Breast Cancer After Treatment of Hodgkin's Disease.

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Introduction

The risks of second malignancy are increased in patients treated with chemotherapy and radiotherapy(41-43). The impact of such an occurrence, usually occurring at some time after treatment, is disproportionately born by a younger population, such as Hodgkin's disease patients.

In the past, exposure to ionising radiation has been associated with increased rates of solid malignancy (e.g., lung cancer, thyroid cancer) and leukaemias. The induction of breast cancer by Hodgkin's disease treatment has been controversial. Relative risks are variable(44), and larger in females(45) but much of the data has not reached sufficient maturity to confidently assess the risk. There is no evidence to suggest a worse prognosis for induced breast cancers(46).

The Stanford University Medical Centre is a unique institution in the history of Hodgkin's Disease (HD) treatment. Systematic treatment of early stage HD with radiotherapy is due in no small part to their pioneering work. They have treated many patients and maintained longer and more assiduous follow-up than most centres. The use of their database to further delineate the effects of exposure to ionising radiation and breast cancer is therefore likely to illuminate the debate.

A definite increase in the risk of second malignancy, especially if confined to a subset, will have implications for subsequent trials and for followup of treated patients.

Summary

This report describes a single institution's experience of treatment of Hodgkin's Disease (including both chemotherapy and radiotherapy) and subsequent breast cancers in 885 female patients accrued between January 1961 and December 1989.

Trial Design

This is a retrospective cohort study rather than a trial, classifying patients on the basis of exposure to HD treatment. The test cases are provided by the Stanford University Medical Centre, while the "comparison group" was provided by the population assessed by the NCI's Surveillance, Epidemiology, and End Results (SEER) program. The "comparison group" are race-, age- and gender-specific annualised incidence and mortality rates. The yearly rates when combined with the person-years at risk derive a numerical quantity for the expected cases/deaths from breast cancer in the time period of observation.

Study Aim

The author's aim was to quantify the risks of breast cancer development after treatment for Hodgkin's Disease. They also hoped to clarify issues of latency of induction of breast cancer and the association with age for any increased risks.

Sample size and Statistical Power

The cohort study is very useful for delineating the effects of an uncommon exposure (such as HD treatment), especially in the setting of a common disease where the exposure effect will be swamped by a high natural background rate (such as breast cancer).

Predetermined calculations of sample size are not utilised in cohort studies. The sample size need not contain all those exposed, but should maintain follow-up on all those identified. Restricting the exposed sample size affects external validity, while failure to follow affects internal validity.

Trial Conduct

Eligible Population

The test cases are identified retrospectively from records of the Stanford University Medical Centre who were diagnosed with HD. The treatment received (radiotherapy, chemotherapy) as part of their management

was noted. The subset of this population with breast cancer was determined from records if still actively being followed, or by letter to patient and local physician if lost to follow up. Where breast cancer was nominated, pathological evidence was sought.

The "comparison group" comprised the sample covered by an NCI epidemiological survey (SEER) from which were derived population rates of breast cancer specific to different ages, genders and races.

Patient Selection - Exposed to HD treatment

The exposed population included all patients treated in the study period. There are complete data on the degree of exposure to HD treatment. All patients are accounted for in the Methods section.

The exposure data is reliable since it was recorded at the time of treatment and was not based on patient recollection.

Patient Selection - Unexposed to HD treatment

In a cohort study, the comparison group ought to be identical except for the exposure occurrence.

The SEER database allowed for matching of age, gender and race, but not of occurrence of HD. There is unlikely to be database of untreated HD patients, and measures of breast cancer incidence in such a group is even more unlikely because of limited survival.

The 1983-1988 cohort was chosen for comparison. The acknowledged changes in breast cancer incidence (higher) are likely to underestimate the effect of exposure.

Data Sources

Exposure data derived from hospital records are well detailed (see above).

Outcome data is confined to the 26 cases of breast cancer. The case finding and verifying procedures with description of the group for whom breast status could not be identified, should be included.

Patient Exclusion

No patient exclusion was reported.

The patient with DCIS who subsequently died of metastatic breast cancer was included in mortality assessment, but not incidence assessment. The exclusion of DCIS from the definition is in direct contradistinction to the NSABP-B17 trial (also analysed in this report) where DCIS was classed as a breast cancer!

Treatment Description

Surgery

There are no surgical details, particularly numbers of splenectomy.

Radiotherapy

The radiotherapy details are not well described here, but Stanford's methods of TLI, SLI, IF and mantle field irradiation are published in textbooks(47). As a single institution experience, the doses are likely to reflect a standard method of prescription. This allows meaningful intra-institution comparison.

Chemotherapy

The chemotherapy details identify agents used, but not dose or dose reductions.

Pathology

Rigorous pathological verification of the diagnosis of breast cancer was not reported. The veracity of diagnosis presumably relied on histopathological review, written report or verbal evidence. The text is unclear about the numbers of cases of breast pathology evaluated and the methods used. Fortunately, recall of a previous diagnosis of cancer has been shown to be reliable(48).

Trial Analysis

Statistical Analysis

With long follow-up and many deaths in the case population, breast cancer free survival was appropriately calculated using the actuarial methods of Kaplan and Meier, however only survival after development of breast cancer was reported.

Incidence and mortality rates were quantified since the exposed population and diseased populations were well defined, as was the time period of observation. Rates were defined per person, rather than per breast. No case of bilateral breast cancer was reported.

Breast cancer incidence and mortality rates were calculated by designating each year a patient was alive without breast cancer as one person-year. The person-year was assigned to one of three groups (radiotherapy alone, chemotherapy alone or combined therapy) depending on the treatments already received before that year. The comparison rates were selected for 1983-1988, but given the length of follow-up, other comparison rates (1960s, 1970s) should have been used.

The Poisson distribution risk estimation is a reflection of the stochastic nature of carcinogenesis, where probability of occurrence rather than 'severity' of breast cancer is related to therapy.

The observed and expected incidence/mortality rates were combined to provide estimates of relative risk (risk enhancement as a result of exposure, this quantifies personal risk) and absolute risk (excess cases over expected due to exposure, this gives a quantification for the impact of an exposure reduction program). The absolute risk is also known as the attributable risk.

Subset analysis was undertaken and revealed a possible enhanced risk of breast cancer for the first 15 years after combined MOPP chemotherapy with radiotherapy. No equivalent subset analysis was done for chemotherapy alone (one breast cancer only). This analysis should be regarded as suggestive only since repeated subset analysis increases the likelihood of finding an 'isolated' statistically significant result.

The analysis undertaken is appropriate. The problems evident include the small numbers of events, the use of single breast cancer incidence rates when rates were changing over the study duration. The analysis can only show a correlation between HD treatment and breast cancer, not a causal link since the important counfounding variable, Hodgkin's Disease, cannot be controlled.

Erratum p.26

"Among patients treated with limited field irradiation, 144 had mantle fields or supradiaphragmatic radiation fields that included at least one axilla."

In Table 1, the fourth column "LF including breast" describes 166 patients (40 radiotherapy alone, 102 radiotherapy plus adjuvant chemotherapy, 24 radiotherapy plus salvage chemotherapy).

Confounding Variables

a. interaction of HD and breast cancer. The rates of breast cancer for patients with HD, in the absence of treatment, are unknown. The increased rates may reflect a common carcinogen or widespread genetic alterations in oncogene and tumour suppressor gene function that are phenotypically expressed as both HD and breast cancer.

This is the primary confounding variable and can only be addressed in a randomised trial which would unethical to say the least.

b. co-existent risk factors for breast cancer. Risk factors not elicited that may confound results include oral contraceptive use, family history of breast cancer, numbers of children and breast feeding history.

c. the occurrence of early menopause and the use of exogenous hormones is not explored. Both factors may alter breast cancer rates.

d. combined modality sequence. There may be a difference between chemotherapy plus radiotherapy when given sequentially and when given in salvage.

e. comparison using a time invariate incidence of breast cancer. The exposed population (1961-1989) are compared with a comparison period (1983-1988).
This period was selected because of "increasing incidence and decreasing mortality". Just as analysis was undertaken for age at development of breast cancer, analysis using prevailing breast cancer rates

at time of development should be undertaken.

f. The cases of breast cancer in the exposed population (1983-1988) were included in the breast cancer rates for the comparison population.

This might have been a problem except that the rates of breast cancer in the unexposed would be unaffected by a reduction of 25 in breast cancer cases, and a reduction of 885 in population at risk.

Trial Outcome

Criteria for Evaluation

Endpoints

Patients were analysed for relevant endpoints, namely the development of breast cancer, death and date of last follow-up.

Bias

Since classification of exposure was independent of outcome (development of breast cancer) there is no bias.

There would be little bias in detection since patient recall of breast cancer is excellent, and population-based registries record most cases. This applies equally to breast cancer cases in the HD and SEER population. However the small number of cases of breast cancer diagnosed makes subset analysis uncertain.

The authors classified DCIS as a non-cancer but make no comment on the inclusion of DCIS in the 1983-1988 SEER data. This will affect the SEER population rates making them atificially high and exaggerating any difference between the two groups.

Loss to follow-up

No loss to follow-up occurred.

Non-participants

The non-inclusion of patients from other institutions does not affect the internal validity of this comparison. The lack of demographic data (race, socioeconomic status) and medical data (HD stage at presentation) reduce the generalisability of results.

Results

The analysis showed that :

a. women treated for HD have a higher incidence/mortality rate of breast cancer than the general population. (RR 4.1 incidence, 5.1 mortality)

b. increasingly younger women treated for HD have an increasingly higher incidence of breast cancer up to the age of 30. (RR; <15y:136, 15-24y:19, 25-29y: 7.3)

c. the risk of breast cancer increases disproportionately after a 15 years interval post-treatment for HD (RR; 0-4y:0.5, 5-9y:2.9, 10-14y:2.7, 15-19y:15, >20y:11)

d. there is no radiation dose-response in breast cancer risk, either in the presence or absence of chemotherapeutic agents

e. there is an increased risk of breast cancer with MOPP chemotherapy in the first 15 years only (RR; MOPP+RTh:6.3,RTh:0.8)

f. there is an increased risk of breast cancer with radiotherapy after the first 15 years only (RR;<15y latency:0.8, >15y latency:13.0)

g. radiotherapy for HD may have a protective effect for older patients in the first 15 years only (RR;>30y age, < 15y latency:0.2)

h. the latency between average age at HD treatment and breast cancer diagnosis is 15 years

i. chemotherapy alone confers only a modestly elevated risk of breast cancer

Conclusion

The authors concluded that both ionising radiation and chemotherapeutic agents (especially MOPP) are associated with increased rates of breast malignancy, as had been found in analyses from Denmark and Connecticut.

They suggest that women under the age of 30 years be considered for HD therapy which will spare breast irradiation and fertility, as has occurred in paediatric HD. Wisely they caution that this should not be at the cost of cure rates for HD. Ideally this should occur in a trial setting.

The role of MOPP is correctly emphasised as uncertain, although consistent with previous data. They do not address the issue of increased surveillance with mammography in the patients at high risk.OVERVIEW

This study is well conducted. The completeness of data on patients treated over a 28 year period is noteworthy.

Following an uncommon disease, the large exposed population is fully accounted for with apparently complete data over a long period. While this study cannot address the issue of a common aetiology for HD and breast cancer, the major deficiency is lack of analysis of prognostic factors for breast cancer and early menopause.

The conclusions drawn are fair. The imperfections either cannot be addressed or are unlikely to explain the large differences, and the results confirm a trend existing in other data sets.