Eur J Cancer Clin Oncol, Vol. 18, No. 11, pp. 1187–1195, 1982.
Printed in Great Britain.

0277-5379/82/111187-09$03.00/0


# An Estimate of the Radiation-induced Cancer Risk from the Whole-body Stray Radiation Exposure in Neutron Radiotherapy

J. P. GERACI, K. L. JACKSON and M. S. MARIANO

*Division of Radiological Sciences, Department of Environmental Health, School of Public Health and Community Medicine, University of Washington, Seattle, WA 98195, U.S.A.*

**Abstract**—*The 1980 BEIR III risk factors have been used to estimate the secondary cancer risks from the whole-body stray radiation exposures which occur in neutron radiotherapy. The cancer risks have been calculated using the linear, linear–quadratic and quadratic dose–response models for the gamma component of the stray radiation. The linear dose–response model has been used to calculate the risk for the neutron component of the stray radiation. These risk estimates take into consideration for the first time the age and sex distribution of cancer patients undergoing neutron therapy. Changes in the cancer risk as a function of the RBE (10–100) assigned to the stray neutron radiation component have also been assessed. The excess risks in neutron-treated patients have been compared to the excess cancer risks for photon-treated patients and with the expected incidence of cancer in a normal population having the same age and sex distribution. These risk estimates clearly indicate that it will be necessary to tolerate a higher incidence of secondary cancers in patients undergoing fast neutron therapy than is the case with conventional photon therapy. However, for neutron RBEs of less than 50 the increased cancer risk is only a fraction of the normal expected incidence of cancer in this population. Moreover, comparison of the radiation-induced cancer risk with reported normal tissue complication rates in the treatment volume indicates that the excess cancer risk is substantially lower than the risk from other late normal tissue effects.*

## INTRODUCTION

THE EFFICACY of cyclotron-produced neutrons in treating human cancers is currently being evaluated at various radiation therapy centers throughout the world [1]. One disadvantage of the use of neutrons is that they are more difficult to shield and to collimate than the photons used in conventional radiotherapy. Therefore, relative to the primary beam dose, the radiation dose to the patient's body outside the primary beam will be higher than in comparative photon radiation therapy [2]. Consequently, there is concern regarding increased risk of secondary cancers from the stray whole-body radiation exposure of patients undergoing neutron therapy. The purpose of the present paper is to estimate this risk in patients successfully treated with neutrons using the 1980 BEIR III risk factors [3].

Accepted 12 May 1982.

## METHODS AND RESULTS

*Neutron and gamma dose composition of the stray radiation in rems*

At the University of Washington the average whole-body dose from stray radiation during neutron radiotherapy is 2.8% of the central axis rad dose. This is based on measurements made in a 100 × 100 cm area surrounding a 20 × 20 cm primary beam field with a human phantom in the beam [4]. Proportional counter measurements and neutron activation analysis indicate that approximately 50% of the dose is due to neutrons of mean energy less than those in the primary beam [4, 5]. The other 50% of the stray radiation dose is from gamma rays. For comparison, the stray radiation in a conventional photon teletherapy facility is assumed to be 1% of the primary beam dose. This value probably represents the upper limit since the criterion used in the design of conventional photon therapy facilities is that the radiation penetrating the source shielding should not exceed

0.1% of the primary beam dose [6]. Actual measurements with TLD and Victoreen R Chambers with a 2000 C $^{137}$Cesium teletherapy source with a scattering phantom in an 18 × 18 cm radiation field indicate that the average dose is less than 1% in the surrounding 100 × 100 cm area (unpublished data).

The three treatment schemes employed at the University of Washington are shown in Table 1. Patients are assigned to treatment schedules of either 5 fractions of photons/week (conventional therapy), 2 fractions of neutrons and 3 fractions of photons/week (mixed beam) or 4 fractions of neutrons/week (neutron). The approximate total treatment dose is 6000 rad of photons for conventional therapy, 720 rad of neutrons plus 3600 rad of photons for mixed beam therapy and 1800 rad for all neutron therapy. The total treatment time for all the above radiation schemes is between 6 and 7 weeks. Using these parameters the calculated neutron and gamma dose components of the stray radiation in photon equivalent units (rems) for the various treatment arms in clinical trials at the University of Washington are shown in Table 2. For most of the 'rem' dose calculations a neutron quality factor of 10 was used, as suggested by standard setting organizations for radiation protection purposes [7, 8]. The use of a quality factor of 10 is considered more fully in the Discussion section.

*Dose–response models*

For high LET radiation such as neutrons, it is generally assumed that the risk of cancer will be proportional to the dose. Conversely, for gamma radiation there is controversy regarding the appropriate dose–response model for carcinogenesis. Some investigators believe that the dose–response curve for gamma radiation is also proportional to dose (linear dose–response model). Others think the dose–response model for gamma radiation is proportional to dose squared (quadratic model); however, much of the radiobiological data suggest a combination of both models in which at low doses the linear model is dominant but at high doses the quadratic model predominates (linear–quadratic model). It is obvious that for a small radiation dose the linear model will result in the highest incidence of cancer, whereas the quadratic model will result in the lowest incidence. For the purpose of the present paper, we decided to use the convention suggested in the BEIR III report [3] in which "an envelope of risk estimates bounded by the linear model and the pure quadratic models with the linear–quadratic providing the intermediate values" is employed for the gamma component stray radiation. In every case the linear model is used for the neutron component of stray radiation. The resulting annual excess cancer incidence rate for the

*Table 1. Patient treatment schemes*

| Radiation treatment | Weekly fraction schemes | Tumor dose/fraction (rad) |
|---|---|---|
| Conventional therapy | 5 photons (Mon., Tues., Wed., Thurs., Fri.) | 180–200* |
| Mixed beam | 2 neutrons (Mon., Fri.) | 60–75 |
| | 3 photons (Tues., Wed., Thur., ) | 180–200 |
| Neutrons | 4 neutrons (Mon., Tues., Thur., Fri.) | 60–75 |

*Ranges shown are for treatment of cancers at various sites.

*Table 2. Neutron and gamma dose components of stray radiation delivered during entire course of treatment*

| Treatment | Photons | Dose (rad) Mixed beam (neutron and photon) | Neutrons |
|---|---|---|---|
| Tumor dose* | 6000 γ | (720 n) + (3600 γ) | 1800 n |
| Stray radiation | 60 γ | (10 γ + 10 n) + (36 γ) | (25 γ + 25 n) |
| Total stray radiation | 60 γ | 46 γ + 10 n | 25 γ + 25 n |
| | Photon equivalent stray radiation dose† (rem) | | |
| Gamma rays | 60 | 46 | 25 |
| Neutrons | 0 | 100 | 250 |

*Doses given are those typical for neutron and photon therapy.
†Neutron quality factor = 10.

typical stray radiation from photon, mixed beam and neutron treatments in clinical trials at the University of Washington using the different dose–response models are shown in Tables 3–5. Because the risk models for neutron and gamma radiations can differ, it is necessary to calculate the risk separately for the neutron and gamma radiation components. It is also necessary to calculate the radiation-induced excess incidence for leukemia and bone cancer separately from other cancers because the two cancer groups have different latent periods (2 yr for leukemia and bone cancer and 10 yr for other cancers) and different maximum periods of elevated risk (25 yr for leukemia and bone cancer and greater than 20 yr for other cancers) [3].

*Age-specific excess cancer risk*

To calculate the total excess cancer risk as a function of time after radiation treatment, one must take into consideration the latency period for tumor development and the year-by-year shrinkage in the population at risk due to death and new tumor incidence. To do this the standard life table method was used. An example of

*Table 3. Estimated excess incidence of leukemia and bone cancers per $10^6$ people per year for stray gamma radiation*

| | Age (yr) | Photon treatment (60 rem) M | Photon treatment (60 rem) F | Mixed beam treatment (46 rem) M | Mixed beam treatment (46 rem) F | Neutron treatment (25 rem) M | Neutron treatment (25 rem) F |
|---|---|---|---|---|---|---|---|
| | 10–19 | 38 | 25 | 23 | 15 | 7 | 4 |
| | 20–34 | 57 | 36 | 33 | 21 | 10 | 6 |
| Quadratic* | 35–49 | 42 | 27 | 25 | 16 | 7 | 5 |
| | 50+ | 97 | 62 | 57 | 37 | 17 | 11 |
| Linear–Quadratic† | 10–19 | 71 | 46 | 50 | 33 | 24 | 15 |
| | 20–34 | 104 | 66 | 73 | 47 | 35 | 22 |
| | 35–49 | 77 | 50 | 55 | 35 | 26 | 17 |
| | 50+ | 176 | 112 | 124 | 79 | 59 | 37 |
| Linear‡ | 10–19 | 110 | 71 | 85 | 55 | 46 | 30 |
| | 20–34 | 156 | 100 | 120 | 77 | 65 | 42 |
| | 35–49 | 115 | 74 | 88 | 57 | 48 | 31 |
| | 50+ | 259 | 166 | 198 | 127 | 108 | 69 |

*Based on coefficient for '$(Dose)^2$' term obtained from Table V-18, BEIR III report [3].
†Based on coefficient for '(Dose)' and '$(Dose)^2$' terms obtained from Table V-16, BEIR III report [3].
‡Based on coefficient for '(Dose)' term obtained from Table V-17, BEIR III report [3].

*Table 4. Estimated excess incidence of cancer (excluding leukemia and bone cancer) per $10^6$ people per year for stray gamma radiation*

| | Age (yr) | Photon treatment (60 rem) M | Photon treatment (60 rem) F | Mixed beam treatment (46 rem) M | Mixed beam treatment (46 rem) F | Neutron treatment (25 rem) M | Neutron treatment (25 rem) F |
|---|---|---|---|---|---|---|---|
| Quadratic* | 10–19 | 47 | 79 | 27 | 46 | 8 | 14 |
| | 20–34 | 133 | 224 | 78 | 132 | 23 | 39 |
| | 35–49 | 176 | 298 | 104 | 174 | 31 | 52 |
| | 50+ | 248 | 419 | 146 | 246 | 43 | 73 |
| Linear–Quadratic† | 10–19 | 91 | 154 | 64 | 109 | 31 | 52 |
| | 20–34 | 266 | 450 | 188 | 317 | 89 | 150 |
| | 35–49 | 341 | 578 | 241 | 408 | 114 | 193 |
| | 50+ | 516 | 874 | 364 | 617 | 172 | 292 |
| Linear‡ | 10–19 | 160 | 278 | 122 | 213 | 67 | 116 |
| | 20–34 | 475 | 827 | 364 | 634 | 198 | 345 |
| | 35–49 | 580 | 1012 | 445 | 776 | 242 | 422 |
| | 50+ | 966 | 1680 | 741 | 1288 | 403 | 700 |

*Based on coefficient for '$(Dose)^2$' term obtained from Table V-29, BEIR III report [3].
†Based on coefficient for '(Dose)' and '$(Dose)^2$' terms obtained from Table V-27, BEIR III report [3].
‡Based on coefficient for '(Dose)' term obtained from Table V-28, BEIR III report [3].

*Table 5. Estimated excess incidence of cancers per $10^6$ people per year for stray neutron radiation*

| | Age (yr) | Mixed beam treatment (100 rem)* M | Mixed beam treatment (100 rem)* F | Neutron treatment (250 rem) M | Neutron treatment (250 rem) F |
|---|---|---|---|---|---|
| Cancer type | | | | | |
| Leukemia and bone cancer† | 10–19 | 185 | 119 | 462 | 298 |
| | 20–34 | 260 | 167 | 649 | 417 |
| | 35–49 | 192 | 124 | 480 | 309 |
| | 50+ | 432 | 276 | 1,080 | 690 |
| All cancers (excluding leukemia and bone cancers)‡ | 10–19 | 266 | 464 | 666 | 1,160 |
| | 20–34 | 791 | 1,379 | 1,977 | 3,448 |
| | 35–49 | 967 | 1,686 | 2,418 | 4,215 |
| | 50+ | 1,610 | 2,800 | 4,025 | 7,018 |

*Dosages based on quality factor of 10 for neutrons.
†Based on coefficient for '(Dose)' term obtained from Table V-17, BEIR III report [3].
‡Based on coefficient for '(Dose)' term obtained from Table V-28, BEIR III report [3].

the procedure used to calculate the 30-yr cancer risk for male patients 50-yr of age receiving neutron therapy using the linear–quadratic model for the stray gamma radiation component is outlined below.

Definition:
$t$ = age
$\lambda_1(t)$ = No. of deaths/person/yr (Table 25 in ref. [9])
$\lambda_2(t)$ = normal expected cancer incidence/person/yr (Tables 20 D and 20F in ref. [10])
$\lambda_3(t)$ = radiation-induced leukemia and bone cancer/person/yr (Tables 3 and 5)
$\lambda_4(t)$ = radiation-induced 'all other cancer'/person/yr (Tables 4 and 5)
$C(t)$ = total cancer incidence/person/yr = $\lambda_2(t) + \lambda_3(t) + \lambda_4(t)$
$P(50) = P$(survival with no cancers) = 1
$P(51) = P$(survival from 50 to 51 with no cancers) = $1 - \lambda_1(50) - C(50)$
$P(52) = P$(survival from 50 to 52 with no cancers)
$= [1 - \lambda_1(50) - C(50)] \times [1 - \lambda_1(51) - C(51)]$
$P(80) = P$(survival from 50 to 80 with no cancers) = $\prod_{50}^{79} [1 - \lambda_1(t) - C(t)]$.
Generalized to any age and risk period: $P(t)$ $\prod_{t}^{t+j-1} [1 - \lambda_1(t) - C(t)]$
$j$ = risk period
30-yr estimate excess cancer risk:
$P(50) \times [\lambda_3(50) + \lambda_4(50)] + P(51) \times [\lambda_3(51) + \lambda_4(51)] + \cdots P(80) \times [\lambda_3(80) + \lambda_4(80)]$.

In the above example for the male leukemia and bone cancer risk the following parameters are used:

$\lambda_3(50–51) = 0$, 2 yr latency period
$\lambda_3(52–77) = (1089 + 59)/10^6$/yr, the risk due to stray neutron radiation (Table 5) and gamma radiation (Table 3)
$\lambda_3(>77) = 0$, end of 25yr elevated risk period.

For 'all other cancers' for males the following parameters are used:
$\lambda_4(50–59) = 0$, 10-yr latency period
$\lambda_4(60–80) = (4025 + 172)/10^6$/yr, the risk due to stray neutron radiation (Table 5) and gamma radiation (Table 4).

Generalized risk ($R$) for any age and risk period:

$$\text{Male } R(t) = \sum_{t}^{t+j} P(t) \times [\lambda_3(t) + \lambda_4(t)]$$

$$\text{Female } R'(t) = \sum_{t}^{t+j} P'(t) \times [\lambda_3'(t) + \lambda_4'(t)].$$

A sample histogram showing the total excess cancer risk per 100 successfully treated patients at various times after neutron therapy as a function of the patient's age at treatment time is shown in Fig. 1. For this particular figure the linear dose–response model was used to calculate the cancer risk from the stray gamma radiation component. Similar-shaped curves but of lower amplitude have been obtained for other dose–response models as well as for the mixed beam and photon-treated patients. The shapes of the curves show a change in risk with

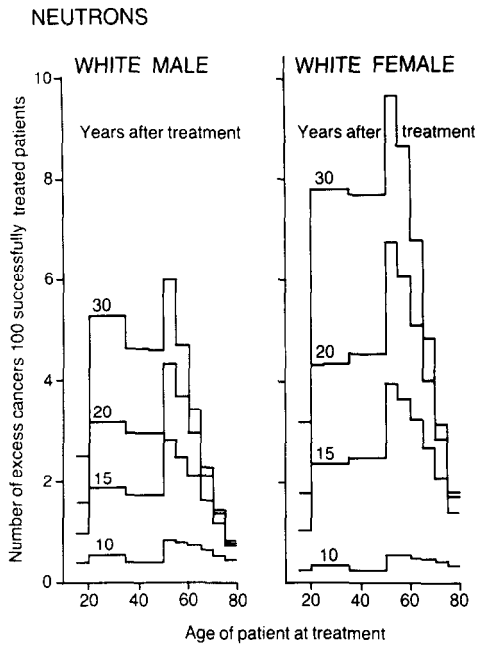


*Fig. 1. Age-specific excess cancer risk as a function of patient age at time of treatment and years after treatment. The data are for neutron therapy and were calculated using the linear dose–response model.*

patient age at time of treatment, with a maximum risk occurring in the 5th decade of life. The decreased risk after the 5th decade reflects the shorter life expectancies of older patients which do not allow for the full expression of the total radiation-induced cancer potential. Figure 1 also shows that the risk is similar for both sexes up to 10 yr post-treatment. After 10 yr the risk for females is greater due to the greater susceptibility of the female breast and thyroid to develop radiation-induced cancers [3], as well as to the longer life expectancies of women.

*Tumor site-specific excess cancer risk*

To estimate the risks for patients (15–80 yr of age) with different types of cancers undergoing neutron therapy, the age-specific risk estimates similar to those shown in Fig. 1 were weighted by the age and sex distribution characteristic of that cancer, i.e.,

$$\text{tumor site-specific excess cancer risk} = \sum_{t=15}^{80} W(t)R(t) + \sum_{t=15}^{80} W'(t)(R'(t).$$

Sex and age distribution ($W$ and $W'$) were obtained from the 1969–1971 U.S. Cancer Incidence Study [10] for the 9 types of cancer currently being treated with neutron therapy (shown in Table 6). Using the pertinent age and sex distribution weighting factors in Table 6, the radiation-induced treatment cancer risks as a function of time after photon, mixed beam or neutron therapy are graphically presented in Fig. 2 for 3 of the 9 cancer sites (head and neck, prostate and cervix). For comparison purposes, the normal expected incidence of cancer for a population with the same age and

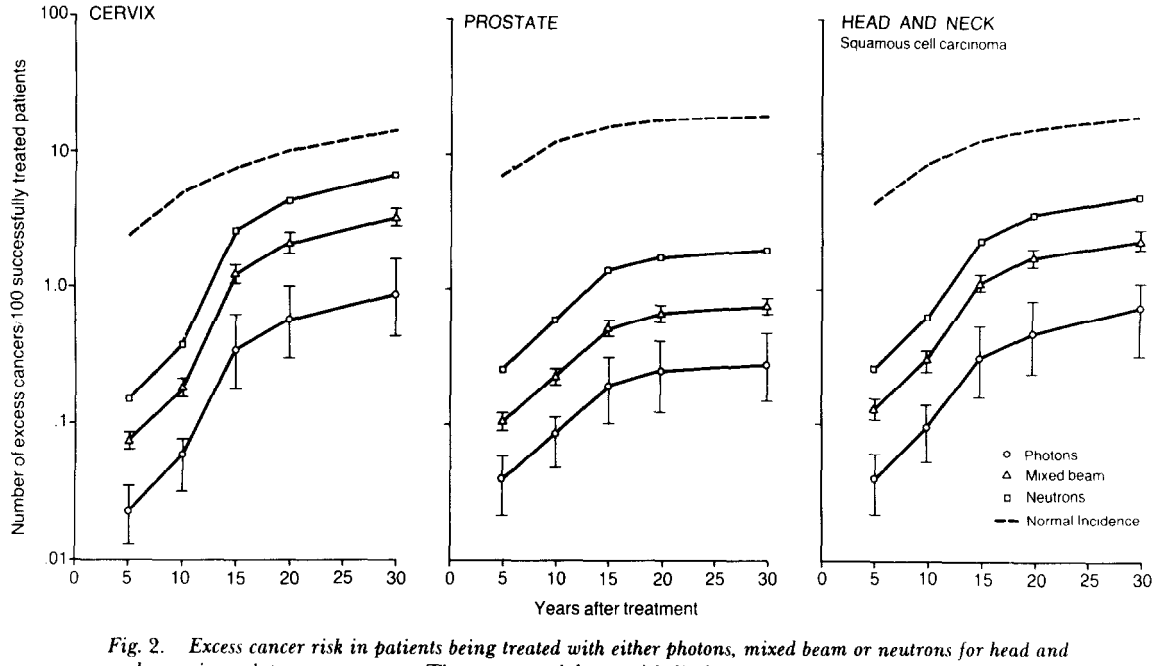


*Fig. 2. Excess cancer risk in patients being treated with either photons, mixed beam or neutrons for head and neck, cervix and prostate cancers. The upper and lower risk limits were calculated using the linear and quadratic dose–response models respectively. The curve itself represents a risk estimate assuming a linear-quadratic dose–response model. For comparison purposes, the normal expected incidence of cancer for a population with the same age and sex distribution as the indicated cancer population is represented by the dotted line.*

*Table 6. Characteristic age and sex distribution for various tumor sites**

| Age | Tumor site | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Head and neck† | | Prostate | | Cervix | | Esophagus | | Salivary gland | | Brain | | Bladder | | Lung | | Skin melanoma | | All sites‡ | |
| | M | F | M | F | M | F | M | F | M | F | M | F | M | F | M | F | M | F | M | F |
| 15–19 | 0.001 | 0.000 | 0.000 | — | — | 0.003 | 0.002 | 0.000 | 0.008 | 0.010 | 0.013 | 0.016 | 0.001 | 0.001 | 0.000 | 0.000 | 0.003 | 0.010 | 0.001 | 0.002 |
| 20–24 | 0.001 | 0.001 | 0.000 | — | — | 0.019 | 0.000 | 0.000 | 0.013 | 0.019 | 0.021 | 0.012 | 0.003 | 0.000 | 0.001 | 0.001 | 0.018 | 0.025 | 0.002 | 0.004 |
| 25–29 | 0.001 | 0.001 | 0.000 | — | — | 0.059 | 0.001 | 0.000 | 0.025 | 0.029 | 0.020 | 0.018 | 0.003 | 0.001 | 0.001 | 0.000 | 0.029 | 0.036 | 0.003 | 0.008 |
| 30–34 | 0.002 | 0.002 | 0.000 | — | — | 0.073 | 0.001 | 0.001 | 0.010 | 0.021 | 0.022 | 0.014 | 0.005 | 0.002 | 0.003 | 0.002 | 0.037 | 0.036 | 0.005 | 0.009 |
| 35–39 | 0.008 | 0.002 | 0.000 | — | — | 0.093 | 0.004 | 0.001 | 0.025 | 0.021 | 0.023 | 0.021 | 0.007 | 0.003 | 0.008 | 0.004 | 0.039 | 0.049 | 0.008 | 0.013 |
| 40–44 | 0.022 | 0.010 | 0.002 | — | — | 0.112 | 0.009 | 0.008 | 0.025 | 0.033 | 0.036 | 0.027 | 0.019 | 0.006 | 0.023 | 0.009 | 0.054 | 0.061 | 0.018 | 0.019 |
| 45–49 | 0.057 | 0.022 | 0.008 | — | — | 0.131 | 0.034 | 0.011 | 0.056 | 0.044 | 0.058 | 0.037 | 0.037 | 0.010 | 0.048 | 0.020 | 0.056 | 0.060 | 0.037 | 0.027 |
| 50–54 | 0.100 | 0.037 | 0.026 | — | — | 0.108 | 0.069 | 0.021 | 0.042 | 0.054 | 0.079 | 0.055 | 0.060 | 0.020 | 0.085 | 0.028 | 0.057 | 0.055 | 0.064 | 0.032 |
| 55–59 | 0.149 | 0.043 | 0.070 | — | — | 0.102 | 0.121 | 0.049 | 0.050 | 0.056 | 0.083 | 0.057 | 0.085 | 0.030 | 0.122 | 0.031 | 0.055 | 0.042 | 0.096 | 0.035 |
| 60–64 | 0.149 | 0.043 | 0.139 | — | — | 0.093 | 0.149 | 0.043 | 0.083 | 0.050 | 0.074 | 0.066 | 0.118 | 0.032 | 0.149 | 0.033 | 0.042 | 0.040 | 0.123 | 0.035 |
| 65–69 | 0.118 | 0.029 | 0.207 | — | — | 0.078 | 0.135 | 0.049 | 0.060 | 0.054 | 0.064 | 0.055 | 0.144 | 0.041 | 0.148 | 0.028 | 0.041 | 0.036 | 0.134 | 0.031 |
| 70–74 | 0.098 | 0.022 | 0.263 | — | — | 0.073 | 0.108 | 0.041 | 0.070 | 0.039 | 0.042 | 0.041 | 0.145 | 0.048 | 0.125 | 0.023 | 0.023 | 0.037 | 0.130 | 0.027 |
| 75–79 | 0.062 | 0.020 | 0.283 | — | — | 0.054 | 0.108 | 0.037 | 0.039 | 0.058 | 0.026 | 0.020 | 0.130 | 0.049 | 0.091 | 0.018 | 0.030 | 0.030 | 0.115 | 0.023 |

*Data are expressed as a fraction of the total number of people between the ages of 15 and 80 yr that develop the indicated cancer. This information was obtained from 1969–71 Cancer Incidence Study (Table 20C and 20E, ref. [10]).

†Head and neck cancers include the following sites: tongue, gum and mouth, nasopharynx, tonsil, other pharynx.

‡Data are for the nine cancers listed in this table.

sex distribution for each type of cancer is also presented. In general, for all cancers the shape of the curves are similar in that there is a steep increase in the risk from 5 to 20 yr after treatment followed by a slowing or leveling in the cancer risk. The highest long-term risk is for patients with cervical cancer and the lowest risk is for prostate cancer patients. These reflect the fact that cervical cancers occur relatively frequently in females during the 4th and 5th decades of life (Table 6), when the risk from radiation-induced cancer is the greatest, whereas prostate cancers occur relatively late in life in males, when the cancer risk from radiation is relatively small (Fig. 1).

## DISCUSSION

Previous estimates of the secondary cancer risk from stray radiation resulting from neutron therapy have been based solely on the whole-body dose received by these patients [4, 11, 12]. Bewley and Page [12] have correctly questioned the validity of such estimates, in part because they did not take into consideration the age of the patient and it is the patient's age at the time of exposure that is a major factor in this risk of cancer ([3]; Fig. 1). These estimates also did not take into account the fact that the long-term risk is different for female and male patients (Fig. 1). The latter is significant because, depending on the type of cancer, the percentage of males or females being treated can vary from 0 to 100% (Table 6). Therefore there are different risk estimates for different types of cancers being treated with neutrons (Fig. 2). This is the first report in which the age and sex distribution of cancer patients undergoing neutron therapy are considered in estimating the secondary cancer risk for whole-body stray neutron radiation exposures.

It should be recognized that these risk estimates are based on several assumptions and include the uncertainties inherent in the risk estimates of the BEIR III report [3]. The principal assumption is that $\lambda_1(t)$, $\lambda_2(t)$, $\lambda_3(t)$ and $\lambda_4(t)$ are the same for a patient population *cured* with neutrons as in a normal population with the same age and sex distribution. However, it is probable that the age-specific mortality rate $\lambda_1(t)$ will be higher for cured cancer populations than in normal populations. Furthermore, $\lambda_2(t)$ may also be higher in cured cancer populations because they may be more liable than normal populations to develop a non-radiation-induced secondary cancer [12]. Thus, although the risk to successfully treated patient populations could be lower than estimated in this study, this may be partially compensated for by $\lambda_3(t)$ and $\lambda_4(t)$ being higher in the cured cancer population due to a greater than normal sensitivity to cancer induction by radiation.

A large uncertainty in making an estimate of the excess cancer risk from neutron radiotherapy is the RBE value assigned to the stray neutron radiation [11]. The uncertainty in the RBE value is in part due to the fact that the RBE for most biological effects, including tumor production, increases with decreasing neutron dose per fraction and that there is a lack of information concerning RBE values for carcinogenesis at the low neutron doses per fraction of 1–2 rad encountered in the shielded area of a neutron therapy facility. Most of the experimental animal and the epidemiological data concerning the RBE for carcinogenesis are for much larger radiation doses. Therefore to estimate the RBE values at the lower neutron dose per fraction an extrapolation of RBE values from high to low neutron dose per fraction must be done. This is complicated because the human [3] and experimental animal data [13] indicate that the dose–response curve may not be the same for all cancers. Estimates of RBE from the atomic bomb survivor data may now be particularly futile with the recent revelation of a negligible neutron dose component at Hiroshima [14, 15].* A further complication is that the neutron RBE for carcinogenesis may be dependent on the cancer being induced. This would be significant since some tissues, such as the female breast, in comparison to other tissues are very susceptible to radiation carcinogenesis and therefore would have a greater influence on the effective RBE for radiation carcinogenesis as a whole in a mixed population. Because of these ambiguities in the estimates of RBE values for radiation carcinogenesis, as a starting point it was decided to use a quality factor of 10 for neutrons, as suggested by the ICRP and NCRP [7, 8].

Assuming radiation-induced life-shortening is primarily due to carcinogenesis [16], studies with mice suggest the neutron RBE at 1 rad per fraction may be several times greater than 10 [17]. Other experiments in mice show that the RBE for tumor production is greater than 10 at low doses [13]. Therefore it is important to also calculate excess cancer risks using higher RBE

*The reduction in the estimate of the neutron dose component at Hiroshima has been accompanied by a substantial increase in the estimate of the gamma dose component [14, 15]. Therefore, if these new dose estimates are correct, there probably will be no appreciable change in the BEIR III risk factors [14, 15].

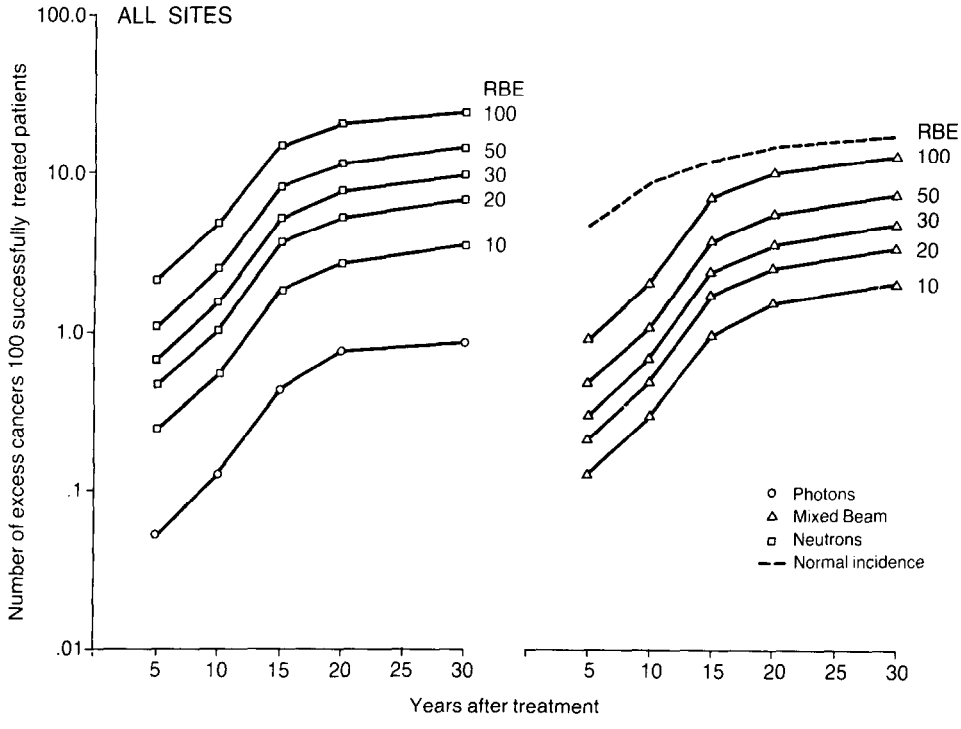


*Fig. 3. Estimated excess secondary cancer risk as a function of the RBE assigned to the stray neutron radiation. The doses in photon equivalent units were calculated by multiplying the stray neutron rad dose by the indicated RBE and adding to that value the rad dose of stray gamma rays. Similar to the results in Fig. 1, the excess cancer risk was calculated as a function of age and sex using the linear dose–response model. These values were then weighted by the age and sex distribution for all 9 cancer sites in Table 6. The weighted values were then summed to get the excess cancer risk at different times after treatment.*

values and to compare these with the excess cancer risks for photon-treated patients and with the expected incidence of cancer in a normal population of the same age and sex distributions. These additional risk estimates are presented in Fig. 3. From these data and those presented in Fig. 2, it is clear that it will be necessary to tolerate a higher incidence of secondary cancers in patients undergoing fast neutron therapy than is the case with conventional photon therapy. Statistically, unless the RBE for carcinogenesis is greater than 50, this increased cancer risk may not be detected in the ongoing 10-yr randomized clinical neutron trials. The reason for this can be seen if one assumes a neutron RBE of 50 for carcinogenesis and a median follow-up time of 5 yr. To attain a statistically significant increase in secondary cancers ($P = < 0.05$) with a 5-yr follow-up time would require a population of approximately 1200 successfully treated neutron and 5000 successfully treated mixed beam patients. Since the advanced cancers being treated with neutrons generally have a 5-yr survival rate of only 5%, and neutrons at best are expected only to result in a 15% improvement [18], at least 6000 patients would have to undergo neutron therapy and 25,000 patients mixed beam therapy to see a significant increase in secondary cancers.

It is also noteworthy that for a neutron RBE of 100 the 5-yr excess cancer risk is only 2.2% for neutrons and 0.9% for mixed beam therapy (Fig. 3). This value is lower than the 5-yr late normal tissue complication rate of 5% in the treatment volume considered acceptable for conventional photon therapy [19]. Moreover, even the long-term excess cancer risk is lower than the risk from other late normal tissue effects reported in the early and more recent neutron clinical trials. For example, in the early clinical trials of Stone, severe late effects were observed in all of the survivors within 5 yr after treatment [20]. More recently, Laramore *et al.* [21] reported a 50% incidence of radiation myelitis in neutron-treated oropharyngeal cancer patients surviving 10 months or longer. These results suggest that the cancer risk from whole-body stray neutron irradiation is of secondary importance compared to the risk of other late normal tissue effects in the treatment volume. This is especially true because some radiation-induced cancers such as thyroid and skin neoplasms often are not life-threatening. In addition, if neutrons are superior to photons in cancer treatment, the long latency

period for radiation-induced solid tumors should result in many additional years of useful life even if neutron treatment eventually results in a lethal secondary malignancy.

Finally, much greater effort should now be made to quantify and qualify the whole-body stray radiation neutron and gamma doses received during neutron and conventional photon therapy and to record the lifetime subsequent secondary cancer incidence in these treated patients. If, as it now appears, the neutron dose component at Hiroshima was extremely small, these neutron therapy patients may be the only data base for a large human population whole-body exposed to a significant dose of neutrons. This information may eventually be useful in estimating the neutron RBE for carcinogenesis and possibly the shapes of the dose–response curves for neutron and gamma radiation, even though this is a select patient population which may have a greater than normal sensitivity to cancer induction by radiation.

**Acknowledgement**—The authors thank Dr. A. V. Peterson (Department of Biostatistics) for his suggestion regarding the statistical method used in this study.

## REFERENCES

1. RAJU MR. Neutrons. In: *Heavy Particle Radiotherapy.* New York, Academic Press, 1980, 78–187.
2. MIJNHEER BJ, BROERSE JJ. Dose distributions of clinical fast neutron beams. In: *Proceedings of the Third Symposium on Fundamental and Practical Aspects of Fast Neutrons and Other High-LET Particles in Clinical Radiotherapy.* Oxford, Pergamon Press, 1979, 109–115.
3. BEIR III. National Academy of Science-National Research Council. In: *The Effects on Population Exposures to Low Levels of Ionizing Radiation.* Washington, DC, National Academy Press, 1980.
4. GERACI JP, JACKSON KL, THROWER PD, FOX MS. An estimate of the patient risk in cyclotron neutron radiotherapy using mouse testes as a biological test system. *Health Phys* 1975, **29**, 729–737.
5. WEAVER K, BICHSEL H, EENMAA J, WOOTTON P. Measurement of photon dose fraction in a neutron radiotherapy beam. *Med Phys* 1977, **4**, 379–386.
6. NCRP. *Structural Shielding Design and Evaluation for Medical Use of X Rays and Gamma Rays of Energies up to* 10 *MEV.* Washington, DC, NCRP Report 49, 1976.
7. ICRP. *Recommendations of the International Commission on Radiological Protection.* ICRP Report 26, Oxford, Pergamon Press, 1977.
8. NCRP. *Basic Radiation Protection Criteria.* Washington, DC, NCRP Report 39, 1971.
9. DHEW. *Facts of Life and Death.* DHEW Publication No. (PHS) 79–1222, 1978.
10. DHEW. Third national cancer survey: incidence data. *J Natl Cancer Inst Monogr* 1975, **41**.
11. PARNELL CJ, KELSEY CA. Shielding of fast neutron cancer therapy sources. *Health Phys* 1972, **23**, 576–577.
12. BEWLEY DK, PAGE BC. On the nature and significance of the irradiation outside the beam in neutron therapy. *Br J Radiol* 1978, **51**, 375–380.
13. FRY RJM. Experimental radiation carcinogenesis: what have we learned? *Radiat Res* 1981, **87**, 224–239.
14. LOEWE WE, MENDELSOHN E. Revised dose estimates at Hiroshima and Nagasaki. *Health Phys* 1981, **41**, 663–666.
15. JABALON S, LOEWE WE, MENDELSOHN E, DOBSON RL, STRAUME T, KAUL DC. Radiation estimates. *Science* 1981, **213**, 7–8.
16. BEEBE GW, KATO H, LAND CE. Studies of the mortality of A-bomb survivors: 4. Mortality and radiation dose, 1950–1966. *Radiat Res* 1971, **48**, 613–649.
17. THOMSON JF, WILLIAMSON FS, GRAHN D, AINSWORTH EJ. Life shortening in mice exposed to fission neutrons and $\gamma$ rays: 1. Single and short-term fractionated exposures. *Radiat Res* 1981, **86**, 559–572.
18. WITHERS HR, ALMOND RP, BROWN BW. Considerations in planning a clinical trial with fast neutrons. *Eur J Cancer* 1971, **7**, 231–235.
19. COMMITTEE FOR RADIATION ONCOLOGY STUDIES. Normal tissue tolerance and damage. *Cancer* 1976, **37**, 2046–2055.
20. STONE RS. Neutron therapy and specific ionization, Janeway memorial lecture. *Am J Roentgenol* 1948, **59**, 771–785.
21. LARAMORE GE, BLASKO JC, GRIFFIN TW, GROUDINE MT. Fast neutron teletherapy for advanced carcinomas of the orpharynx. *Int J Radiat Oncol Biol Phys* 1979, **5**, 1821–1827.