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# Cancer following cardiac catheterization in childhood

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| **Background** | Low-dose ionizing radiation is one of the definitive risk factors for cancer development. Nevertheless, only a few follow-up studies of children subjected to cardiac catheterization have been performed, yielding inconsistent results. |
| **Methods** | Our study group included 674 children who underwent cardiac catheterization due to congenital anomalies, between the years 1950–1970 in three major medical centres in Israel. A registered nurse conducted a review of the children's medical files in each hospital. Demographic data and vital status were ascertained from the Israeli National Registry, using a unique identity number. Subsequently, the study cohort was linked with the Israeli National Cancer Registry, in order to identify cancer cases that had been diagnosed through December 1996, the last follow-up date of the study. |
| **Results** | Over 75% of the study participants were native-born; 56.2% were males. Approximately 78% of the cohort subjects were alive at the end of follow-up; 28.6% of the participants underwent more than one procedure. All of the diagnosed cases occurred in males. Expected number of malignancies for all sites was 4.75, while the observed number was 11.0 (standardized incidence ratio [SIR] = 2.3; 95% CI : 1.2–4.1). Of the 11cancer cases, 4 lymphomas were observed (0.63 were expected, SIR = 6.3; 95% CI : 1.7–16.2). One of these was Hodgkin's Disease. There were also three cases of melanoma as opposed to 0.62 expected (SIR = 4.9; 95% CI : 1.0–14.2). |
| **Conclusions** | This finding is compatible with current knowledge about the carcinogenic effect of low-dose irradiation but differs in the occurrence of an excess of lymphoma in the absence of an excess of leukaemia, which has not been reported before. The dissonance between males and females is yet to be resolved. |
| **Implications** | Radiation doses that are used currently during cardiac catheterization are lower than in the past. Yet, the procedure is more common and frequently involves longer duration due to therapeutic interventions. The possible long-term results of such an exposure should be kept in mind. |



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Only a few follow-up studies of children subjected to cardiac catheterization have been performed,[1–11] yielding inconsistent results. The aim of the current study was to assess the potential carcinogenic outcome in children undergoing such a procedure in Israel in the 1950s and 1960s.

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## Methods

The study group consists of children who underwent catheterization between the years 1950–1970 in three major Israeli medical centres, Sheba, Beilinson and Hadassah. These medical centres covered at least 75% of such procedures that were carried out during the respective time period.

A review of the medical files of study subjects was conducted by a registered nurse in each hospital. Demographic information was ascertained by matching the study population to the population registry using a unique identity number. Out of 864 subjects who underwent this procedure, 730 (84.5%) were individually identified through the National Population Registry.

Identification was somewhat lower for females than for males (80.4% versus 88.5% respectively). Since adult girls might have changed their family names, a specific search was performed for females to update their new names. Fifty-six children (7.7%) who died during the first year following the catheterization (27 boys and 29 girls), (i.e. not having had the chance to develop cancer during their lifespan) were excluded. Thus, this report is based on a follow-up of 674 children.

The medical information recorded from the hospital file included the primary diagnosis of heart disease, physical measurement of height and weight, date of catheterization, number of procedures and date of last follow-up. Dose information was unavailable for 90% of the children. According to the literature, skin dose during heart catheterization ranged from 5–40 cGy, and bone marrow dose averaged 1.1 cGY (1–10).

Subsequently, the study cohort (with the updated surnames of girls) was linked with the Israeli National Cancer Registry to identify cancer cases that had occurred through December 1996, the last date of completed reporting to the Registry.

The Israeli Cancer Registry was established in 1960 and maintains data on all malignancies (excluding non-melanoma skin cancer) and some benign tumours (primarily of the central nervous system) in the country. It receives notification of all malignancies from hospital discharge reports, as well as oncology and pathology departments throughout the country, by law.

Record linkage was accomplished by computer matching of patients' ID numbers, as well as names, and other demographic variables with the Cancer Registry data file. For all patient matches, the Cancer Registry provided cancer diagnosis, coded according to the International Classification of Diseases, Ninth Revision, along with date and place of diagnosis. Diagnoses were verified by reviewing the original histopathological report for each case.

### Statistical analysis

Standardized incidence ratios (SIR) were computed as a ratio of observed to expected cancers. The 95% CI were estimated using the procedure described by Rothman and Boice.[12] To allow at least for a 5-year latency period, person-years at risk were computed following 5 years from the date of first catheterization until date of last follow-up (31 December 1996, the last update of the registry at the time of study), or until date of death or date of cancer diagnosis. Expected numbers of cancer were computed by applying the appropriate age, sex, place of birth, and year-specific national cancer incidence rates to person-years at risk.

## Results

The 674 children in the final study cohort contributed 12 978 person-years of follow-up with a mean follow-up of 28.6 years (Table 1). Of the children, 379 (56.2%) were male. Over 75% of the study participants were native-born; about 17% were of Middle Eastern or North African origin, and 7% were born in Europe or America.

Approximately 78% of the participants were alive at the end of follow-up. Mean age at study entry was 8.96 years (range: <1 year to 18 years); mean age at end of follow-up was 37.5 years.

About 29% of the participants underwent more than one cardiac procedure with a range of 2–6. No differences between males and females were found in the above characteristics.

Descriptive details of study subjects who developed cancer are provided in Table 2. The malignancies were diagnosed 5–38 years post cardiac catheterization. The two earliest ones which occurred only 5–6 years after irradiation were non-Hodgkins lymphomas. The cancer list was as follows: four cases of lymphoma (two non-Hodgkin's lymphoma originating in the inguinal area and the mediastinum, Burkitt's Lymphoma and one case of Hodgkin's disease), three cases of malignant melanoma and one each of adenocarcinoma of the stomach, transitional cell carcinoma of the bladder, prostate, and cancer of testis. Unexpectedly, all the cases were found among males (Table 3). Overall, there were 11 cancer cases observed as compared with 4.75 expected in the total Israeli male population of the respective age groups (SIR = 2.3; 95% CI : 1.2–4.1). When looking at the four cases of lymphoma compared with 0.7 expected the resulting SIR is 5.7; (95% CI : 1.5–14.6). Excluding the single case of Hodgkin's lymphoma, we still obtain a significant SIR of 6.7 (95% CI : 1.3–19.5). No dose-response

**Table 1** Selected characteristics of the study group by gender

| | Males (n = 379) % | Females (n = 295) % | Total (n = 674) % |
|---|---|---|---|
| **Person-years of follow-up** | 7282 | 5696 | 12 978 |
| **Origin** | | | |
| Israeli born | 72.6 | 80.3 | 75.9 |
| Asian-African born | 19.0 | 13.9 | 16.8 |
| European born | 8.4 | 5.8 | 7.3 |
| **Vital status** | | | |
| Deceased | 21.9 | 22.4 | 22.1 |
| **Mean age at study entry** | 8.85 (±5.1) | 9.10 (±5.1) | 8.96 (5.1) |
| **Mean age at end of follow-up**[a] | 37.38(±11.8) | 37.61(±11.6) | 37.48(±11.7) |
| **No. of procedures** | | | |
| 1 | 71.7 | 71.5 | 71.4 |
| >1 | 28.8 | 28.5 | 28.6 |

[a] End of follow-up: 31 December 1996.

**Table 2** List of cancer cases by latent period

| Latent period | Age at first catheterization | No. of procedures | Age at cancer diagnosis | Cancer site |
|---|---|---|---|---|
| 5 | 10 | 1 | 15 | Non-Hodgkin's lymphoma |
| 6 | 17 | 1 | 23 | Non-Hodgkin's lymphoma |
| 14 | 16 | 3 | 30 | Burkitt's lymphoma |
| 17 | 13 | 1 | 30 | Melanoma |
| 22 | 2 | 1 | 24 | Hodgkin's disease |
| 31 | 18 | 1 | 49 | Cancer of stomach |
| 32 | 11 | 1 | 43 | Bladder |
| 32 | 9 | 3 | 41 | Melanoma |
| 33 | 5 | 3 | 38 | Cancer of testis |
| 37 | 11 | 1 | 48 | Melanoma |
| 38 | 11 | 3 | 49 | Prostate |

**Table 3** Observed and expected[a] cancer by sex and site

| | Observed | Expected | Standardized incidence ratio (95% CI) |
|---|---|---|---|
| **Males (n = 379)** | | | |
| Non-Hodgkin's lymphoma | 3 | 0.45 | 6.7 (1.3–19.5) |
| Hodgkin's disease | 1 | 0.25 | 4.0 (0.05–22.2) |
| Total lymphomas | 4 | 0.70 | 5.7 (1.5–14.6) |
| Melanoma | 3 | 0.62 | 4.87 (1.0–14.2) |
| Bladder | 1 | 1.86 | 0.54 (0.01–3.0) |
| Stomach | 1 | 0.13 | 7.8 (0.1–43.6) |
| Testis | 1 | 0.34 | 2.9 (0.04–16.2) |
| Prostate | 1 | 0.93 | 1.1 (0.01–6.0) |
| **All sites** | 11 | 4.75 | 2.3 (1.2–4.1) |
| **Females (n = 295)** | | | |
| All sites | 0 | 6.80 | |

[a] Excluding first 5 years of follow-up.

**Table 4** Observed and expected[a] cancer by number of procedures. Males only

| | Observed | Expected | Standardized incidence ratio (95% CI) |
|---|---|---|---|
| **One procedure only (n = 275)** | | | |
| Non-Hodgkin's lymphoma | 2 | 0.33 | 6.1 (0.7–22.1) |
| Hodgkin's disease | 1 | 0.18 | 5.5 (0.1–30.8) |
| Total lymphomas | 3 | 0.51 | 5.9 (1.2–17.2) |
| Melanoma | 2 | 0.46 | 4.4 (0.5–15.7) |
| **All sites[b]** | 7 | 3.46 | 2.0 (0.8–4.2) |
| **More than one procedure (n = 109)** | | | |
| Non-Hodgkin's lymphoma | 1 | 0.12 | 8.2 (0.1–45.5) |
| Hodgkin's disease | 0 | 0.07 | |
| Total lymphomas | 1 | 0.19 | 5.3 (0.1–29.3) |
| Melanoma | 1 | 0.16 | 6.4 (0.08–35.4) |
| **All sites[c]** | 4 | 2.93 | 1.4 (0.4–3.5) |

[a] Excluding first 5 years of follow-up.

[b] Bladder + stomach.

[c] Prostate, testis.

association was found when the above analysis was stratified by number of procedures performed (Table 4). Using the bone marrow dose reported in the literature, and a factor of 1.3 to account for additional procedures in some of the subjects, the excess relative risk was 0.84 per cGy.

## Discussion

Low-dose ionizing radiation is one of the definite risk factors for cancer development.[13–20] It has been demonstrated in an array of epidemiological studies such as in nuclear industry workers,[21–26] residents in the proximity of nuclear installations[27–29] or in

high radon content environments,[30–32] among civil or military populations exposed in the course of experimental nuclear testing,[33–36] and in patients exposed to scattered medical irradiation.[19]

Certain molecular studies may be of relevance. In 1978, Adams *et al.* removed blood samples before and immediately after cardiac catheterization in 20 infants and children, and demonstrated chromosomal damage in all of them. The damage was equal to an *in vitro* absorbed dose in the range of 20–50 rads. However, since the effect was considerably greater than that calculated on the basis of the X-ray exposure dose to the patient, it was suggested that the damage was mainly due to the contrast agent used in angiography.[37,38] We feel that this explanation is debatable.

A retrospective cohort study conducted by Spengler *et al.* and McLaughlin *et al.*[38,39] in Canada, based on 4891 children with congenital heart disease who underwent cardiac catheterization between 1946 and 1968 did not demonstrate a significant increase in leukaemia or of other tumours during an average follow-up period of 13 years.

Lymphoma has been described before, though infrequently, as a radiogenic outcome.[40,41] One possible explanation raised was an impaired immunity,[42] similar to the one encountered following renal transplantation.[43]

Current data concerning congenital cardiac malformations suggest a molecular basis—most frequently single-gene defects—for the malformation.[44] Lymphoma, too, is consistently associated with chromosomal translocations, gene rearrangements[45] and chromosome X numerical abnormalities.[46] Still, our results differ from current knowledge about the carcinogenic effect of low-dose irradiation, since, to the best of our knowledge, an excess of lymphomas in the absence of excess of leukaemia, has not been reported before.

Also, it is puzzling why the effect observed by us is restricted to males only. One possible explanation is that females are more difficult to follow in a long-term study due to change of family name post marriage. It should be stressed that this follow-up was performed using updated names for most adult women and using ID numbers which did not change. Moreover, even if this was the case, an artificial lack of females with lymphoma would not have occurred in the younger age groups. On the other hand, there is at least one observation where a similar gender preference following radiation has been noted. Preston *et al.*,[47] in a recent follow-up of the Hiroshima irradiated cohort, found an excess of non-Hodgkin's lymphoma among irradiated males, but not in females. Rates for women were about 60% of those for men ($P = 0.002$).

Three cases of malignant melanoma were detected in our cohort, though this is of only borderline significance; one in the trunk, one in the lower limb and the third in the groin. Malignant melanoma is mostly associated with solar ultraviolet radiation,[48,49] but in 1997 Austin *et al.*[50] reported a fourfold excess of malignant melanoma among laboratory workers, who had been exposed to sources of ionizing radiation (OR = 2.3; 95% CI : 1.0–7.6). Taking into consideration the fact that skin exposure is usually higher than bone marrow exposure, cardiac catheterization may be suspected as an etiologic factor in our case as well.

The primary limitation of our study is its small sample size and therefore its limited power; for which a chance event cannot be ruled out. However, in spite of this small sample size, our positive results cannot be ignored. As for the causality level, we should also consider the possibility—based on the association of prenatal low-dose irradiation and congenital malformations[51]—that either pregnancies resulting in a congenital malformation receive extra diagnostic attention, or that in utero exposure to X-rays may also cause cardiac malformations.

Finally, current technology uses lower radiation doses; Yet, nowadays, cardiac catheterizations are more common, and frequently involve longer exposures to irradiation, due to therapeutical interventions. Thus, even though our data may have practically no clinical implications from the cardiological standpoint, they may add to the limited knowledge of the effects of low-dose radiation, despite lack of detailed dosimetry.

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