

E14. Second cancer risk following breast cancer

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Adjuvant chemotherapy, hormonal treatment and radiotherapy, and combinations of these modalities, are being administered to a growing proportion of breast cancer patients. In view of the proven therapeutic benefit of these treatments [1,2] and the prolonged life expectancy of those treated, it has become exceedingly important to evaluate the carcinogenic potential of adjuvant treatment. In any discussion of treatment-related second malignancies, it is of primary importance to remember that not all second cancers are due to therapy. The occurrence of two primary malignancies in the same individual may result from host susceptibility (genetic predisposition or immunodeficiency), common carcinogenic influences, a clustering of risk factors, treatment for the first tumour, diagnostic surveillance, a chance event, or the interaction of these factors. In view of the high prevalence of cancer in the general population and the increasing incidence of most cancers with age, it is important to exclude the role of chance in the development of second cancers. To this end, comparison with cancer incidence statistics derived from the general population is crucial. If a second malignancy is demonstrated to occur in excess, the contributions of other risk factors need to be ruled out convincingly before the increased risk can be attributed to treatment.

Numerous studies have demonstrated that women with breast cancer are at a 3- to 4-fold increased risk of developing a new primary cancer in the contralateral breast [3,4]. Significant excesses relative to the general population have also been observed for cancers of the ovary, uterus, lung, oesophagus, colon-rectum, connective tissue, thyroid, melanoma and leukaemia [3,4]. For some of these cancers, such as those of the contralateral breast, ovary and uterus, the excesses may be fully or partly explained by a common aetiology (e.g., genetic predisposition or hormonal risk factors). Other excess risks may be treatment-related.

Contralateral breast cancer accounts for 40% to 50% of all second tumours in women with breast cancer [3] and the 15-year cumulative risk of developing contralateral disease amounts to 10% to 13% [5]. With this high risk, even small effects of treatment may have a large impact in terms of absolute numbers of contralateral breast

cancers. The effect of radiation treatment for the initial breast cancer was evaluated in two large case-control studies in Connecticut and Denmark that involved 655 and 529 women with contralateral breast cancer, respectively [6,7]. Both studies found that radiotherapy did not contribute to the high risk of contralateral disease among women treated after the age of 45 years. However, in the Connecticut study significantly elevated risks were observed for women who underwent irradiation before the age of 45 years, with a radiation-associated relative risk of 1.9 among those who survived for at least 10 years [6]. It was estimated that approximately 11% of all second breast cancers in women irradiated before age 45 years could be attributed to radiotherapy. However, the majority of these patients were treated before 1960 with radiation techniques which nowadays are considered sub-optimal.

Several large studies have shown that hormonal treatment with tamoxifen reduces the risk of contralateral breast cancer by approximately 40% [1,8]. Data from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), demonstrated that longer durations of tamoxifen use were associated with greater reductions in risk, such that 1 year, 2 years and 5 years of treatment produced risk reductions of 13%, 26%, and 47%, respectively [1]. It is not yet known whether the protective effect of tamoxifen against contralateral disease persists over prolonged follow-up periods. Some studies have provided evidence that adjuvant chemotherapy may also reduce the risk of contralateral breast cancer, a phenomenon that is likely to be mediated through drug-induced premature ovarian failure [2,9].

Several studies have assessed the risk of leukaemia following adjuvant chemotherapy and radiotherapy for breast cancer. The relationship between acute myeloid leukaemia (AML) risk and drug dose was examined in detail in a large case-control study (90 cases of leukaemia or myelodysplastic syndromes) by Curtis and associates [10]. Compared with patients treated with surgery alone, the risk of AML was significantly elevated after locoregional radiotherapy alone ((Relative Risk (RR), 2.4). Furthermore, cumulative cyclophosphamide doses of less than 20 g were associated with an approximately two-fold, non-significant increase in risk (compared with

women not exposed to alkylating agents), while women treated with 20 g or more had a significant 5.7-fold risk of AML. It was estimated that among 10 000 patients with breast cancer treated for 6 months with a cyclophosphamide-based regimen and followed for 10 years, an excess of only 5 cases of treatment-related AML would be expected to develop (10). The low risk of AML following cyclophosphamide, methotrexate, fluorouracil (CMF)-based chemotherapy was confirmed by others [4,11], with cumulative risks below 0.2% at 10 years [4]. In the Milan series, there was no clear evidence for a synergistic effect of cyclophosphamide and doxorubicin on leukaemia risk, but others recently reported a higher risk of leukaemia following standard dose-intensity fluorouracil, doxorubicin, cyclophosphamide (FAC) treatment (cumulative risk of 1.5% (95% Confidence Interval (CI), 0.7 to 2.9) at 10 years) [4,12].

The risk of AML associated with high dose-intensive chemotherapy has not yet been quantified, but there is evidence that the combination of anthracyclines and alkylating agents may be leukaemogenic [4].

Conclusive evidence has emerged from several studies that tamoxifen is associated with a moderately increased risk of endometrial cancer [4,8,13–15]. The consistent results across these studies, the observed duration–response relationship [4,8,13–15] and the established oestrogen-agonist effects of tamoxifen on the endometrium strongly support a causal relationship [13]. Use of tamoxifen for 2 years is associated with an approximately 2-fold increased risk of endometrial cancer, while use of 5 or more years produces 4- to 8-fold excess risks [4]. The analysis of the EBCTCG not only shows increased incidence of endometrial cancer in women randomised to tamoxifen treatment, but also significantly increased mortality due to endometrial cancer [1]. Elevated risks of endometrial cancer have been observed after daily tamoxifen dosages of 20 mg, 30 mg or 40 mg. In the Netherlands case-control study, daily dosage did not affect endometrial cancer risk in a model accounting for duration of use, and the duration–response trends were similar with daily doses of 40 mg or 30 mg and less [14]. The few studies that examined the risk for ex-users, found similar increases in risk as for recent users. However, only a few patients had discontinued tamoxifen more than 2 years before the diagnosis of endometrial cancer [4,14]. Only two studies have addressed the combined effects of tamoxifen and other risk factors for endometrial cancer [14,15]. In the largest study conducted to date, Bernstein and colleagues [15] recently reported that women who previously used oestrogen replacement therapy (ERT) experienced greater increases in endometrial cancer risk associated with tamoxifen use than women not exposed to ERT. Furthermore, the effects of tamoxifen on endometrial cancer risk were stronger among heavy women than among thin women. In the Dutch study, however,

body weight did not modify the increased risk associated with tamoxifen use [14].

An important question is whether the clinicopathological characteristics and ultimate prognosis of endometrial cancers following tamoxifen treatment are different from those in patients not treated with tamoxifen. In a few small studies, the stage distribution and histological features of endometrial cancers in tamoxifen-treated women were not remarkably different from those diagnosed in non-treated women [4,8]. In the Dutch study, however, which included 309 patients with endometrial cancer following breast cancer, endometrial tumours with the International Federation of Gynecology and Obstetricians (FIGO) stage III and IV occurred more frequently among long-term tamoxifen users (2 or more years) than in non-users (17% versus 5%, $P = 0.006$). Based on centralised review of diagnostic pathology slides, long-term tamoxifen users more often developed malignant mixed mesodermal tumours or sarcomas of the endometrium than did non-users (15% versus 3%, $P = 0.02$). Furthermore, the tumours diagnosed among long-term tamoxifen users were more often p53-positive and oestrogen receptor-negative. The three-year actuarial endometrial cancer-specific survival in this study was significantly worse for long-term tamoxifen users than for non-users, largely due to the less favourable tumour characteristics associated with tamoxifen use [14].

Increased risks of lung cancer following breast cancer have been largely attributed to radiotherapy [16,17]. No appreciable risk increase has been observed within 10 years of treatment, but 2- to 3-fold elevated risks have been reported in 10-year survivors [16]. The association between breast radiotherapy and subsequent lung cancer risk was found to be stronger for the ipsilateral lung, which supports a radiogenic effect [4,17]. Using individual patient dosimetry, Inskip and associates [16] reported a non-significant increase in lung cancer risk with increasing radiation dose to the affected lung, with an approximate 3-fold excess risk for patients who received 5–10 Gy. Risk seemed to level off at doses higher than 10 Gy. In one study, smokers were found to be at greater risk of radiation-associated lung cancer than non-smokers [4,17].

Recently, heightened concern with regard to the subsequently increased risk of angiosarcomas in the irradiated conserved breast has been expressed [18]. In a nationwide study, 21 Dutch patients with angiosarcoma of the breast following breast-conserving treatment and localised radiation were reported, with a median latency of 6 years [18]. The incidence of angiosarcoma in the breast was estimated at 1.6 per 1000 patients treated with breast conservation per year. Although the absolute excess risk is small, the RR is more than 1000-fold increased in comparison with the incidence of this very rare disease in the general population.

In conclusion, only part of the elevated risk of second malignancies following breast cancer is due to treatment. The intrinsically increased risk of developing a contralateral tumour is unlikely to be meaningfully affected by current radiotherapy for the initial breast cancer, whereas tamoxifen reduces the risk of contralateral disease. Standard dose intensity CMF treatment is associated with a low excess risk of leukaemia, whereas conventional FAC treatment may be associated with a somewhat higher risk. Whether the risk of leukaemia will increase further with the recent introduction of dose intensification strategies should be explored. Although tamoxifen causes a moderate increase in endometrial cancer risk, the proven clinical benefit of this drug in controlling breast cancer [1] far outweighs the excess morbidity and mortality due to endometrial cancer. Clinicians should be alert to signs and symptoms in women taking tamoxifen, and long-term users should be advised to seek prompt gynaecological evaluation upon the development of symptoms. The effectiveness of screening for endometrial cancer has not been demonstrated. Consequently, outside of research settings there is no basis for regular gynaecological examinations in asymptomatic patients taking tamoxifen. The absolute excess risk of lung cancer is likely to be small with current radiotherapy techniques for breast cancer. Nevertheless, there is ample reason to advise breast cancer patients to stop smoking when they receive radiation treatment.

Acknowledgements

This work was supported by the Dutch Cancer Society (NKI 98-1933)

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