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Editorial

Multiple Primary Cancers in Population-based Cancer Registries

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COHORT AND case–control studies of multiple primary cancers, using data from population-based cancer registries, provide information of importance for several aspects of the care and treatment of patients with types of cancer associated with good long-term survival prospects. Such studies often provide insight into radiation and chemical carcinogenesis [1–6]. Risk estimates from such studies provide a basis for counselling survivors and their families in relation to potential complications of cancer and its treatment, and for planning surveillance or interventions in subgroups of survivors at particularly high risk of developing second cancer [3–7]. The determination of elements of treatment associated with an increased risk of second cancer may lead to changes in future treatment protocols, with the objective of maintaining survival prospects, but with a reduction in the risk of subsequent cancer [4, 5]. Such studies have advantages compared with hospital-based studies in that they often cover large populations and therefore provide reliable estimates of risk [7–10]. Population-based studies also reduce the potential for bias which may affect hospital-based studies. For example, one potential source of bias, sometimes summarised as "no news is good news", concerns the tendency for patients with problems including second cancers to maintain closer contact with treatment hospitals than the healthy survivors. Having more complete follow-up on patients developing second cancers would clearly bias risk estimates. However, there are disadvantages associated with studies using population-based cancer registry data. For example, it is often not practicable to review the pathology, using representative specimens of cancers from patients apparently developing multiple primary cancers, to confirm distinct malignant disease. Therefore, rules must be established to identify the occurrence of possible multiple primary cancers based on information which is routinely available to population-based cancer registries. Hence the importance of the paper published on pages 1366–1370 of this issue by Crocetti and associates.

Crocetti and associates investigated the extent of agreement of coding of multiple primary cancers between two population-based cancer registries—the Danish Cancer Registry and the Tuscany Tumour Registry in Italy. Extent of agreement is assessed when a coder in each registry used local registry rules of classification, and also when these same coders used an internationally proposed set of rules of classification. From among patients recorded locally as having developed multiple primary cancers, 100 patients were chosen at random from each registry. After accounting for the differences between local rules for the classification of multiple primary cancers, there was very close agreement between coders in the numbers of primary cancers which had occurred, using both local and international rules. As Crocetti and colleagues propose, there is a strong case for cancer registries to publish their data concerned with multiple primary cancers in accordance with the internationally proposed rules [11], and if it is considered necessary to deviate from these internationally proposed rules, then it is important that a clear indication be given of the precise way in which local rules deviate from those internationally proposed.

Although there was no evidence of important disagreements concerning morphological classification between registries, coders in the Crocetti study neither had access to original registry documents nor did they have the opportunity to request further information. A need for such additional clarifying information was identified in 22% of the Italian series by the Danish coder and in 15% of the Danish series by the Italian coder. As a development of their present study it would be of considerable interest to compare results obtained by Crocetti and associates with a classification of cancers (in terms of number of primaries and morphology) after central review of representative pathological sections of each apparent primary cancer.

The importance of collaborative studies between population-based cancer registries is not in doubt. It has been amply demonstrated that such collaborative studies provide insights into the leukaemogenicity and carcinogenicity of radiotherapy and various forms of chemotherapy. A pioneering study involving the collaboration of 15 population-based cancer registries in eight countries was initially concerned with almost 100 000 women treated for invasive carci-

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noma of the cervix [8, 9]. This study has provided further clarification of the leukaemogenicity of such radiotherapy [1, 2], the radiosensitivity of organs heavily exposed as a result of irradiation of the uterine cervix [8, 9] and the effect of such radiation on the risk of breast cancer, including the effect of radiation–induced menopause [12].

A more recently established collaborative cohort study, involving 11 population-based cancer registries, has provided useful information on the absolute risks of various types of second cancer among more than 130 000 patients treated for testicular cancer, ovarian cancer or Hodgkin's disease [10]. A subsequent case–control study of leukaemia following ovarian cancer, largely nested within the original cohort study, clearly demonstrated the leukaemogenicity of chlorambucil, cyclophosphamide, melphalan, thiotepa and treosulfan [4]. In this same study, the authors noted that the greater efficacy of increased exposure to these agents had not been demonstrated, and therefore, given the dose–response between cumulative exposure and second primary leukaemia, they cautioned against uncritical increases in cumulative exposures [4]. This same collaborative group also executed a case–control study of the occurrence of leukaemia after Hodgkin's disease [3], again largely nested within the original cohort study. The principal findings were that after treatment with more than six cycles of combinations of chemotherapy, including procarbazine and mechlorethamine, the risk of leukaemia was 14-fold higher than after radiotherapy alone. The use of radiotherapy in combination with chemotherapy did not increase the risk of leukaemia above that produced by the use of chemotherapy alone, but there was a dose-related increase in the risk of leukaemia in patients who received radiotherapy alone.

The discussion so far in this editorial has related almost entirely to survivors of cancer treated in adulthood. Survivors of childhood cancer require separate consideration for two reasons. Firstly, considerable improvements in survival in recent decades have resulted in approximately 60% of children being cured [13], and most of these survivors have the whole of their adult life ahead for the possible development of second primary cancers. Secondly, although the mainly topographical approach to classifying adult cancers is justified, it is essential to consider the classification of childhood cancer in terms of morphology [14]. As a consequence of this last point, any system of identification and classification of second primary cancers following childhood cancer needs to include consideration of morphology. In Britain, cohort and case–control studies of second primary cancer after childhood cancer, using the population-based National Registry of Childhood Tumours, have invariably involved the central review of representative sections of all apparent multiple primary cancers for which pathological material was still available. This is in addition to consideration of all diagnostic reports from the relevant local treatment hospitals. Using these methods, the risks of the main types of second primary cancer occurring after childhood cancer have been studied [7], and more detailed studies of the risks and causes of second primary leukaemia [5] and second primary bone cancer [6] have been executed.

It is important that internationally agreed rules for the identification and classification of multiple primary cancers within population-based cancer registries are established and used in practice. With increasing survival after many cancers, and the increasing use of treatments which improve survival but may themselves be, to some extent, leukaemogenic or carcinogenic, the need for such international rules can only increase. The International Agency for Research on Cancer and the International Association of Cancer Registries guidelines [11] serve as a useful international standard for comparative purposes. These guidelines are relatively simple to apply and conservative. Conservative in the sense of classifying fewer apparent second primary cancers as 'true' second primary cancers than many other schemes. However, local registries may still need more complicated and comprehensive rules. Certainly, in relation to second primaries following childhood cancer, more consideration of morphology, cytochemistry, cytogenetics or cell marker studies are sometimes required than are contained in the international guidelines. However, for comparative purposes between registries, it is always possible to describe local deviations from internationally proposed guidelines.

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