiation damage.

The Cumulative UV Radiation Scale

The two factors, history of skin cancer and skin-type, clearly suggest the probability of a relationship between the cumulative effects of chronic exposure to UV radiation. The Cumulative UV Radiation Scale was developed from a need to find a non-invasive method of estimating the impact of exposure to UV radiation over time. Initial development was through interviewing patients in the Department and healthy adults to determine a meaningful way of collecting information on exposure to the sun. The reliability and validity testing conducted were adequate to continue with the scale in the research. Although it was disappointing to find that the scores for this scale were not significantly related to the severity of skin reactions, the finding that a history of skin cancer and skin type were related to the radiation skin reactions in the sternum and UOQ shows that there is probably merit in pursuing some measure of UV radiation damage. The Cumulated UV Radiation may provide the basis for future development in this area.

Radiation Dose

Dose of radiation was a significant predictor in severe reactions in all quadrants of the breast and the nipple in week five; the sternum, upper outer quadrant and inframammary fold in week four and the sternum in week three. The significance of dose as a predictor is obvious and certainly expected, thus the fact that several models do not include dose as a predictor is, in fact, a more interesting finding.

For example, the dose factor, although significantly related to the sternum reaction on a univariate level in weeks three, four and five, and on a multivariate level in weeks three and four, was not included in the prediction model in week five. This is a noteworthy finding, as it appears to indicate that the influence of a history of skin cancer is greater by week five than dose of radiation alone. The relative risk of dose is 3.5 in the week three model and 2.8 in the week four model. It would

seem that the influence of dose diminishes over the weeks of treatment to be replaced by an increasing relative risk for a history of skin cancer of 6.1 in week three, and almost 12 in weeks four and five.

The finding that dose does not appear in the axilla predictions is interesting given that it is an area prone to more severe reactions, including moist desquamation. These results suggest that wound healing factors have a significant influence in predicting the risk of a severe skin reaction in the axilla. The influence of having a lymphocele aspirated, having chemotherapy and the size of the breast were better predictors than radiation dose. Both a radiation enhancement mechanism and a healing mechanism can explain the influence of breast size and chemotherapy. On balance, however, it seems that in the axilla, at least, the influence of impaired healing is greater than that of dose or other direct radiation factors.

Chemotherapy

It is noteworthy that chemotherapy is included in models predicting early onset reactions (week four) in the axilla and the inframammary fold. These sites are prone to moist desquamation as indicated in the descriptive results; supporting clinical experience. The well established theoretical basis for chemotherapy exacerbating radiation skin reactions was presented in Chapter Two and centres on the cytotoxic properties of chemotherapy and the potential for enhancing radiosensitivity (Bentzen & Overgaard, 1993; Fu, 1985; Hirshfield-Bartek, 1992; O'Rourke, 1987; von der Maase, 1994).

In addition to their damaging effect on normal cells, cytotoxic drugs also have a suppressing effect on the immune system and thus wound healing. The principle risks of immune suppression are infection and bleeding. Healing is specifically impaired by the delay in clearance of debris through reduced white cell activity (Laurence & Bennett, 1987). As a result, patients receiving chemotherapy are

expected to be at risk of infection. This would be extended to patients receiving chemotherapy as an adjuvant to radiotherapy, thereby increasing the risk of infection in any skin reaction particularly where moist desquamation has occurred

From a clinical perspective it was surprising to find that chemotherapy did not significantly influence the prediction of week five reactions. It is possible that the impact of chemotherapy occurs earlier; but overall the reaction may not be worse during the treatment period. This study was limited to observations of skin reactions during the seven weeks of treatment only. It would be useful to follow those who developed moist desquamation after treatment to measure the healing time required and determine the variables that influence healing time.

Pedersen, Bentzen and Overgaard (1994) discussed the notion of the "burden of side effects" suggesting the score for the reaction at the end of treatment alone does not supply sufficient information to comprehend the impact of side effects on the patient. This suggests that the length of time a patient experiences the side effect, as well as the severity, is important to note. Certainly in preparing an individual for radiotherapy the ability to determine the likelihood of earlier onset side effects would be reassuring to women facing radiation therapy and assist in coping with the experience.

Age

Age is frequently cited as being a probable risk factor in the development of radiation skin reactions (Bentzen & Overgaard, 1994b; Holmes, 1988; Perez & Brady, 1992). However, in this research, age was found to be a predictor only in the week five sternum reaction. Furthermore, an inverse relationship was revealed. As age increased the probability of a more severe reaction in the sternum decreased. This finding was not anticipated as the radiation literature had indicated a belief, at least, that increasing age would have impacted negatively on the development of skin reactions. From the wound management literature, the

diminishing capacity of the body to heal as age increases is due to a multitude of physiological and social reasons that suggests recovery from ionizing radiation would be at least delayed if not impaired. Data from this study was contrary to the expected view.

Possible explanations for this finding may lie in three areas. Firstly, it is an accepted practice that chemotherapy is not used as frequently with older women. In this study the small group of participants receiving chemotherapy were significantly younger than those not receiving chemotherapy. Further testing of the potential relationship between chemotherapy and age determined that there was no significant interaction, suggesting that in this sample chemotherapy was not a covariant in the model. However, a larger sample with a greater proportion of participants receiving chemotherapy may shed light on this hypothesis.

The second explanation is that as the rate of mitosis in normal skin cells reduces as age increases then the cells directly and indirectly affected by ionizing radiation would reduce. The effect on the tumour would not be the same, as the rate of mitosis is higher than that of normal cells. Jacobson and Flowers (1996) state that there is a notable decrease in the turnover rate of the epidermis by up to 50% in the elderly. This decrease may be sufficient to provide some protection against the effects of ionizing radiation in the skin.

The third possible explanation is one of difference in lifestyle of older participants in relation to chronic exposure to UV radiation. It is possible that the older generation was more likely to have been fully clothed when in the sun both in their youth and even in recent years. Although this is speculation, the data did indicate a significant inverse relationship between age and the protection used as a child as reported in the Cumulative UV Radiation Scale.

Boost Energy

The results of the logistic regression for the skin reactions recorded during the two weeks boost treatment found that boost energy was a significant predictor of severe reactions in UOQ reaction during week six of treatment (first week of the electron boost). The relationship between the boost energy levels and the relative risk was demonstrated by higher energy levels (> 16MeVe') increasing the risk of a more severe reaction over 16 times in the UOQ. However, boost energy did not predict the reactions in week seven. This was a somewhat unexpected finding as it could have been anticipated that as more skin-sparing effect occurs as higher energy levels increase, the relationship should have been inverse.

Nevertheless, boost energy, as a predictor of severe skin reactions in week six, is a straightforward factor for use in clinical practice as the nurse can easily check the energy prescribed for the electron boost. The patient can then be prepared appropriately and be identified for close monitoring.

Stage of the Tumour

The inclusion of the stage of the tumour in the predictive model for the upper outer quadrant was an interesting finding. The model indicated that having a stage II or higher more than doubled the risk of a severe skin reaction. Inclusion of stage in the prediction models for the upper outer quadrant of the breast only was probably due the majority of tumours being located in the upper breast in this sample. The wound management literature identifies advanced cancer as a risk for wound healing but, only one participant was classified as stage IV. The more probable explanation is that more participants classified at stage II or higher had larger tumours. Thus, the surgical bed would be larger, generally resulting in more trauma to the surrounding tissue and increasing the risk of haematoma, entrapped air, infection and/or abscess.

Comparing the Conceptual Framework with the Empirical Evidence

After critical reflection on the predictive factors identified in this research, there is substantive evidence to support the original conceptual framework developed theoretically in comparison with the framework that emerged empirically. Figure 5.1 reproduces the original framework, introduced in Chapter Two.

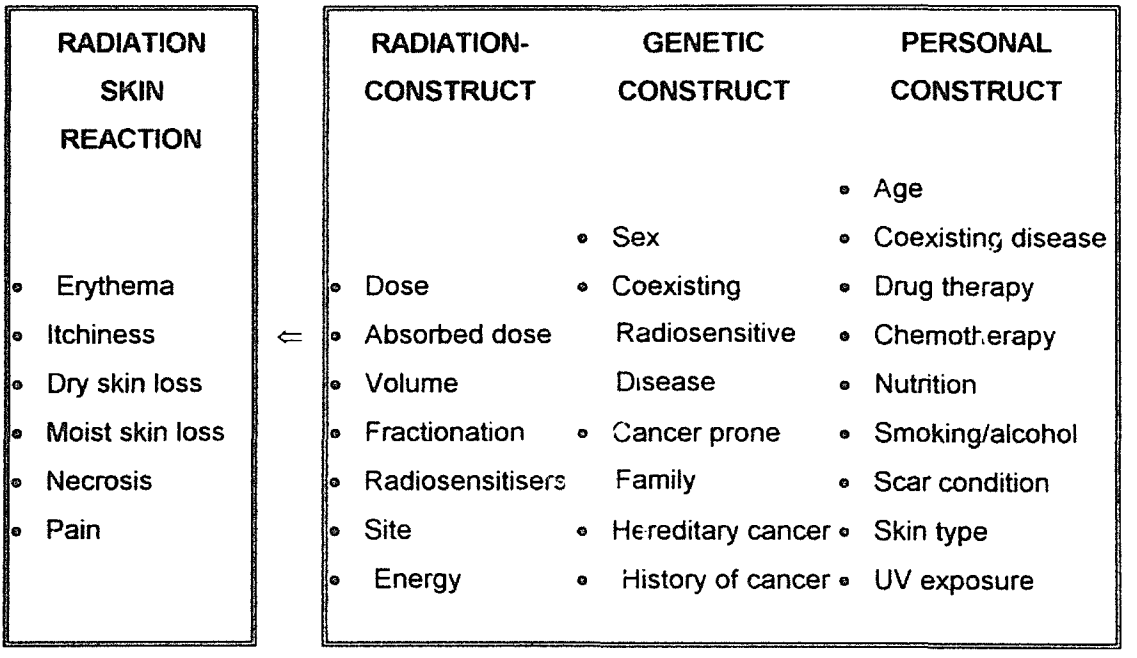


Figure 5.1 Conceptual Framework of Potential Predictors of Radiation Skin Reactions

In considering the hypotheses generated to explain the relationships between predictors and the severity of the radiation skin reaction, there appears to be evidence for two main constructs to represent the empirical findings of this research. Figure 5.2 illustrates these factors.

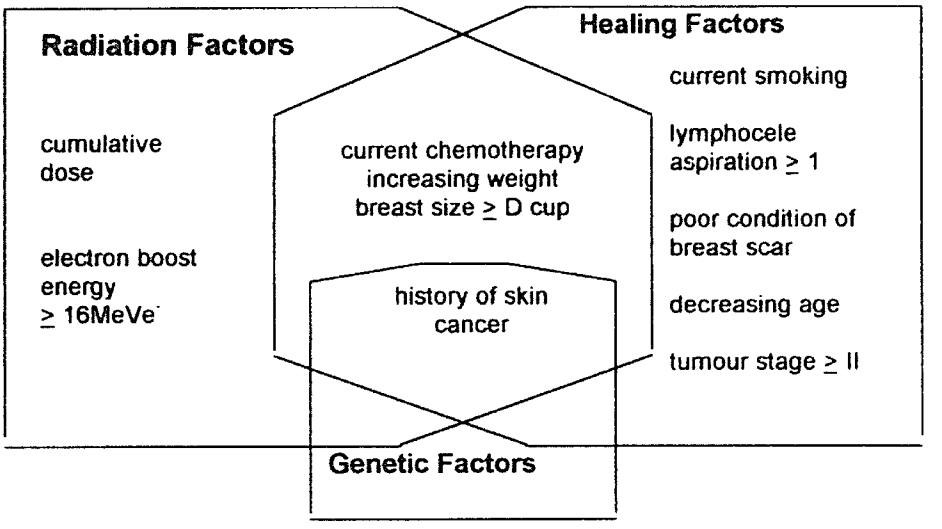


Figure 5.2 Empirically Based Framework Developed from the Findings

The factors that entered the predictive models during the analysis are listed in Figure 5.2. This empirical evidence supports the theoretical relationships with the severity of radiation skin reactions, but they do not represent an exclusive list. Replication of this work must include all factors from the original conceptual framework until the limitations of this sample have been addressed. Furthermore, development of measures for concepts such as nutritional status and exposure to UV radiation may contribute to understanding this phenomenon.

Measurement Issues

The research process included a number of measures in order to operationalise the conceptual framework. The complexity of the framework required the development of new measures for some factors. These were combined with data from review of medical notes and reasonably concrete measures such as age and weight. Furthermore, another consideration in selecting

and developing measures was the ease with which nurses could make assessments on a routine basis in the clinical setting. No measure was either too difficult or too expensive, either in time or equipment, to prohibit its use in practice.

The process of establishing rudimentary psychometric properties of the new measures was a focal point of the development work. The results of content validity and interrater reliability testing, as discussed in Chapter Three, indicate that the instruments were able to measure reliably the concepts under investigation.

RTOG Scoring System for Skin Reactions

Measuring the severity of skin reactions has been an important focus in radiation oncology since the inception of ionizing radiation as a therapeutic modality. The RTOG Scoring System used in this study was developed from clinical practice for clinical assessment rather than research. Denham et al. (1995) criticised the use of the system for research asserting that reflectance spectrometry has more specificity and reliability when compared with the RTOG as assessed by a number of radiation oncologists. The study by Denham et al. Revealed, however, that the pattern of skin reaction development was the same using the two methods. In the current research, reliability was ensured through careful training of research assistants and regular IRR testing. The results of the IRR testing, as described in Chapter Three, showed a high degree of correlation between all data collectors, certainly within acceptable ranges.

The RTOG scoring system was modified early in the data collection period by the introduction of a score to separate "tender or bright erythema" from "patchy moist desquamation". Where patchy moist desquamation occurred, a score of 2.5 instead of 2 was recorded. In the final analysis, only a few participants experienced any moist desquamation and even fewer experienced "confluent moist desquamation" (RTOG = 3). Despite this finding, there may be merit in retaining the differentiation between a score of 2 or 2.5 to increase the specificity of the RTOG

system. Denham et al. (1995) suggested separating the RTOG = 1 category into two with "follicular or dull erythema" as "1" and "dry desquamation" as "1.5". It is likely that these modifications will improve the specificity of the RTOG particularly for research. Further validity testing of the modifications is essential.

Limitations

The limitations of the study relate to three issues. Firstly there is the acknowledgement that other factors may increase the explanatory power of the prediction models. Despite this, the prediction models were able to predict the severity of radiation skin reactions with an overall accuracy of between 68% and 82%. Other factors, such as the oxygenation of the skin or its temperature, specific nutritional deficiencies, or the impact of psychological state, could be tested in future research.

Secondly, the limitations in measurement of the independent and dependent variables must be considered. Measures adapted or developed for use in the study were subject to content validity testing and to interrater and test-retest reliability testing. Refinement and further testing of this exploratory work will determine the utility of these measures for risk assessment in clinical practice.

Thirdly, attention should be given to the limitations of the sample. The recruitment of participants continued over a 12 month period. Despite the extremely high response rate, the final sample size was 126. The sample did show significant similarity on socio-demographic data and on tumour histology suggesting that the data from the sample is trustworthy and further research with larger samples would be worthwhile.

These limitations are tempered by the strengths of the study. The study developed a strong theoretical foundation and considerable effort was spent on ensuring that the measurements and protocols conducted frequently over a long

period of time remained accurate so that quality data were collected. Also, the sampling criteria were restricted as Denham (1996) cautioned that the investigation of predictive factors for skin reactions was subject to considerable extraneous variation particularly in relation to radiation factors and gender. The use of a sample drawn from women only, all of whom were receiving a standard post lumpectomy radiation protocol for breast cancer minimised the variation so that the focus of the analysis could be on the influence of factors from the Personal Construct.

Application of the Predictive Models of Radiation Skin Reactions to Clinical Practice

Underpinning this research was the aim of developing an empirical base for assessing patients' risk of a more severe radiation skin reaction. This study has developed and presented both theoretical and empirical evidence to support this aim. The application of this knowledge lies not just in improving clinical assessment in radiation oncology, but provides the theoretical basis for introducing interventions to support the patient physically and psychologically throughout the treatment period.

As discussed in Chapter Two, Hendry (1994) suggested the possibility of moderating normal tissue damage through modifying individual characteristics such as diet and supporting the individual's resistance to infection with prophylactic antibiotics. Hendry recognised the impact of surgery and chemotherapy on the promotion of cell proliferation and suggests that appropriate supportive therapy in the form of fluids, electrolytes and antibiotics may positively affect morbidity, ultimately resulting in an ability to give higher doses of radiation. This study supports Hendry's conclusion that not only can "other factors" affect the individual

expression of radiation reactions, but that the modification of these factors may moderate the impact of genetically determined radiosensitivity.

Despite this research being exploratory and further research being required to confirm the psychometric properties of the assessment tool, specific knowledge arises from these findings that can be used in practice as a result of the findings. For example, a practicing nurse can incorporate the knowledge that smoking during treatment increases the likelihood of a more severe reaction; that a patient receiving chemotherapy will probably manifest a severe skin reaction earlier; and that patients with large breast sizes are at an increased risk of severe skin reaction and skin loss.

Results also indicate that the models, as they have been developed with this sample, are extremely accurate in predicting patients who will develop only a mild (RTOG = 1) reaction or no reaction (RTOG = 0). Knowing who will not have a severe reaction is as important in clinical practice as knowing who will. If, when preparing a patient for radiation at the commencement of treatment, the nurse can tell the patient that she/he is 90% sure that there will be no more than a mild reaction, the patient is likely to be reassured and experience a reduction in anxiety (Poroch, 1995).

The lower level of accuracy in predicting those who can expect a severe reaction means that fewer patients than predicted will have a severe reaction; a greater risk of making a Type II error. This is a cautious and safe approach because the prediction of a false positive will initiate close monitoring by both the nurse and the patient. Logically, a reaction that is not as severe as predicted would be better received by the patient than one that is worse.

The potential to assess risk on an individual basis has several benefits. For the patient it means knowing what to expect, and when. For the nurse, it provides an empirical base for prioritising care and developing individualised skin

management. Risk assessment may also provide additional information for determining the effectiveness of different skin care and dressing products on a day-to-day basis.

A Rudimentary Assessment Tool

It is possible, using the formula described in detail in Chapter Four, to calculate the probability of an individual's risk for developing a radiation skin reaction of RTOG $\geq$ 2 in women commencing a standard protocol of post lumpectomy radiation for breast cancer. Appendix L presents a series of tables constructed for each of the eight sites observed in this study that can be used to estimate individual risk. These tables are rudimentary and are not intended for immediate clinical use, but rather to indicate a useful form through which the findings of the study may be applied to practice in the future.

Future Research Directions

This study has explored and tested the relationships between the severity of radiation skin reactions and radiation, genetic and personal factors. Although described and hypothesised in texts and other publications, these relationships had not been tested before in a prospective study. The benefits of applying this knowledge to practice have been presented. Taking into consideration the limitations and strengths of the research it would be worthwhile to continue to develop this programme of research to develop a trustworthy method of risk assessment in radiation skin reactions.

The first line of future research is in the development or modification of the measures used for the independent variables. For example, further development of the non-invasive measure of sun damage, and the addition of other predictors such as psychological state, skin oxygenation and skin temperature. Larger samples from more diverse populations will confirm and clarify the prediction models found

thus far. The process of validation studies would also require trials of prediction models where the person assessing the developing skin reaction would be blinded to the prediction.

The second line of future research would extend the methodology developed here and apply it to skin sites other than the breast area and then to other normal tissue damage such as gastrointestinal tract mucosae. The skin has been used as the model for understanding the adverse effects of ionizing radiation on normal tissue (Denham et al., 1996). The application of this methodology to other radiation side effects is a logical trajectory to follow.

The empirical basis for decision making in radiation skin management has been quite limited. One of the reasons for this has been that due to the problem of patient-to-patient variation, large random samples are required. The findings of this study provide support for stratification of samples based on known predictors, for example, smoking, breast size and lymphocele aspiration. For example. in testing the effectiveness of a topical ointment or cream, sample recruitment would be stratified by current smoking, breast size and lymphocele aspiration.

Finally, it may be possible to use the predictions in the process of testing the effectiveness of topical medications and dressing materials. Earlier work by Downes, Porock and Upright (1997) indicated that using retention dressing tapes, such as Fixomull or Hypafix, may minimise skin loss through creating an artificial *stratum corneum.* By predicting who is most likely to develop a severe skin reaction, selection criteria for research in this area can be more appropriately structured, avoiding the exposure of patients to an unnecessary intervention when they are unlikely to develop a severe reaction.

Summary and Conclusions

This research was conducted in three stages reflecting the overall aims of the research. Two assumptions underscored the research process: firstly that in addition to the effects of ionizing radiation, factors and mechanisms known to impair wound healing also affect the development of radiation skin reactions through impairment of the normal process of tissue healing; and secondly that these factors were measurable.

The first stage involved identification of factors from both wound healing and radiation literature along with clinical knowledge and development of a conceptual framework that could be tested. From this framework it was hypothesised that the severity of radiation skin reactions was a function of some or all of the genetic and personal factors plus the radiation factors.

Development of the research protocol and completion of data collection formed the second stage. All measures were subject to testing for content validity. The research protocol was piloted which included testing for stability over time, using test-retest reliability. During the data collection, the three, trained observers were rigorously tested for interrater reliability and accuracy of transferring information from the medical record. The psychometric properties of the tool used exceeded the pre-set criteria.

The sample of 126 women, recruited over a 12-month period, was representative of the WA general female population on socio-demographic criteria and representative of the breast cancer population in terms of histology type.

The third phase involved testing of the theoretical relationships on a univariate level with chi-square and t-test statistics, and on a multivariate level through stepwise logistic regression analysis. Through this analytical process, a predictive model was developed for each of the eight sites observed for the

reactions recorded in weeks three to seven of standard post lumpectomy radiation for breast cancer.

The final aspect of the third phase was the critical reflection on the research process and findings. The purpose was threefold: Firstly, to form hypotheses explaining the mechanisms underpinning the significant predictors; secondly, to interpret the findings for nurses practising in radiation oncology and; thirdly, to map out the logical next steps for continuing the research work in this important area.

Despite the limitations of this exploratory study, the findings contribute to both the knowledge and practice of radiation oncology nursing. The theory base has been developed through bringing together the radiation literature and the wound healing literature. Testing the theoretical relationships between the severity of radiation skin reactions and radiation factors and personal healing factors, provides the empirical foundation for the creation of a tool for individualising the assessment of risk for a severe radiation skin reaction. A trustworthy assessment tool will evolve with further research and development, adding to the repertoire of skills used by the radiation oncology nurse to promote optimal, individualised patient care.

Reference List

Abadir, R. & Hakami, N. (1983). Ataxia telangiectasia with cancer. An indication for reduced radiotherapy and chemotherapy doses. *The British Journal of Radiology, 56,* 343-345.

Andrews, (1981).

Australian Bureau of Statistics (ABS) (July, 1997). 1996 Census of Population and Housing. Selected Social and Housing Characteristics for Statistical Local Areas Western Australia, Cocos (Keeling) and Christmas Islands. Canberra, Australia : ABS

Australian Cancer Network. (May, 1997). *The Pathology Reporting of Breast Cancer. A Guide for Pathologists , Surgeons and Radiologists. Recommendations of the Australian Cancer Network Working Party.* Author

Bentzen, S.M. & Overgaard, J. (1993). Early and late normal tissue injury after postmastectomy radiotherapy. *Recent Results in Cancer Research, 130,* 59-78.

Bentzen, S.M. & Overgaard, J. (1994a). Seminars in radiation oncology, Introduction. *Seminars in Radiation Oncology, 4*(2), 53-54.

Bentzen, S.M. & Overgaard, J. (1994b). Patient-to-patient variability in the expression of radiation-induced normal tissue injury. *Seminars in Radiation Oncology, 4*(2), 68-80.

Bentzen, S.M., Overgaard, M. & Overgaard, J. (1993). Clinical correlations between late normal tissue endpoints after radiotherapy: Implications for predictive assays of radiosensitivity. *European Journal of Cancer, 29A*(10), 1373-1376.

Bergstrom, N., Braden, B., Laguzza, A. & Holman, V. (1987). The Braden Scale for predicting pressure sore risk. *Nursing Research 36*(4), 205

Bibby, B.A., Collins, B.J. & Ayliffe, G.A.J. (1986). A mathematical model for assessing the risk of post-operative wound infection. *Journal of Hospital Infection, 8,* 31-39.

Braden, B. & Bergstrom, N. (1987). A conceptual schema for the study of the etiology of pressure sores. *Rehabilitation Nursing, 12*(1), 8.

Braden, B. & Bergstrom, N. (1989). The clinical utility of the Braden Scale for prediction pressure sore risk. *Decubitus, 2*(3), 44-46, 50-51.

Browder, J.F. & Beers, B. (1993). Photoaging: cosmetic effects of sun damage. *Postgraduate Medicine, 93,* 74-92.

Brown, J.K. (1993). Gender, age, usual weight and tobacco use as predictors of weight loss in patients with lung cancer. *Oncology Nursing Forum, 20*(3), 466-472.

Brown, JM., Biaglow, JF., Hall, EJ., Kinsella, TJ., Phillips, TL., Uratson, RC., Utley, JF. & Yuhas, JM. (1984) Sensitizers and protectors to radiation and chemotherapeutic drugs. *Cancer Treatment Symposia, 1,* 85-101.

Browman, G.P., Wong, G., Hodson, I., Sathya, J., Russell, R., McAlpine, L, Skingley, P & Levine, M.N. (1993). Influence of cigarette smoking on the efficacy of radiation therapy in head and neck cancer. *The New England Journal of Medicine, 328,*159-163.

Bruera, E. & MacDonald, R.N. (1988). Nutrition in cancer patients: an update and review of our experience. *Journal of Pain and Symptom Management, 3*(3), 133-140.

Burnett, N.G., Nyman, J., Turesson, I., Wurm, R. Yarnold. & Peacock, J.H. (1992). Prediction of normal-tissue response to radiotherapy from in-vitro cellular radiation sensitivity. *Lancet, 339,*1570-1571.

Cassarett, G.W. (1980). *Radiation Histopathology* (Vol 1). Boca Raton, Fl: CRC Press.

Carville, K. (1995). *Wound Care Manual. (Revised Ed)*. Western Australia: Silver Chain Foundation.

Cassarett, (1980).

Chak, L.Y., Gill, P.S., Levine, A.M., Meyer, P.R., Anselmo, J.A. & Petrovich, Z. (1988). Radiation therapy for acquired immunodeficiency syndrome-related Karposi's sarcoma. *Journal of Clinical Oncology, 6*(5), 863-876.

Cohen, I.K., Diegeimann, R.F., & Lindblad, W,J. (I 992*) Wound Healing: Biochemical and Clinical Aspects*. Philadelphia: W.B. Saunders Co.

Cox, J.D., Stetz, J. & Pajak, T.F. (1995). Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research an Treatment of Cancer (EORTC). *International Journal of Radiation Oncology Biology Physics 31*(5), 1341-1346.

Cruse, P.J.E. & Foord, R. (1973). A five-year prospective study of 23,649 surgical wounds. *Archives of Surgery, 107*, 206-217.

Dealey, C. (1994). *The care of wounds: a guide for nurses*. Oxford: Blackwell Scientific Publications.

De Conno, F., Ventafridda, V. & Saita, L. (1991). Skin problems in advanced and terminal cancer patients. *Journal of Pain and Symptom Management, 6*(4), 247-255.

Des-Rochers, C., Dische, S. & Saunders, M.I. (1992). The problem of cigarette smoking in radiotherapy for cancer in the head and neck. *Clinical Oncology Royal College of Radiologists, 4*, 214-216.

Denham, J.W., Hamilton, C.S., Simpson, S.A., Ostwald, M., O'Brien, P.M., Kron, T., Joseph, D.J. & Dear, K.B.G. (1995). Factors influencing the degree of erythematous skin reactions in humans. *Radiation and Oncology, 36*, 107-120.

Dische, S. (1991). A review of hypoxic cell radiosensitization. *International Journal of Radiation Oncology Biology Physics, 20*, 147-152.

Dische, S. (1994). The uniform reporting of treatment-related morbidity. *Seminars in Radiation Oncology 4*(2), 112-118.

Dische, S., Saunders, M.I. & Warburton, M.F. (1986). Hemoglobin, radiation, morbidity and survival. *International Journal of Radiation Oncology Biology Physics, 12*, 1335-1337.

Dische, S., Warburton, M.F. & Saunders, M.I. (1988). Radiation myelitis and survival in the radiotherapy of lung cancer. *International Journal of Radiation Oncology Biology Physics, 15*, 75-81.

Dow, K.H. & Hilderley, L.J. (1992). *Nursing Care in Radiation Oncology* Philadelphia: W.B. Saunders Company.

Downes, M. Porock, D. & Upright, C. (1997). Retention dressings: An alternative for patient comfort in radiation skin reactions *Primary Intention 5*(3), 16-22.

Dutriex, J. (1986). Radiotherapy studies in skin: clinical and experimental. *British Journal of Radiology, 19* suppl., 22-28.

Dwyer, T., Blizzard, L. & Ashbolt, R. (1996, November). *A new measurement of skin colour.* Paper presented at the 23rd Annual Scientific Meeting of the Clinical Oncology Society of Australia, Brisbane, Queensland, Australia.

Ellis, F. (1969). Dose, time and fractionation: A clinical hypothesis. *Clinical Radiology, 20*, 1-7.

Exton-Smith, AN. (1971). Nutrition of the elderly *British Journal of Hospital Medicine, 5*, 639-645.

Fleck, R., McNeese, M.D., Ellerbroek, N.A., Hunter, T.A. & Holmes, F.A. (1989). Consequences of breast irradiation in patients with pre-existing collagen vascular diseases. *International Journal of Radiation Oncology Biology Physics, 17,* 829-833.

Fowler, J.F. (1979). New horizons in radiation oncology. *British Journal of Radiaology, 52,* 523-535.

Fowler, J.F. & Stern, B.E. (1960). Dose-rate effects: some theoretical and practical considerations. *British Journal of Radiology, 33,* 389-395.

Fu, K. (1985). Biological basis for the interaction of chemotherapeutic agents and radiation therapy. *Cancer, 55,* 2123-2130. (Suppl).

Geara, F.B., Peters, L.J., Ang. K.K., Wike, J.L. & Brock, W.A. (1992). Radiosensitivity measurement of keatinocytes and fibroblasts from radiotherapy patients. *International Journal of Radiation Oncology Biology Physics, 24,* 287-293.

Gilchrist, B.A. (1984). *Skin and Aging Processes.* Boca Raton, Florida: CRC Press Inc.

Gray, L.H., Conger, A.D., Ebert, M., Hornsey, S. & Scott, O.C.A. (1953). The concentration of oxygen dissolved in tissues at the time of irradiation as a factor in radiotherapy. *British Journal of Radiology, 26*(312), 638-648.

Goldfarb, M.T., Ellis, C.N. & Voorhees, J.J. (1990). Dermatology. In C.K. Cassel, D. E. Reisenberg, L.B. Sorensen & J.R. Walsh (Eds). *Geriatric Medicine 2nd Edition.* New York, Springer Verlag. pp 383 - 393.

Hall, E.J. (1985). Radiation biology. *Cancer, 55,* 2051-2057.

Hamilton, C.S., Denham, J.W., O'Brien, M., Ostwald, P., Kron, T., Wright, S. & D¬rr, W. (1996). Underprediction of human skin erythema at low doses per fraction by the linear quadratic model. *Radiation and Oncology, 40,* 23-30.

Harber, L.C. & Bickers, D.R. (1981). *Photosensitivity Diseases. Principles of Diagnosis and Treatment.* Philadelphia : W.B. Saunders.

Hart, R.M., Kinler, B.F. & Evans, R.G. (1987). Radiotherapeutic management of medulloblastoma in a paediatric patient with ataxia telangiectasia. *International Journal of Radiation Oncology Biology Physics, 13,* 1237 - 1240.

Hayward, J. (1975). Information - a prescription against pain. RCN Publications, London.

Hendry, J.H. (1994). Biological response modifiers and normal tissue injury after irradiation. *Seminars in Radiation Oncology, 4*(2), 123-132.

Hilderley, L.J. (1992) Radiation oncology: historical background and principles of teletherapy. In Dow, K.H. & Hilderley, L.J. *Nursing Care in Radiation Oncology.* Philadelphia: W.B. Saunders Company.

Hilderley, L.J. (1993). Radiotherapy. In Groenwald, S.L., Frogge, M.H., Goodman, M. & Yarbro, C.H. *Cancer Nursing. Principles and Practice (3rd ed).* Jones and Bartlett Publishers : Boston.

Hirshfield-Bartek, J. (1992). In Dow, K.H. & Hilderley, L. J. *Nursing Care in Radiation Oncology* Philadelphia: W.B. Saunders Company.

Holmes, S. (1988). *Radiotherapy.* Austin Cornish : London.

Jacobson, R.G. & Flowers, F.P. (1996). Skin changes with aging and disease. *Wound Repair and Regeneration, 4*(3), 311-315.

Johnson, J.E., Fieler, V.K., Wlasowicz, G.S., Mitchell, M.L. & Jones, L.S. (1997a). *Self-regulation theory: Applying theory to your practice.* Pittsburgh: Oncology Nursing Press.

Jolles, B. & Harrison, R.G. (1966). Enzymatic processes and vascular changes in the skin radiation reaction. *British Journal of Radiology, 39,* 12-18.

Kaplan, H.S. (1970). Radiobiology's contribution to radiotherapy: Promise or Mirage? Failla Memorial Lecture. *Radiation Research, 43,* 460-476.

King, K.B., Nail, L.M., Kreamer, K., Strohl, R.A. & Johnson, J.E. (1985). Patients' descriptions of the experience of receiving radiation therapy. *Oncology Nursing Forum, 12*(4), 55-61.

Kirk, J., Frey, W.M. & Watson, E.R. (1971). Cumulative radiation effect 1: Fractionated treatment regimens. *Clinical Radiology, 122,* 145-155.

Knighton, DR., Silver, IA. & Hunt, TK., (1981). Regulation of wound healing angiogenesis - effect on oxygen gradients and inspired oxygen concentration. *Surgery 90,* 262-70.

Kucera, H., Enzelsberger, H., Eppel, W. & Weghaupt, K. (1987). The influence of nicotine abuse and diabetes mellitus on the results of primary irradiation in the treatment of carcinoma of the cervix. *Cancer, 60,* 1-4.

Kurtz, J.M., Jacquemier, J., Torhorst, J., Spitalier, J., Amalric, R., Hſnig, R., Walther, E., Harder, F., Almendral, A., Brandone, H., Ayme, Y. & Roth, J. (1989). Conservation therapy for breast cancers other than infiltrating ductal carcinoma. *Cancer, 63,* 1630-1635.

Laurence, D. & Bennett, P. (1987). *Clinical Pharmacology (6th ed.)* London: Churchill Livingstone.

Lynn, M.R. (1986). Determination and quantification of content validity. *Nursing Research, 35*(6), 382-285.

Maciejewski, B. Withers, H.R., Taylor, J.M.G. & Hliniak, A. (1990). Dose, fractionation and regeneration in radiotherapy for cancer of the oral cavity and oropharynx II. Normal tissue responses: Acute and late effects. *International Journal of Radiation Oncology Biology Physics, 18,* 188-196.

Mahon, S.M. & Casperson, D.S. (1995). Hereditary Cancer Syndrome: Part 1 - Clinical and Educational Issues. *Oncology Nursing Forum, 22* (5), 763-771

McDonald, A. (1992). Altered Protective Mechanisms, In Dow, K.H. & Hilderley, L.J. *Nursing Care in Radiation Oncology,* Philadelphia: W.B. Saunders Company.

McNally, J.C. Campbell Stair, J. & Somerville, G.T. (eds) (1985). *Guidelines for Cancer Nursing Practice*. Orlando: Grune and Stratton, Inc, 170-177.

Mosely, L.H., Finseth, F. & Goody, M. (1978). Nicotine and its effect on wound healing. *Plastic and Reconstructive Surgery, 61*(4), 570-575.

Nixon, D., Heynesfield, S. Cohen, A. et al. (1980). Protein-calorie undernutrition in hospitalised cancer patients. *American Journal of Medicine, 68,* 683-690.

Noll, A. (1992). In Dow, K.H. & Hilderley, L.J. *Nursing Care in Radiation Oncology,* Philadelphia: W.B. Saunders Company.

Ogawa, C.M. (1975). Degenerative skin disorders: toll of age and sun. *Geriatrics, 30,* 65-69.

O'Rourke, M.E. (1987). Enhanced cutaneous effects in combined modality therapy. *Oncology Nursing Forum, 14*(6), 31-35.

Overgaard, J. (1989). The current and potential role of hyperthermia in radiotherapy. *International Journal of Radiation Oncology Biology Physics, 16,* 535-549.

Overgaard, J., Nielson, J.E. & Gray, (1992). Effect of carboxyhemoglobin on tumor oxygen unloading capacity in patients with squamous cell carcinoma of the head and neck. *International Journal of Radiation Oncology Biology Physics, 22,* 407-410

Pedersen, D., Bentzen, S.M. & Overgaard, J. (1994). Early and late radiotherapeutic morbidity in 442 consecutive patients with locally advanced

carcinoma on the uterine cervix. *International Journal of Radiation Oncology Biology Physics, 29*(5), 941 – 952.

Perez, C.A. & Brady, L.W. (1992). *Principles and Practice of Radiation Oncology (2nd ed)*. Pennsylvania: J.B. Lippincott Co.

Peters, L.J. (1990). The ESTRO Regaud Lecture. Inherent radiosensitivity of tumour and normal tissue cells as a predictor of human tumour response. *Radiotherapy and Oncology, 17,* 177-190.

Phillips, T. (1980). Tissue toxicity of radiation-drug interactions. In Skol, G. & Maikel, R. (eds). *Radiation-Drug Induced Interactions in the Treatment of Cancer.* New York : John Wiley & Sons.

Poroch, D. (1995). The Effects of Preparatory Patient Education on the Anxiety and Satisfaction of Cancer Patients Receiving Radiation Therapy *Cancer Nursing 18.(*3), 206-214.

Ross, J.G., Hussey, D.H., Mayr, N.A. & Davis, C.S. (1993). Acute and late reactions to radiation therapy in patients with collagen vascular diseases. *Cancer, 71,* 3744-3752.

Rugg, T., Saunders, M.I. & Dische, S. (1990). Smoking and mucosal reactions to radiotherapy. *British Journal of Radiology 63*, 554-556.

Santucci, I. (1995). *The use of Thiols in Preventing the Trans to Cis Photoisomerisation of Urocanic Acid.* Unpublished Doctoral Thesis Flinders University of South Australia.

Senter, H. & Pringle, A. (1985). *How Wounds Heal.* Calmic Medical Division of the Welcome Foundation.

Siana, JE., Franklid, S & Gottrup, F. (1992). The effect of smoking on tissue function. *Journal of Wound Care, 1*(2), 37-41.

Sitton, E. (1992). Early and late radiation-induced skin alterations. Part 1: Mechanisms of skin changes. *Oncology Nursing Forum, 19*(5), 801-807.

Smale, A.F., Mullen, J.L., Buzby, G.P. & Rosato, E.F. (1981). The efficacy of nutritional assessment and support in cancer surgery. *Cancer, 47*, 2375-2381.

Staab, A.S. & Hodges, L.C. (1996). *Essentials of Gerontological Nursing. Adaptation to the Aging Process*. Philadelphia: JB Lippincott Company.

Strohl, R.A. (1992). The elderly patient receiving radiation therapy: Treatment sequelae and nursing care. *Geriatric Nursing*, May/June, 153-156.

Tabachnik, B.G. & Fidell, L.S. (1996). Using Multivariate Statistics (3rd ed). Califormia: Harper Collins College Publishers.

Taylor, M.B., Moran, B.J. & Jackson, A.A. (1989). Nutritional problems and care of patients with far-advanced disease. *Palliative Medicine, 3*, 31-38.

Teo, P., Tai, T.H. & Choy, D. (1989). Nasopharyngeal carcinoma with dermatomyositis. *International Journal of Radiation Oncology Biology Physics, 16*, 471-474.

Tucker, S.L., Turesson, I. & Thames, H.D. (1992). Evidence of individual differences in the radiosensitivity of human skin. *European Journal of Cancer, 28A*(11), 1783-1791.

Turesson, I. (1989). The progression rate of late radiation effect in normal tissue and its impact on dose and response relationships. *Radiation and Oncology, 15*, 217-226.

Turesson, I. (1990). Individual variation and dose dependency in the progression rate of skin telangiectasia. *International Journal of Radiation Oncology Biology Physics, 19*, 1569-1574.

Turesson, I. & Notter, G. (1984). The influence of the overall treatment time in radiotherapy on the acute reaction: comparison of the effects of daily and

twice-a-week fractionation on human skin. *International Journal of Radiation Oncology Biology Physics, 10,* 607-618.

Turesson, I & Notter, G. (1986). The predictive value of skin telangiectasia for late radiation effects in different normal tissues. *International Journal of Radiation Oncology, Biology Physics, 12,* 603-609.

Turesson, I., Nyman, J., Holmberg, E. & Odén, A. (1996). Prognostic factors for acute and late skin reactions in radiotherapy patients. *International Journal of Radiation Oncology Biology Physics, 36*(5), 1065-1075.

Turesson, I. & Thames, H.D. (1989). Repair capacity and kinetics of human skin during fractionated radiotherapy: erythema, desquamation and telangiectasia after 3 and 5 year's follow-up. *Radiotherapy and Oncology, 15,* 169-188.

Vander, A.J., Sherman, J.H. & Luciano, D.S. (1994). *Human Physiology. The Mechanisms of Body Function (5th Ed).* New York: McGraw-Hill Publishing Company.

von der Maase, H. (1994). Complications of combined radiotherapy and chemotherapy. *Seminars in Radiation Oncology, 4*(2), 81-94.

Westaby, S. (1985). *Wound Care.* London: William Heinemann Medical Books Ltd.

Withers, H.J. (1992). Biologic basis of radiation therapy. In Perez, C.A. and Brady, L.W. *Principles and Practice of Radiation Oncology (2nd ed).* Pennsylvania: J.B. Lippincott Co.

Yasko, J.M. (1992). Care of the patient receiving radiation therapy. *Nursing Clinics of North America, 17,* 631-648.

Young, A.R. (1990). Cumulative effects of ultraviolet radiation on skin cancer and photoaging. *Seminars in Dermatology, 9,* 25-31.

Appendix A

Anatomy and Physiology of Normal Skin

Normal Skin

The skin is the largest organ of the body accounting for approximately 15% of body weight and along with its appendages, hair, nails, sebaceous and sweat glands, forms the integumentary system. Carville (1995) describes the integument as a complex system that performs five major functions: protection of underlying structures; sensation; communication; thermoregulation and metabolic synthesis.

The skin is divided into two layers, the epidermis and the dermis, each with a distinct structure and function. The epidermis is further divided into five layers and the dermis into two.

Epidermis

The innermost of the five epidermal layers is the *stratum germinativum* or basal layer where constant mitotic reproduction of squamous cells occurs. The second layer is the *stratum spinosum* and the third, the *stratum granulosum*. These three layers together are also known as the Malphygian layer. The thickness of the Malphygian layer varies throughout the body and is related to the amount of friction occurring in each area. The fourth layer, *stratum lucidum*, is only present in the thick skin of the soles and palms. The cells of the fifth and outermost layer, the *stratum corneum*, are dead, having been converted to a water-repellent protein called keratin. This layer sheds (desquamates) continually.

The epidermis is avascular; the capillary beds in the upper layer of the dermis supply nutrition through the thin basement membrane between the dermis and the epidermis. Interstitial fluid infiltrates the intercellular spaces of the *stratum germinativum* from the capillaries in the underlying dermis.

About 10% of the human epidermis undergoes mitosis daily (Breathnach & Wolff, 1979) and it has been estimated that the basal cells of the skin take eight

hours to replicate (Withers, Peters, Thames & Fletcher, 1992). Frequency of mitosis in the *stratum germinativum* varies directly with the rate of desquamation at the epidermal surface. Under normal conditions the rate of mitosis in the basal layer is able to maintain the supply of these overlying non-dividing squamous cells. The cells of the *stratum germinativum* are vegetative intermitotic cells relatively sensitive to radiation (Casarett, 1980).

Cells other than those in the germinal layer are primarily fixed postmitotic squamous cells. These are first cylindrical, and subsequently polyhedral. They then differentiate to become flattened, anucleated, keratinised, superficial skin layers that are extremely refractory to radiation and are highly radioresistant (Casarett, 1980; McDonald, 1992).

Other structures found in the epidermis are melanocytes, hair, and sebaceous and sweat glands all of which are composed of specialised epithelial cells continuous with the *stratum germinativum* of the epidermis.

Melanocytes

Melanocytes are found at the junction of the pigmented basal layer of the *stratum germinativum* and the dermis. Melanocytes determine the colour of the skin along with the inherent yellow colour of the skin and the vasculature of the dermis. Melanin production is stimulated by ultraviolet radiation (UV) as a fine granular substance that is passed through the cell layers of the epidermis showing at the surface as hyperpigmentation. Melanocytes are probably reverting postmitotic cells and are relatively radiosensitive (Casarett, 1980; McDonald, 1992).

Hair.

The hair consists of the visible hair shaft and the root situated in the hair follicle which is a continuation of the *stratum germinativum.* Approximately 85-90% of hair follicles on the scalp are in the active growing (anagen) phase at any one

time. The root of the hair divides rapidly, pushing the previously produced cells up the shaft. After the talogen (resting) phase, the hair is shed as the new growth starts in the hair follicle.

Due to its active reproduction the hair is relatively radiosensitive with more rapidly growing hair having higher radiosensitivity. Lacassagne and Gricouroff (1956, cited in McDonald, 1992) ranked the radiosensitivity of hair in decreasing order thus: scalp hair, male beard, eyebrows, axilla, pubis and last, fine body hair

Sebaceous glands.

Sebaceous glands secrete oil for the hair and skin as a natural moisturiser preventing excessive water evaporation from the skin and water absorption through the skin. The presence of sebum on the surface of the skin conserves heat loss from the body. Sebaceous glands are classified as holocrine glands. Secretions produced by holocrine glands consist of the disintegrated cells of the gland. Secretion of sebum is followed by mitotic regeneration of the secretory cells. These regenerating cells are vegetative intermitotic cells and are relatively radiosensitive. The epithelial cells not involved in secretion, are fixed postmitotic cells and are relatively radioresistant (Casarett, 1980; McDonald, 1992).

The radiosensitivity of sebaceous glands is approximately equivalent to hair follicles (Casarett, 1980). After a dose of radiation high enough to cause depilation, a reduction in secretion of sebaceous glands begins within a week. After a month, few glands persist and in those that do, degenerative changes are apparent.

Sweat glands.

Sweat glands are small but numerous in the body performing an important part in maintaining homeostasis of fluid and electrolytes and body temperature. Sweat glands are classified as merocrine glands. Merocrine glands produce their secretion within the cells and are not destroyed in the process. This makes them

less vulnerable to damage as the frequency of mitosis required to repair or replace sweat glands is less than for sebaceous glands. The epithelial cells that line this simple, coiled tubular gland are reverting postmitotic cells and are, therefore, relatively radioresistant (Casarett, 1980; McDonald, 1992).

Dermis

The dermis is divided into two layers, the dermis and the hypodermis or subcutaneous layer. The dermis is a very vascular layer also containing nerve endings, lymphatics, connective tissue and collagen fibres (Bryant, 1987). The components of the dermis are principally responsible for tissue repair. The hypodermis is a layer of loose connective tissue with variable amounts of adipose tissue. Its principal function is in connecting the dermis to underlying fascia or periosteum.

In radiation skin reactions, damage to the dermis, either in the acute or chronic phases, is rarely seen with modern radiotherapy techniques, therefore, the epidermal layer is of primary concern (McDonald, 1992).

Appendix B

Normal Tissue Repair

Repair of Normal Tissue

A background to radiotherapy and the effects of ionizing radiation on normal tissues would not be complete without some information on the mechanisms involved and the factors affecting the repair of epithelial tissue. Many factors influence the progress of healing, whether the cause of the tissue damage is from ionizing radiation or any other trauma. These factors are essential to understanding the theoretical underpinnings of the proposed model. The factors are described and discussed in the second section of this chapter in relation to their potential impact on the severity of radiation reactions. Although the mechanism by which radiation causes trauma to normal tissue is different from other injury, meaning that radiation reactions cannot be strictly defined as a wound, the process and mechanisms of healing are the same in principle. The differences, due to the permanent damage caused by radiation, are described in detail in the section on radiohistopathology.

The healing process of damaged tissue is usually described as occurring by first or second intention. Healing by primary intention is the union of the edges of a wound, progressing to complete healing without scar formation or granulation. Healing by secondary intention is wound closure in which the edges are separated, granulation tissue develops to fill the gap and epithelium grows over the granulations, producing a scar (Mosby, 1990).

Phases of Tissue Repair

Inflammatory phase.

Tissue damage initiates the inflammatory response where a cascade effect leads to the release of histamine along with other vasoactive chemicals causing vasodilation in surrounding tissue. As more blood flows to the area, erythema,

oedema, heat and discomfort ensue. The inflammatory response includes the arrival of polymorphonuclear leucocytes (polymorphs/neutrophils), to protect the wound from bacterial invasion, and macrophages, to clear the wound of debris

Reconstruction phase.

A primary mechanism in the reconstruction phase occurs through the attraction of fibroblasts to the wound as a result of growth factors produced by macrophages. Growth factors stimulate fibroblasts to produce collagen and to form new blood vessels (angiogenesis) which are then capable of bringing oxygen to the wound.

Epithelialisation phase.

Epithelialisation is an important phase in the healing of radiation skin ar mucosal reactions and is the phase where skin loss is repaired by renewal of epithelial cells. Squamous cells at wound margins and around hair follicle remnants proliferate and migrate over the wound surface in a leap-frog fashion (Dealey, 1994). Migration stops when cells meet, either in the centre of the wound forming islets of cells, or at the edges. This is known as contact inhibition. Epithelial cells can only migrate where the tissue is viable and the wound environment is moist (Winter, 1962).

Maturation phase.

Maturation occurs over a long period often taking more than a year. The mechanisms involved are reduction in vascularity, re-organisation of collagen fibres and remodelling of scar tissue. During the maturation phase, tensile strength increases and the ability of the wound to resist friction and breakdown increases commensurately.

Appendix C

Mechanisms of Radiation Enhancement with Cytotoxic Agents

Mechanism of Cytotoxicity and Possible Mechanism of Enhancement of Radiation Effects in 15 Commonly Used Chemotherapeutic Drugs

Drug	Mechanism of Cytotoxicity	Possible mechanism of radiation enhancement
Dactinomycin	Intercalates DNA and inhibits DNA and RNA synthesis; causes single-strand breaks in DNA	↑ slope of radiation dose response curves, ↓ SLD and PLD repair
Adriamycin (doxorubicin)	Intercalcates DNA and inhibits DNA, RNA, and protein synthesis	Additive cytotoxicity, ↓ accumulation of SLD, ↓ PLD repair
Bleomycin	Causes single- and double-strand breaks in DNA, inhibits DNA synthesis, preferencially kills cells in G_2 and M phases.	? ↓ of repair of drig damage by radiation, ? perturbations in cell kinetics
BCNU, CCNU	Causes DNA strand breaks and crosslinks by alkylation and inhibits DNA, RNA, and protein synthesis	Additive cytotoxicity, ? ↓ of SLD repair, ? perturbations in cell kinetics
Cisplatin	Causes DNA intrastrand crosslinks and changes in DNA conformation and inhibits DNA, RNA, and protien synthesis	↓ SLD and PLD repair, ↑ slope of hypoxic cell radiation dose response curves
Cyclophosphamide	Causes DNA crosslinks by alkylation and inhibits DNA synthesis	Additive cytotoxicity
Cytosine arabinoside	Inhibits DNA synthesis, selectively kills cells in the S phase	↓ PLD repair, ? ↓ SLD repair, perturbations in cell kinetics
5-Fluorouracil	Binds and inhibits thymidylate synthetase and inhibits RNA processing and function	↑ slope of radiation dose response curve postdrug exposure, ? perturbations in cell kinetics
Hydroxyurea	Inhibits ribonucleoside diphosphate reductase and DNA synthesis, selectively kills cells in the S phase	Perturbations in cell kinetics

Drug	Mechanism of Cytotoxicity	Possible mechanism of radiation enhancement
Methotrexate	Inhibits dihydrofolate reductase and synthesis of thymidylate and purine nucleotide	? perturbations in cell kinetics
Mitomycin C	Causes intrastrand and interstrand crosslinks in DNA by alkylation and inhibits DNA synthesis	Additive cytotoxicity
Nitrogen mustard	Causes single-strand breaks and crosslinks in DNA by alkylation and inhibits DNA, RNA, and protein synthesis	Additive cytotoxicity
Vincristine; vinblastine	Binds tubulin, poisons the mitotic spindle and causes mitotic arrest	?perturbations in cell kinetics

SLD = sublethal damage; PLD = potentially lethal damage

From Fu, K (1985). Biological basis for the interaction of chemotherapeutic agents and radiation therapy. *Cancer* (Suppl), May 12, p 2127.

Appendix D

Agents That May Cause Photosensitivity Reactions

Agents That May Cause Photosensitivity Reactions

Chemotherapy
* Decarbazine
Fluorouracil
Methotrexate
Procarbazine
Vinblastine
Adiamycin

Antidepressants
Imipramine
Amitryptyline
Amoxapine
Desipramine
Doxepin
Maprotiline
Isocarboxazid
Nortriptyline
Protriptyline
Trimipramine

Antihistamines
Cyproheptadine
Diphenhydramine

Antimicrobials
Demeclocycline
Doxycycline
Griseofulvin
Methacycline
Minocycline
*Nalidizic
Oxytetracycline
Sulfacytine
Sulfamethazine
Sulfamethazole
Sulfamethoxazole-trimethoprim
Sulfasalazine
Sulfathiazole
Sulfisoxazole
Tetracycline

Antiparasitic Drugs
*Bithionol
Pyrvinium pamoate
Quinine

Antipsychotic Drugs
Chlorpromazine
Chlorprothixine
Fluphenazine
Haloperidol
Perphenazine
Promethazine
Piperacetazine
Promethazine
Thioridazine
Trifluoperazine
Thiothixene
Triflupromazine
Trimeprazine

Diuretics
Acetazolamide
Chlorothiazide
Furosemide
Hydrochlorothiazide

Hypoglycemics
Chloropropamide
Glyburide

Nonsteroidal Anti-inflammatory
Ketoprofen
Naproxen
Phenylbutazone
Piroxicam
Sulindac

Sunscreens
Benzophenones (Aramis, Clinique)
Cinnamates (Aramis, Estee Lauder)
Oxybenzone (Eclipse, PreSun)
PABA and PABA esters (Block Out, Sea & Ski)

Miscellaneous Drugs
*Amiodarone

*Bergamot oil, oils of citron, lavender, lime, sandalwood, cedar
Carbamazapine
Contraceptives
Disopyramine

* Reactions occur frequently (McDonald, 1992).

Appendix E

Weekly Skin Reaction Observation Record

weekly skin reaction observation record ID _ _ _ _ _

DATE WEEK	SITE R / L	RTOG SCORE	DOSE	TOPICAL Rx DATE	DRESSING	PAIN SCORE	COMMENTS
week 1	midline chest wall						
	axilla						
	upper outer quadrant						
	upper inner quadrant						
	lower outer quadrant						
	lower inner quadrant						
	nipple						
	inframammary fold						
week 2	midline chest wall						
	axilla						
	upper outer quadrant						
	upper inner quadrant						
	lower outer quadrant						
	lower inner quadrant						
	nipple						
	inframammary fold						
week 3	midline chest wall						
	axilla						
	upper outer quadrant						
	upper inner quadrant						
	lower outer quadrant						
	lower inner quadrant						
	nipple						
	inframammary fold						

weekly skin reaction observation record continued ID

DATE WEEK	SITE R / L	RTOG SCORE	DOSE	TOPICAL Rx DATE	DRESSING	PAIN SCORE	COMMENTS
week 4	midline chest wall						
	axilla						
	upper outer quadrant						
	upper inner quadrant						
	lower outer quadrant						
	lower inner quadrant						
	nipple						
	inframammary fold						
week 5	midline chest wall						
	axilla						
	upper outer quadrant						
	upper inner quadrant						
	lower outer quadrant						
	lower inner quadrant						
	nipple						
	inframammary fold						
week 6	midline chest wall						
	axilla						
	upper outer quadrant						
	upper inner quadrant						
	lower outer quadrant						
	lower inner quadrant						
	nipple						
	inframammary fold						

weekly skin reaction observation record continued ID

DATE WEEK	SITE R / L	RTOG SCORE	DOSE	TOPICAL Rx DATE	DRESSING	PAIN SCORE	COMMENTS
week 7	midline chest wall						
	axilla						
	upper outer quadrant						
	upper inner quadrant						
	lower outer quadrant						
	lower inner quadrant						
	nipple						
	inframammary fold						
Spare	midline chest wall						
	axilla						
	upper outer quadrant						
	upper inner quadrant						
	lower outer quadrant						
	lower inner quadrant						
	nipple						
	inframammary fold						
Spare	midline chest wall						
	axilla						
	upper outer quadrant						
	upper inner quadrant						
	lower outer quadrant						
	lower inner quadrant						
	nipple						
	inframammary fold						

Appendix F

Data Collection Form for Predictive Factors

URMN sticker

PRIVATE AND CONFIDENTIAL

Predicting the severity of skin reactions in patients receiving radiotherapy for cancer.

Data Collection Form - Breast Patients

ID code _ _ _ _

1. **Age** (in years at last birthday) _ _ _

Diagnosis and Treatment

2. **Diagnosis/Histology** _____ _ _

3. **Time since diagnosis(weeks, months,years)**

_____ _ _

Reasons for delay

_____

_____

_____

4. **a. Stage at diagnosis**

Stage 0	Tis	N0	M0	0
Stage I	T1	N0	M0	1
Stage IIA	T0	N1	M0	2
	T1	N1	M0	
	T2	N0	M0	
Stage IIB	T2	N1	M0	3
	T3	N0	M0	
Stage IIIA	T0	N2	M0	4
	T1	N2	M0	
	T2	N2	M0	
	T3	N1,N2	M0	
Stage IIIB	T4	Any N	M0	5
	Any T	N3	M0	
Stage IV	Any T	Any N	M1	6

b. Recurrences

No 0

Yes, number of times ___

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Sir Charles Gairdner Hospital

ID ___

Combined Treatment Modality Details

5. **a. Condition of Breast Scar**

Yes, scar fading	1
Yes, inflamed	2
Yes, haemoserous discharge	3
Yes, purulent discharge	4

b. Axilla scar

No axillary clearance	0
Yes, scar fading	1
Yes, inflamed	2
Yes, haemoserous discharge	3
Yes, purulent discharge	4

c. Lymphocele requiring drainage

No	0
If yes, approximate number of times	__ __

6. **a. Chemotherapy (Combined Modality Treatment)**

No (go to # 7)	0
Yes	1

Regimen _____

If yes, go on to part b.

b. Chemotherapy commenced before radiotherapy

No (go to # 7)	0
Yes	1

c. Chemotherapy completed before radiotherapy commenced

No	0
Yes	1

Personal and Family Cancer History

7. a. Previous cancer

No	0
Yes, how many times	__ __

Please specify _____

_____

8. a. Chemotherapy for Previous Cancer

No	0
Yes	1

b. Type and how long ago?

_____

_____

9. a. Radiotherapy for Previous Cancer

No	0
Yes, but not at same site	1
Yes, includes some or all of current treatment site	2

b. How long ago?

_____

_____

10. a. Family history of cancer (1st and 2nd degree relatives only)

No	0
Yes, how many family members	__ __

Specify type of cancer and relationship _____

_____

_____

_____

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General health

11. Co-existing chronic disease

No	0
Yes, not known radiosensitive disease	__
Yes, known radiosensitive disease	__

12. a. Prescribed medications

No	0
yes, drugs not known to adversely affect healing	__
yes, drugs known to adversely affect healing	__

b. Other medications (over the counter/complementary/alternative therapies)

No	0
i general health	1
ii aid healing	1
iii anticancer	1

13. Smoking

a. Have you ever smoked regularly?

No (go to question 15)	0
Yes	1

b. if yes, when did you start smoking? 19 __ __

c. Average, number of cigarettes did/do you smoke each day? __ __ __

d. Do you smoke now?

i) if no, when did you quit?	19 __ __
ii) if yes, how many per day?	__ __ __

14. Alcohol

a. Have you ever drunk alcohol regularly?

No (go to question 16)	0
Yes	1

b. if yes, when did you start drinking regularly? 19 __ __

c. Average, standard drinks did/do have each time?

i) did __ __

ii) do __ __

d. Do you drink now?

i) if no, when did you stop	19 __ __
ii) if yes, once or twice per month or less	1
Yes, about once per week	2
Yes, 2-3 times per week	3
Yes, 4-6 times per week	4
Yes, everyday	5

15. a. Current weight __ __ __ **kg**

b. Usual weight __ __ __ **kg**

c. Lowest weight during this illness __ __ __ **kg**

d. Height __ __ __ **cm**

16. Bra/cup size

a. dress size

10 12 14 16 18 20 22 24 ·24

b. cup

A	1
B	2
C	3
D	4
DD	5
>DD	6

17. a. Nutritional intake

Excellent: 1

Eats most of every meal. Never refuses a meal.
Usually eats a total of 4 or more servings of proteins.
Occasionally eats between meals. Does not require supplementation.

Adequate: 2

Eats over half of most meals.
Eats a total of 4 servings of proteins each day.
Occasionally will refuse a meal. but will take a supplement if offered.
OR
Is on adequate tube feeding or TPN regimen

Probably inadequate: 3

Rarely eats a complete meal and generally eats on 1/2 of any food offered.
Protein intake only 3 servings per day.
Occasionally will take dietary supplement.
OR
Receives less than optimum amount of liquid diet or tube feeding

Very poor: 4

Never eats a complete meal, Rarely eats more than a 1/3 of any food offered.
Eats 2 servings or less of protein each day.
Takes fluids poorly. Does not take a liquid diet supplement.
OR
Is nil by mouth and/or maintained on clear liquids
or IV's for more than five days.

18. f. Alternative/Complementary Diet

_____

_____

Skin Type and Condition

19. Skin type

Aways burns easily, never tans (sensitive)	1
Always burns, tans minimally (sensitive)	2
Burns moderately, tans gradually (light brown, normal)	3
Burns minimally, always tans well (moderately brown, normal)	4
Rarely burns, tans profusely (dark brown, insensitive)	5
Never burns, deeply pigmented (insensitive)	6

20. Skin type in treatment area

Oily	0
Normal	1
Dry	2

21. Skin allergy problems eg contact dermatitis, eczema etc.

No (go to question 20)	0

If yes, please specify

_____

_____

a. Frequency

Occasional problem (≤ 4 times per year)	1
Frequent problem (once per month)	2
Constant problem (virtually always present)	3

b. Severity

Mild (dry and peeling)	1
Moderate reaction (as above plus red, itchy)	2
Severe reaction (as above plus blisters/oozing)	3

c. Family History (1st and 2nd degree relatives only)

No	0
Yes, how many family members	__ __

_____

_____

Accumulative UV Exposure

22. a. How long have you lived in Australia? (years) ___

b. Predominant place you have lived up to the age of 15?

City/ Town _____ Country _____

c. Predominant place you have lived after the age of 15?

City/Town _____ Country _____

23. Cumulative UV exposure scale

*Which of the following statements best describes **your exposure to the sun** up to the age of 15:*

a. Did you spend most of your free time ...

in indoor activities	1
in both indoor and outdoor activities	2
in outdoor activities	3

b. When outdoors, how much did you protect yourself from the sun with a hat, clothing and/or sunscreen ...

almost always	1
often	2
sometimes	3
almost never	4

*Which of the following statements best describes **your exposure to the sun after the age of 15:***

c. Was or is your work mainly ...

indoors	1
both indoors and outdoors	2
outdoors	3

d. Did/do you spend most of your free time ...

in indoor activities	1
in both indoor and outdoor activities	2
in outdoor activities	3

e. When outdoors, how much did/do you protect yourself from the sun with a hat, clothing and/or sunscreen ...

almost always	1
often	2
sometimes	3
almost never	4

24. Demographics

a. Marital status

never married	1
permanent relationship married/de facto	2
separated	3
widowed	4
divorced	5

b. occupation

unemployed	1
retired	2
home duties	3
skilled trade	4
professional	5
unskilled	6
clerical	7
student	8

c. education completed

primary school (years 1 - 7)	1
lower secondary school (years 8 - 10)	2
upper secondary school	3
trade/secretarial training	4
undergraduate diploma/degree	5
higher degree	6

d. usual accomodation

own home/flat	1
rent home/flat	2
nursing home	3
hostel	4
other, specify _____	5

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f. area code (from addressograph) _ _ _ _

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Sir Charles Gairdner Hospital

ID _ _ _ _ _ _

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Treatment Details

25. **Electrons** **site** _____

energy _____ __ __Gy

Overall length of whole breast treatment (in days) __ __

Overall length of electron boost treatment (in days) __ __

Comments

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

Appendix G

Content Validity Check List

Content Validity Check

This set of questions relate to basic demographics and diagnosis and treatment details

Variable and Scoring	*1. Not relevant*	*2. Unable to assess without item revision*	*3. Relevant but needs minor alteration*	*4. Very relevant and succinct.*	*Comments on clarity, scoring etc.*
1. Age __ __ __(in years at last birthday)					
3. Histology					
4. Time since diagnosis					
5. TNM Staging.					
7. Recurrence					
9. Chemotherapy regimen					
Chemo commenced with XRT					
Chemo commenced before XRT					
How many cycles?_____					

Diagnosis and treatment details continued

Variable and Scoring	*1. Not relevant*	*2. Unable to assess without item revision*	*3. Relevant but needs minor alteration*	*4. Very relevant and succinct.*	*Comments on clarity, scoring etc.*
10. Chemotherapy for previous cancer					

The next set of questions relate to cancer 'proneness'

Variable and Scoring	*1.*	*2.*	*3.*	*4.*	*Comments on clarity, scoring etc.*
11 a. Has patient had cancer before ?					
b. Family history of cancer					

This set of questions relate to the patient's general state of health

Variable and Scoring	*1.*	*2.*	*3.*	*4.*	*Comments on clarity, scoring etc.*
12. Co-existing disease					
13. Prescribed medications					
Number of medications List medications					
14. Smoking habits					
Cigarette years__ __ __ Current smoker If yes (how many per day?) __ __ __					
15. Alcohol intake					

General health continued

Variable and Scoring	*1.*	*2.*	*3.*	*4.*	*Comments on clarity, scoring etc.*
16. Nutritional intake					
Weight					
Height					
Excellent: Eats most of every meal. Never refuses a meal. Usually eats a total of 4 or more servings of proteins. Occasionally eats between meals. Does not require supplementation					
Adequate: Eats over half of most meals. Eats a total of 4 servings of proteins each day. Occasionally will refuse a meal, but will take a supplement if offered. OR Is on adequate tube feeding or TPN regimen					
Probably inadequate: Rarely eats a complete meal and generally eats only 1/2 of any food offered. Protein intake only 3 servings per day. Occasionally will take dietary supplement.OR Receives less than optimum amount of liquid diet or tube feeding					

General health continued

Variable and Scoring	*1.*	*2.*	*3.*	*4.*	*Comments on clarity, scoring etc.*
Very poor: Never eats a complete meal, Rarely eats more than a 1/3 of any food offered. Eats 2 servings or less of protein each day. Takes fluids poorly. Does not take a liquid diet supplement.OR Is nil by mouth and/or maintained on clear liquids or IV's for more than five days.					

The following items relate to skin type and condition

Variable and Scoring	*1.*	*2.*	*3.*	*4.*	*Comments on clarity, scoring etc.*
17. Skin type					
Always burns easily, never tans (sensitive) 1 Always burns, tans minimally (sensitive) 2 Burns moderately, tans gradually (light brown, normal) 3 Burns minimally, always tans well (moderately brown, normal) 4 Rarely burns, tans profusely (dark brown, insensitive) 5 Never burns, deeply pigmented (insensitive) 6					

Skin type and condition continued

Variable and Scoring	*1.*	*2.*	*3.*	*4.*	*Comments on clarity, scoring etc.*
18. Skin allergy problems eg contact dermatitis, eczema etc.					
a. Frequency Nil 0 Occasional problem (≤ 4 times per year) 1 Frequent problem (once per month) 2 Constant problem (virtually always present) 3 **b. Severity** Nil 0 Mild/moderate reaction (red, itchy dry and peeling) 1 Severe reaction (as above plus blisters/oozing) 2 **c. Family History** No 0 Number of family members —					

Skin condition - Ultraviolet exposure

Variable and Scoring	*1.*	*2.*	*3.*	*4.*	*Comments on clarity, scoring etc.*
19. UV exposure					
a. Number of years in Australia					
b. Predominant place lived in under 15 years of age					
c. Predominant place after 15 years of age					
20. Accumulative UV exposure					
*Which of the following statements best describes **your exposure to the sun area** up to the age of 15 years?* I spent most of my free time in Indoor activities 1 And outdoor activities 2 Outdoor activities 3					
I went out in the sun without the protection of a hat, clothing and/or sunscreen almonst never 1 Sometimes 2 Often 3 Almost always 4					

Skin condition - Ultraviolet exposure continued

Variable and Scoring	*1.*	*2.*	*3.*	*4.*	*Comments on clarity, scoring etc.*
*Which of the following statements best describes **your exposure to the sun** during your adult life:* I mainly had jobs that were Indoors 1 Both indoors and outdoors 2 Outdoors 3					
I spent most of my free time in Indoor activities 1 And outdoor activities 2 outdoor activities 3					
I went out in the sun without the protection of a hat, clothing and/or sunscreen almonst never 1 Sometimes 2 Often 3 almost always 4					

Appendix H

Approval Letters from Ethics Committees

EDITH COWAN UNIVERSITY

Committee for the Conduct of Ethical Research

Ms Davina Porock

Dear Ms Porock

Re: **Ethics Approval**

Code: 95-107

Project Title: *Predicting the severity of skin and oral mucosal reactions in individual patients receiving radiotherapy for cancer.*

This project was considered by the Committee for the Conduct of Ethical Research at its meeting on 28 July 1995.

I am pleased to advise that the project complies with the provisions contained in the University's policy for the conduct of ethical research, and has been cleared for implementation.

Period of approval is from 31 July 1995 to 30 June 1998.

Yours sincerely

ROD CROTHERS
Executive Officer

31 July 1995

Please note: Students conducting approved research are required to submit an ethics report as an addendum to that which they submit to their Faculty's Higher Degrees Committee.

cc: Dr Patricia Percival, Supervisor
Mrs Gerrie Sherratt, Faculty Admin Officer
A/Prof S. Barnie, Doctoral Studies Committee

Sir Charles Gairdner Hospital

Our ref FS/pt167/letpjm/5005
Your ref
Enquiries to Ext. 2684
Date 22 March 1996

Ms Davina Porock

Dear Ms Porock

The research proposal "Predicting the Severity of Skin & Oral Mucosa Reactions in Individuals receiving Radiotherapy for Cancer" was considered at the Nursing Research and Ethical Review Committee meeting on 12 March 1996.

Your proposal has been approved for implementation.

Please contact Linda Murray, Co-Director (Nursing), Heart & Lung CSU on 346 1828 for further information.

Yours sincerely

p.p.

CHAIRMAN
NURSING RESEARCH AND ETHICAL REVIEW COMMITTEE

cc: Di Twigg, A/Executive Director of Nursing Services

WP ref: d:\docs\letters\pt167.doc
File ref: 5005

Appendix I

Participant's Information Letter and Consent Form

Research Title: **Predicting the degree of skin reaction in patients receiving radiotherapy**

Researcher: **Davina Porock, RN MSc(Curtin) PhD (Candidate), School of Nursing, Edith Cowan University**

Skin reaction is a fairly common side effect of radiotherapy and individual patients react to the treatment in different ways. Primarily the degree of skin reaction patients will experience depends on the dose of radiation they receive. However, previous research and clinical experience has shown that the skin reaction varies from person to person even when the same dose is given. This research project aims to develop a method of accurately predicting the degree of skin reaction to be expected. The benefits to future patients from this research will be in individualised education to prepare for this side effect and individualised skin care management.

You are invited to take part in this research project. It will involve completing a questionnaire now that details personal information about you and your skin and then a weekly check by me or a research nurse to document any skin reaction you experience. No risks are envisaged during this research. Your name will be kept on the data collection forms to assist following your progress through treatment These details will be kept confidential along with the normal medical record and your name will not be used in any report or publication from this research.
You are free to choose whether you take part in this research and to withdraw from the study at a later date should you so wish. Naturally, your decision will not affect the treatment you receive from the radiotherapy department in any way. If you should have any questions now or later, please do not hesitate to discuss them with my research assistants Marie Downes and Louise Good or contact me, Davina Porock on 273 8623 or my supervisors, Dr Sue Nikoletti at the University on 273 8593 or Dr Fiona Cameron in the Radiotherapy Department on 346 4900.

Thank you for your consideration

Davina Porock
PhD (Candidate)

Consent Form

I .....(print name) agree to take part in the research project being conducted by Davina Porock entitled "Predicting the degree of skin reaction in patients receiving radiotherapy" The study has been fully explained and I understand what is involved in taking part. I know that I am free to withdraw from the research at any time. I have been given the opportunity to ask questions now and given details for contacting the researcher at any time.

Patient's signature

.....date..... .....

Witness' signature

.....date.....

Appendix J

Self-medication and Complementary Therapies Used Regularly by Participants

Self-medication and Complementary Medicines Used Regularly by Participants

Medicine	General Health	Aid Healing	Anticancer
Echinacea	2		
Multivitamins	7	5	
Vitamin C	6	7	1
Iron	1		
Calcium	2		
Sandomycin	1		
Garlic	1	3	
Phenergrick	1		
Vitamin A	1	1	
Selenium	1		
Vitamin B	3	5	
Vitamin E	3	3	1
Cod liver oil / fish oil	2	2	
Evening Primrose Oil	2	3	
Cote a cola leaves	1		
Bioace	1		
Magnesium	1		
Silicone Calcium Fluoride (SCF)	1		
Lactoacid tablets	1		
Zinc Silica Calcium		2	
Celery Salt		1	
Ginko Biloba		3	
Cordio Silva			1
Antioxidants / Betacarotene			7
Chinese herbs (naturopaths own prescription)			2
Naturopaths tonic			2
Manchuria / Kambucha tea			2
combination of wormwood, black walnut drops and ground clove tablets			1
Jungle Juice			1
Flower essence tea			1
Native Cuppa			1
H_2O_2 DTX			1

Appendix K

Cross Validation Results

Cross Validation Results

Random Sample 1 – 40% of total sample

Random sampling by SPSS produced a subset of 54 cases for this analysis

Logistic Regression Results for the Week Five Sternum Reaction

Data from 54 cases were available for analysis: 30 (55.6%) had a scores of D-RTOG0 and 24 (44.4%) scored D-RTOG1. Two variables entered the model: history of skin cancer and age. These variables correctly predicted 80.00% of cases with mild or no reaction, and 41.67% of cases with a severe reaction giving an overall accuracy of 62.96% for the model. The model is significantly reliable when compared with the constant only model, $\chi^2(2) = 11.135$, $p = 0.0035$.

Variables	B	SE	Wald	DF	Sig	R	Exp(B)	95% CI
History of skin cancer	2.941	1.166	6.364	1	.012	.242	18.934	1.927 – 186.050
Age	-.059	.032	3.421	1	.0644	-.138	.943	.866 – 1.004
(Constant)	2.582	1.696	2.318	1	.128			

Logistic Regression Results for the Week Five Axilla Reaction

Due to missing values, data from 53 cases were available for analysis: 28 (52.8%) had a score of D-RTOG0 and 25 (47.2%) scored D-RTOG1. One variable entered the model: lymphocele aspiration. This variable correctly predicted 71.43% of cases with mild or no skin reactions and 52.00% of severe reactions, giving an overall accuracy of 62.26% of cases overall. The model was significantly reliable when compared with the constant only model, $\chi^2(1) = 3.053$, $p = 0.0806$.

Variables	B	SE	Wald	DF	Sig	R	Exp(B)	95% CI
Lymphocele aspirated	.996	579	2.961	1	.085	115	2 708	.871 – 8 425
(Constant)	-.511	365	1.957	1	.162			

Logistic Regression Results for the Week Five UOQ Reaction

Due to missing values, data from 53 cases were available for analysis. 34 (64.1%) had a score of D-RTOG0 and 19 (35.9%) scored D-RTOG1. Three variables entered the model: breast size, lymphocele aspirated and smoking. These variables correctly predicted 79.41% of mild or no skin reactions and 52.63% of severe skin reactions giving an accuracy of 69.81% overall. The model was significantly reliable when compared with the constant only model, $\chi^2(4) = 13\ 179$, $p = 0.0104$.

Variables	B	SE	Wald	DF	Sig	R	Exp(B)	95% CI
Breast size	1.378	.743	3.439	1	.064	.144	3.967	.925 – 17.017
Lymphocele aspirated	1.306	.679	3.698	1	.055	.157	3.693	.975 – 13.982
*Smoking			4.302	2	.116	.066		
Ex-smoker	1.092	.714	2.344	1	.126	.071	2.982	.736 – 12.073
Current smoker	1.827	.994	3.378	1	.066	.141	6.213	.886 – 43.584
(Constant)	-2.193	.650	11.387	1	.001			

*Reference group for smoking is the "never smoked" group

Logistic Regression Results for the Week Five LOQ Reaction

Due to missing values, data from 53 cases were available for analysis. 38 (71.7%) had a score of D-RTOG0 and 15 (28.3%) scored D-RTOG1. One variable entered the model: smoking. This variable correctly predicted 92.11% of mild or no reactions and 26.67% of severe reactions, giving an accuracy of 73.58% overall. The model was significantly reliable when compared with the constant only model, $\chi^2(2) = 6.569$, $p = 0.0375$.

Variables	B	SE	Wald	DF	Sig	R	Exp(B)	95% CI
*Smoking			5.916	2	.052	.174		
Ex-smoker	1.339	.725	3.414	1	.065	.150	3.186	.922 – 15.796
Current smoker	2.079	.935	4.940	1	.026	.216	7.996	1.278 – 50.006
(Constant)	-1.791	.540	11.005	1	.001			

*Reference group for smoking is the "never smoked" group

Logistic Regression Results for the Week Five LIQ Reaction

Due to missing values, data from 53 cases were available for analysis: 38 (71.7%) had a score of D-RTOG0 and 15 (28.3%) scored D-RTOG1. Two variables entered the model: breast size and smoking. These variables correctly predicted 92.11% of mild or no reactions, and 66.67% of severe reactions, giving an accuracy of 84.91% overall. The model was significantly reliable when compared with the constant only model, $\chi^2(3) = 13.515$, $p = 0.0036$.

Variables	B	SE	Wald	DF	Sig	R	Exp(B)	95% CI
Breast size	1.609	.760	4.489	1	.034	.199	4.998	1.128 – 22.143
*Smoking			7.197	2	.027	.225		
Ex-smoker	.915	.778	1.383	1	.240	.000	2.498	.543 – 11.483
Current smoker	2.801	1.046	7.165	1	.007	.286	16.462	2.117 – 127.989
(Constant)	-2.224	.625	12.661	1	.000			

*Reference group for smoking is the "never smoked" group

Logistic Regression Results for the Week Five Nipple Reaction

Due to missing values, data from 53 cases were available for analysis: 38 (71.7%) had a score of D-RTOG0 and 15 (28.3%) scored D-RTOG1. One variable entered the model: smoking. This model correctly predicted 97.37% of mild or no reactions and 26.67% of severe reactions, giving an accuracy of 77.36% overall. The model was significantly reliable when compared with the constant only model, $\chi^2(2) = 12.465$, $p = 0.0059$.

Variables	B	SE	Wald	DF	Sig	R	Exp(B)	95% CI
*Smoking			8.089	2	.018	.255		
Ex-smoker	1.217	.752	2.621	1	.106	.099	3.379	.774 – 14.751
Current smoker	3.407	1.238	7.581	1	.006	.297	30.185	2.670 – 341.320
(Constant)	-1.676	.545	9.466	1	.002			

*Reference group for smoking is the "never smoked" group

Random Sample 2 – 40% of total sample

Random sampling by SPSS produced a subset of 50 cases for this analysis.

Logistic Regression Results for the Week Five Sternum Reaction

Data from 50 cases were available for analysis: 42 (84.0%) had a scores of D-RTOG0 and 8 (16.0%) scored D-RTOG1. Only one variable entered the mode: history of skin cancer. This variable correctly predicted 96.55% of cases with mild or no reaction, and 33.33% of cases with a severe reaction giving an overall accuracy of 70.0% for the model. The model is significantly reliable when compared with the constant only model, $\chi^2(1) = 8.534$, $p = 0.0035$.

Variables	B	SE	Wald	DF	Sig	R	Exp(B)	95% CI
History of skin cancer	2.638	1.118	5.571	1	.018	.229	13.981	1.564 – 124.960
(Constant)	-.693	.327	4.484	1	.034			

Logistic Regression Results for the Week Five Axilla Reaction

Data from 50 cases were available for analysis: 31 (62.0%) had a score of D-RTOG0 and 19 (38.0%) scored D-RTOG1. One variable entered the model: lymphocele aspirated. This variable correctly predicted 72.41% of cases with mild or no skin reactions and 52.38% of severe reactions, giving an overall accuracy of 64.00% of cases overall. The model was significantly reliable when compared with the constant only model, $\chi^2(1) = 3.180$, $p = 0.0746$.

Variables	B	SE	Wald	DF	Sig	R	Exp(B)	95% CI
Lymphocele aspirated	1.060	.603	3.093	1	.079	.079	2.888	.986 – 9.412
(Constant)	-.742	.384	3.729	1	.0535			

Logistic Regression Results for the Week Five UOQ Reaction

Data from 50 cases were available for analysis: 46 (92.0%) had a score of D-RTOG0 and 4 (8.0%) scored D-RTOG1. Two variables entered the model: lymphocele aspirated and stage. These two variables correctly predicted 96.97% of mild or no skin reactions and 17.65% of severe skin reactions giving an accuracy of 70.00% overall. The model was significantly reliable when compared with the constant only model, $\chi^2(2) = 8.182$, $p = 0.0167$.

Variables	B	SE	Wald	DF	Sig	R	Exp(B)	95% CI
Lymphocele aspirated	1.617	.692	5.460	1	.020	.023	5.036	1.298 – 19.541
Stage	1.335	.735	3.298	1	.069	.142	3.801	.900 – 16.057
(Constant)	-1.767	.568	9.6728	1	.C02			

Logistic Regression Results for the Week Five UIQ Reaction

Data from 50 cases were available for analysis: 46 (92.0%) had a score of D-RTOG0 and 4 (8.0%) scored D-RTOG1. Two variables entered the model: lymphocele aspirated and stage. These variables correctly predicted 97.22% of mild or no reactions, and 21.43% of severe reactions giving an accuracy of 76.00% of

cases overall. The model was significantly reliable when compared with the constant only model, $\chi^2(2) = 5.961$, $p = 0.0508$.

Variables	B	SE	Wald	DF	Sig	R	Exp(B)	95% CI
Lymphocele aspirated	1.350	.703	3.685	1	.055	.169	3.857	.972 – 15.305
Stage group	1.255	.736	2.908	1	.088	.1238	3.508	.829 – 14.845
(Constant)	-1.938	.592	10.703	1	.0011			

Logistic Regression Results for the Week Five LOQ Reaction

Data from 50 cases were available for analysis: 42 (84.0%) had a score of D-RTOG0 and 8 (16.0%) scored D-RTOG1. One variable entered the model: smoking. This variable correctly predicted 89.19% of mild or no reactions and 30.77% of severe reactions, giving an accuracy of 74.00% overall. The model was significantly reliable when compared with the constant only model, $\chi^2(2) = 6.449$, $p = 0.0398$.

Variables	B	SE	Wald	DF	Sig	R	Exp(B)	95% CI
*Smoking			5.611	2	.061	.168		
Ex-smoker	1.526	.802	3.619	1	.057	.168	4.600	.955 – 22.160
Current smoker	2.037	.936	4.732	1	.030	.218	7.667	1.223 – 48.046
(Constant)	-2.037	.414	11.011	1	.001			

*Reference group for smoking is the "never smoked" group

Logistic Regression Results for the Week Five LIQ Reaction

Due to missing values, data from 48 cases were available for analysis: 36 (75.0%) had a score of D-RTOG0 and 12 (25.0%) scored D-RTOG1. Two variables entered the model: breast size and smoking. These variables correctly predicted 91.43% of mild or no reactions, and 69.23% of severe reactions, giving an accuracy of 85.42% overall. The model was significantly reliable when compared with the constant only model, $\chi^2(3) = 14.561$, $p = 0.002$.

Variables	B	SE	Wald	DF	Sig	R	Exp(B)	95% CI
Breast size	1.918	.870	4.856	1	.028	.226	6.804	1.236 – 37.449
*Smoking			7.122	2	.028	.236		
Ex-smoker	.882	.84	.995	1	.319	.000	2.416	.427 – 13.668
Current smoker	2.929	1.098	7.111	1	.008	.312	18.700	2.173 – 160.917
(Constant)	-2.389	.695	11.836	1	.001			

*Reference group for smoking is the "never smoked" group

Logistic Regression Results for the Week Five Nipple Reaction

Data from 50 cases were available for analysis: 42 (84.0%) had a score of D-RTOG0 and 8 (16.0%) scored D-RTOG1. Only one variable entered the model: smoking. This model correctly predicted 91.89% of mild or no reactions and 38.46% of severe reactions, giving an accuracy of 78.00% overall. The model was significantly reliable when compared with the constant only model, $\chi^2(2) = 8.249$, $p = 0.0162$.

Variables	B	SE	Wald	DF	Sig	R	Exp(B)	95% CI
*Smoking			7.205	2	.027	.237		
Ex-smoker	1.248	.817	2.334	1	.127	.076	3.485	703 – 17.288
Current smoker	2.548	.954	7.132	1	.008	.300	12.778	1.970 – 82.892
(Constant)	-2.037	.614	11.011	1	.001			

*Reference group for smoking is the "never smoked" group

Logistic Regression Results for the Week Five Inframammary Fold Reaction

Data from 50 cases were available for analysis: 42 (84.0%) had a score of D-RTOG0 and 8 (16.0%) scored D-RTOG1. One variable entered the model: current smoking. This variable was constructed combining those not currently smoking (never smoked and ex-smokers) in one group and current smokers in the other group. This model correctly predicted 90.63% of mild or no reactions and 27.78% of severe reactions giving an accuracy of 68.00% overall. The model was significantly reliable when compared with the constant only model, $\chi^2(1) = 2.784$, $p = 0.0952$.

Variables	B	SE	Wald	DF	Sig	R	Exp(B)	95% CI
Current smoker	1.313	.803	2.675	1	.102	.102	3.718	.771 – 17.938
(Constant)	-.802	.334	5.779	1	.016			

*Reference group for smoking is the "never smoked and ex-smokers" group

Appendix L

Rudimentary Assessment Tool for Radiation Skin Reactions

Probability Estimates for Sternum Reactions during Week Five

No History of Skin Cancer		History of Skin Cancer	
Age (in 5 year increments)	Probability of skin reaction ≥RTOG 2	Age (in 5 year increments)	Probability of skin reaction ≥RTOG 2
20	60%	20	95%
25	56%	25	94%
30	53%	30	93%
35	49%	35	92%
40	45%	40	91%
45	42%	45	89%
50	38%	50	88%
55	34%	55	86%
60	31%	60	84%
65	28%	65	82%
70	25%	70	80%
75	22%	75	77%
80	20%	80	74%
85	17%	85	71%

Probability Estimates for Axilla Reactions during Week 5

No Aspirations for Lymphocele		One or More Aspirations for Lymphocele	
Weight (in 5kg increments)	Probability of skin reaction ≥ RTOG 2	Weight (in 5kg increments)	Probability of skin reaction ≥ RTOG 2
45	15%	45	28%
50	19%	50	35%
55	25%	55	42%
60	32%	60	50%
65	39%	65	58%
70	46%	70	66%
75	54%	75	72%
80	62%	80	78%
85	69%	85	83%
90	75%	90	87%
95	80%	95	90%
100	85%	100	92%
105	88%	105	94%

Probability Estimates for Upper Outer Quadrant Reactions at 45 Gy if Never Smoked

Brassiere cup size ≥ D	Aspirations for Lymphocele	Stage ≥ II	Probability of skin reaction ≥ RTOG 2
X	X	X	19%
X	X	✓	35%
X	✓	X	40%
X	✓	✓	61%
✓	X	X	39%
✓	X	✓	60%
✓	✓	X	65%
✓	✓	✓	81%

Probability Estimates for Upper Outer Quadrant Reactions at 45 Gy if Ex-Smoker

Brassiere cup size ≥ D	Aspirations for Lymphocele	Stage ≥ II	Probability of skin reaction ≥ RTOG 2
X	X	X	27%
X	X	✓	47%
X	✓	X	52%
X	✓	✓	71%
✓	X	X	52%
✓	X	✓	71%
✓	✓	X	75%
✓	✓	✓	87%

Probability Estimates for Upper Outer Quadrant Reactions at 45 Gy if Current Smoker

Brassiere cup size ≥ D	Aspirations for Lymphocele	Stage ≥ II	Probability of skin reaction ≥ RTOG 2
X	X	X	58%
X	X	✓	77%
X	✓	X	80%
X	✓	✓	90%
✓	X	X	80%
✓	X	✓	90%
✓	✓	X	92%
✓	✓	✓	96%

Probability Estimates for Upper Inner Quadrant Reactions at 45 Gy

Brassiere cup size ≥ D	Aspirations for Lymphocele	Probability of skin reaction ≥ RTOG 2
X	X	27%
X	✓	45%
✓	X	46%
✓	✓	65%

Probability Estimates for Lower Outer Quadrant Reactions

Brassiere cup size ≥ D	Never Smoked	Ex-Smoker	Current Smoker	Probability of skin reaction ≥ RTOG 2
X	✓	X	X	16%
X	X	✓	X	20%
X	X	X	✓	45%
✓	✓	X	X	36%
✓	X	✓	X	43%
✓	X	X	✓	70%

Probability Estimates for Lower Inner Quadrant Reactions at 45 Gy if Never Smoked

Brassiere cup size ≥ D	Aspirations for Lymphocele	Probability of skin reaction ≥ RTOG 2
X	X	11%
X	✓	22%
✓	X	28%
✓	✓	48%

Probability Estimates for Lower Inner Quadrant Reactions at 45 Gy if Ex-Smoker

Brassiere cup size ≥ D	Aspirations for Lymphocele	Probability of skin reaction ≥ RTOG 2
X	X	13%
X	✓	26%
✓	X	32%
✓	✓	53%

Probability Estimates for Lower Inner Quadrant Reactions at 45 Gy if Current Smoker

Brassiere cup size ≥ D	Aspirations for Lymphocele	Probability of skin reaction ≥ RTOG 2
X	X	49%
X	✓	69%
✓	X	76%
✓	✓	88%

Probability Estimates for Nipple Reactions at 45 Gy

Probability of skin reaction ≥ RTOG 2 if Never Smoked	Probability of skin reaction ≥ RTOG 2 if Ex-Smoker	Probability of skin reaction ≥ RTOG 2 if Current Smoker
26%	34%	62%

Probability Estimates for Inframammary Fold Reactions during Week Five

Brassiere cup size ≥ D	Never Smoked	Ex-Smoker	Current Smoker	Probability of skin reaction > RTOG 2
X	✓	X	X	15%
X	X	✓	X	36%
X	X	X	✓	64%
✓	✓	X	X	49%
✓	X	✓	X	75%
✓	X	X	✓	91%