

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Exposure to low-dose ionizing radiation from cardiac catheterization and risk of cancer: the COCCINELLE study cohort profile
AUTHORS	Abalo, Kossi Dovene; Malekzadeh-Milani, Sophie; Hascoët, Sébastien; Dreuil, Serge; Feuillet, Tiphaine; Cohen, Sarah; Dauphin, Claire; Di-Filippo, Sylvie; Douchin, Stéphanie; Godart, François; Guérin, Patrice; Helms, Pauline; Karsenty, Clement; Lefort, Bruno; Mauran, Pierre; Ovaert, Caroline; Piéchaud, Jean-François; Thambo, Jean-Benoît; Leuraud, Klervi; Bonnet, Damien; Bernier, Marie-Odile; Rage, Estelle

VERSION 1 – REVIEW

REVIEWER	Hong, Jae-Young Korea University, Department of Orthopedics
REVIEW RETURNED	16-Feb-2021

GENERAL COMMENTS	<p>Authors reported interesting topic with appropriate statistical method. However, a few questions should be answered which may dilute the significance of this study.</p> <ul style="list-style-type: none">- Currently, number of cancer is too small, which can significantly change the result of the study with 1 or 2 up/down of the cancer diagnosis.- I think 2 or 5 years lag period cannot exclude the bias under current study design.- Lack of important information (Dose, OP Time, Machine name etc...)
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REVIEWER	Galderisi, Umberto University of Campania Luigi Vanvitelli
REVIEW RETURNED	22-Feb-2021

GENERAL COMMENTS	<p>The authors presented the result of the COCCINELLE study, which is a retrospective French cohort analysis to determine the cancer risk in patients who undergone cardiac catheterization for diagnosis or treatment of congenital heart disease during childhood. The study is well delineated and the authors clearly indicated the limit of their study that is associated with expected low cancer risk. The manuscript is well written but, in my opinion, lack of future view statement. I mean the authors cited the ongoing Harmonic project to indicate that more data will enforce the finding cancer</p>
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	<p>risk in childhood. Nevertheless, the authors should indicate what are the other parameters that could be considered in future investigations. For example, in patients exposed to low dose radiation what are the other parameters that could increase cancer risk? What about life style, type of diet? Are there other parameters that can be retrieved from patients' medical history. I understand that all these data may be not available for all patients but I am speaking about a theoretical perfect study and what could be some actions that could help to improve present status.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

- Currently, number of cancer is too small, which can significantly change the result of the study with 1 or 2 up/down of the cancer diagnosis.

We agree with the reviewer's comment. The number of cancer cases reported in our study is currently low. This is, to some extent expected since the cancer incidence remains low, even in this specific population, and the duration of follow-up is short. This limitation is also observed in similar epidemiological studies [12, 22]. To deal with such a limit, a way is to conduct combined analyses of several similar studies. Currently, the COCCINELLE cohort is contributing to the European collaborative HARMONIC project with the objective to increase the size of the study population and therefore the statistical power of the study. We modified the discussion section page 19 (tracked version), paragraph 2, to point out this limitation.

“The number of cancer cases reported in the current study is small, due to a short duration of follow-up and low cancer incidence rates. A way to overcome this limitation and increase the statistical power of the study is to conduct combined analyses of several similar studies. The COCCINELLE cohort is contributing to the HARMONIC (for Health effects of cArDiac fluoRoscOpy and mODern radlOtherapy in paediatricS) project [42] that pools together seven large national European cohorts (Belgium, France, Italy, Germany, Norway, Spain, and UK), to increase the statistical power of the analyses. In a few years, HARMONIC will provide information on the risk of cancer associated with exposure to diagnostic radiation received during childhood with a precision that could not be achieved with individual national studies.”

- I think 2 or 5 years lag period cannot exclude the bias under current study design.

We agree that applying exclusion periods cannot exclude indication bias that could be suspected in this study. But the rationale for applying exclusions periods was rather to reflect the latency period before the cancer diagnosis during which a dose cannot explain the occurrence of the disease. The exclusion period is used in our study as a surrogate to the latency period as about 82% of the cohort was subjected to only one procedure. Lag period allows to take into account the fact that a procedure performed during this period of time before the studied outcome will not be associated with the outcome. When doses associated with procedures are available, the cumulative doses will be lagged by 2 or 5 years in the dose-response analysis. The duration of 2 years and 5 years, respectively for leukaemia and solid cancers, are those usually used in radiation studies.

The discussion section has been modified to explain more clearly this point page 15 (tracked version), paragraph 1:

“As about 82% of the cohort received only one procedure, these exclusion periods were used as a surrogate to the latency period, i.e. the minimal delay between exposure and cancer incidence to be considered.”

- Lack of important information (Dose, OP Time, Machine name etc...)

In this descriptive analysis of our cohort, we do not present the dose reconstruction as it is still in progress. The dosimetric parameters used to reconstruct the doses received, which have already been collected, are listed in the Data collection section (page 11, paragraph 1-2, tracked version). More detailed information will be provided in the next article presenting the dose-response analysis when the dose assessment is completed.

Reviewer: 2

The manuscript is well written but, in my opinion, lack of future view statement. I mean the authors cited the ongoing Harmonic project to indicate that more data will enforce the finding cancer risk in childhood. Nevertheless, the authors should indicate what are the other parameters that could be considered in future investigations. For example, in patients exposed to low dose radiation what are the other parameters that could increase cancer risk? What about life style, type of diet? Are there other parameters that can be retrieved from patients' medical history. I understand that all these data may be not available for all patients but I am speaking about a theoretical perfect study and what could be some actions that could help to improve present status.

We are aware that, apart from ionizing radiation due to CC procedures, there are other factors that could increase the studied outcomes: leukemia, CNS tumors and lymphoma risks. A strength of our study was to take into account major predisposing factors to cancer (Down syndrome, transplantation, etc.) and exposure to other medical ionizing radiation (computed tomography, nuclear medicine, conventional radiography), retrieved from the National Health Data System. We also excluded patients with a history of cancer before the exposure to LDIR from CC in order to avoid increased risks of secondary cancer linked to radiotherapy and/or chemotherapy of the first cancer. Other risks factors, as environmental factors (pesticides, pollution) socio-economic status are difficult to study since they cannot be retrieved from medical records or other sources for the whole population. However, the major factors associated with cancer risks such as alcohol or smoking are unlikely to impact the risk estimates as the studied population follow-up is limited to the 18th birth anniversary.

We amended the discussion section to precise this point page 18, paragraph 1 (tracked version)

“The study took into account as much as possible the main factors that could be associated with the studied outcome, as the genetic or hereditary disorders and immunodeficiency factors associated with cancer. In addition, children with history of cancer prior to the CC examination were excluded from the cohort to avoid potential effect of radiotherapy or chemotherapy on a subsequent cancer. However, our study was not designed to directly assess the effect of factors such as obesity, socio-economic status, lifestyle, and environmental factors in the risk estimate models since these data could not be

retrieved directly from medical record databases. However, major known factors associated with cancer risks such as smoking and/or alcohol consumption are unlikely to impact the risk estimates as the studied population includes only children with a follow-up limited to 18 years in this analysis.”

Page 16 paragraph 3 (tracked version):

“This additional information on other medical exposure would be retrieved from the National Health Data System. Further analyses of in the cohort will include doses from CC and other medical diagnosis procedures in the dose-response analyses.”