Pediatr Radiol (2007) 37:109–111
DOI 10.1007/s00247-006-0328-6

LETTER TO THE EDITOR

Diagnostic and therapeutic radiation exposure in children: new evidence and perspectives from a biomarker approach

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Received: 10 August 2006 / Revised: 22 August 2006 / Accepted: 30 August 2006 / Published online: 17 October 2006

Sir,

We read with great interest the recent article by Ruth Kleinerman on cancer risks following diagnostic and therapeutic radiation exposure in children [1]. The author provided important data from major studies of cancer risk following childhood irradiation for treatment of benign disease and postnatal diagnostic radiation exposure. Furthermore, this paper allows us to provide additional comments on an important issue of public health. In fact, medical radiation is the largest man-made source of population dose [2]. The benefits of all diagnostic imaging when used judiciously are unquestionable. Good medical practice warrants knowledge of the doses and long-term risks of these tests, which can be judiciously employed when they are most appropriate [2]. However, it is also true that regulatory bodies estimate that at least 30% of all diagnostic testing is inappropriate [3]. This inappropriateness probably has its roots in the degree of radiological awareness of the long-term risks associated with radiation exposure. Indeed, recent studies have shown a surprising lack of knowledge among physicians of both dose and clinical risk of commonly performed examinations involving ionizing radiation [4–7]. Paediatricians have the greatest responsibility for protecting their patients from the "friendly fire" of inappropriate imaging. Unfortunately, awareness of radiation protection issues among paediatricians is generally low, with widespread underestimation of relative doses and risks [8]. Information on dangers and cautions connected with the use of medical radiation is, therefore, probably the most effective way of achieving patient safety.

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The most recent update of the risk of low-dose radiation-induced carcinogenesis comes from the National Research Council Committee on the Biological Effects of Ionizing Radiation (BEIR VII) of the National Academy of Sciences [9]. BEIR VII indicated that a single adult population effective dose of 10 mSv results in a 1 in 1,000 life-time risk of developing radiation-induced solid cancer or leukaemia. However, a 1-year-old infant is 10–15 times more likely than a 50-year-old adult to develop a malignancy from the same dose of radiation [9]. At low doses, the assessment of health risk has always been a focus of controversy and the estimate is essentially derived by extrapolation of the dose-effect curve obtained from high doses.

Therefore, the health risks of low-dose exposure in humans may not be accurately quantified by any epidemiological study because of numerous confounding factors, such as inherent, environmental and biological variables. In her paper, Kleinerman reported that only two long-term follow-up studies of cancer following cardiac catheterization in childhood have been conducted, yielding inconsistent results [1, 10–12]. These studies are meritorious and important, but they do have the inherent limitation of being statistically underpowered. In fact, it has been estimated that it would require an epidemiological study of more than 5 million people in order to be able to directly quantify the risk of cancer from exposure to doses of radiation of 10 mSv or less—the typical dose range delivered by diagnostic X-rays [13]. In order to overcome the severe practical limitations of the epidemiological approach, we decided to look for surrogate end-points of radiation-induced carcinogenesis in our recent study [14]. Our findings showed that cardiac procedures using ionizing radiation (mostly cardiac catheterization) are associated with a long-lasting increase in chromosome aberrations in circulating lymphocytes, which represent an intermediate

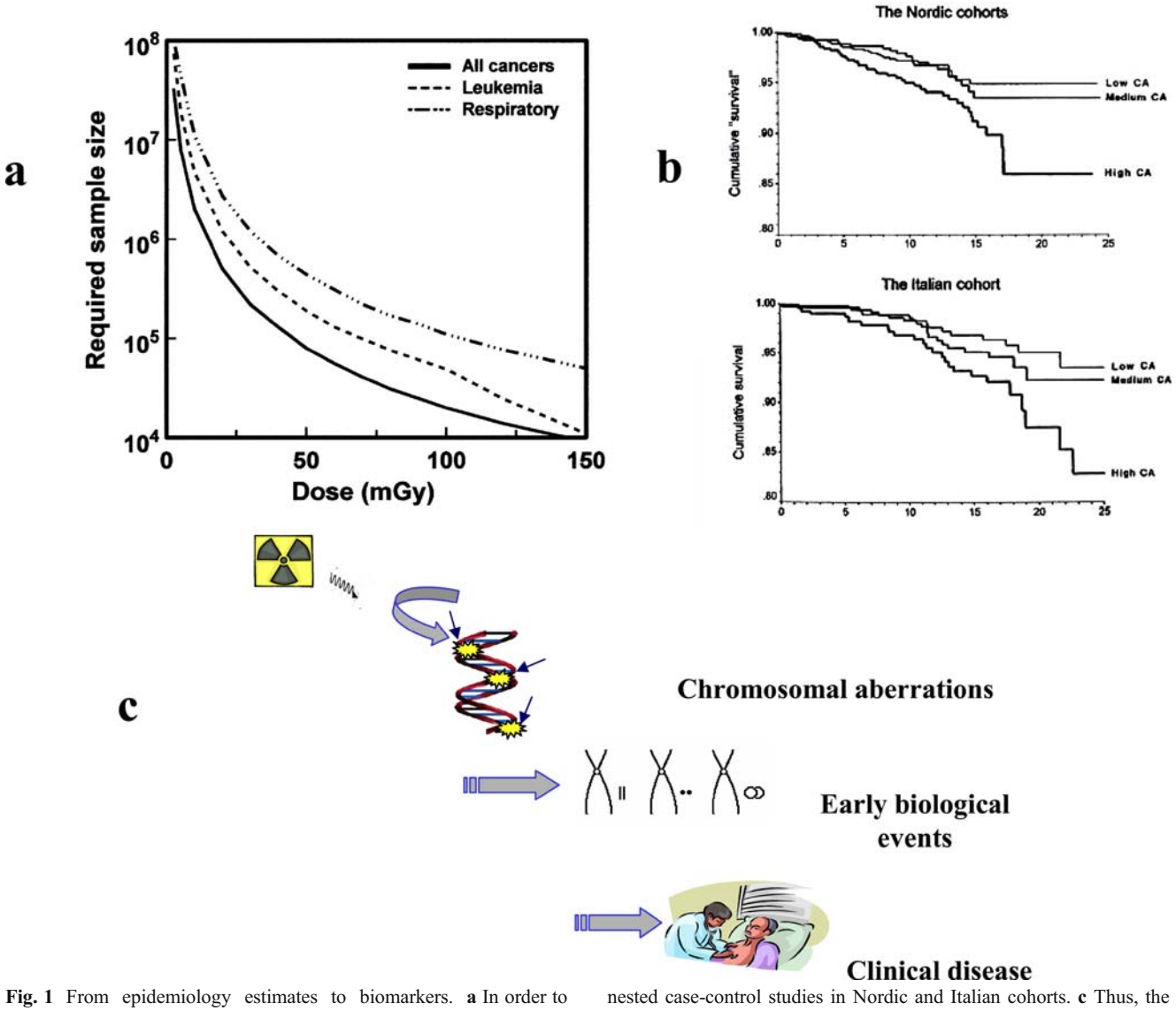

Fig. 1 From epidemiology estimates to biomarkers. **a** In order to maintain statistical precision and power, hundreds of thousands of patients followed up for decades are required to quantify the risks of very low doses of radiation. **b** The evidence of a positive association between the frequency of chromosomal aberrations (*CA*) in peripheral blood lymphocytes and the risk of cancer at different sites came from nested case-control studies in Nordic and Italian cohorts. **c** Thus, the advantages of a surrogate end-point are that, firstly, sample size can be relatively small, and secondly, the lag time between the intermediate phenotype and the clinical end-point is decades, so that appropriate clinical surveillance can be implemented (modified from references 13 and 15)

end-point of carcinogenesis and a surrogate biomarker of increased cancer risk [14]. In fact, during the last decade, prospective cohort studies have shown a significant association between high chromosomal change frequency in peripheral human lymphocytes and the risk of cancer [15].

Therefore, the use of surrogate biomarkers will assist in the difficult task of assessing long-term development of oncogenic effects (Fig. 1). Such studies could have the greatest potential for providing a better understanding of the relationship between low-dose radiation exposure and an individual's susceptibility to the carcinogenic effects of radiation, as recently indicated in the Recommended Research Needs by the BEIR VII report [9]. Finally, more direct evidence of DNA damage may be one of the most efficient ways for improving the awareness of the potential harmful effects of diagnostic radiation and for applying the principles of optimization and justification.

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