Definitive Report on Cancer Risk Among Divers in the River Kishon
from
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Design of the study

The study has a retrospective cohort design. The cohorts are identified from past records of the Navy. Exposure from diving in the Kishon is determined from Navy records and from a personal questionnaire. Subsequent cancer cases are identified from the records of the Israel Cancer Registry. This design allows extension of the follow-up into the future, updating the information on cancer risk as time elapses.

There are three cohorts in the study:
1) the exposed group (E) comprising 1541 members of the Navy diving units who were exposed to diving in the Kishon River;
2) the first control group (C1) comprising 2269 members of the same diving units who were not exposed to diving in the Kishon River; and
3) the second control group (C2) comprising 10897 members of elite Army units.

The time of entry to the cohort is taken as the date of recruitment into the IDF. In our analysis we further divide each of the cohorts into two subgroups:
i) those recruited before 1st January 1975, and
ii) those recruited on and after 1st January 1975.
The reason for this subdivision is that according to reports on pollution in the Kishon River, the sites at which diving was conducted were clearly seriously polluted from 1975 onwards. Reports from 1969/70 are less clear about the pollution, carrying comments that the water appeared clean in the months of late 1969/early 1970. It is at least clear that the divers who were recruited from 1975 onwards and who dove in the Kishon River would have been exposed to heavily polluted waters.

The disease events are defined as any malignant neoplasms (cancers) that are recorded in the Israel Cancer Registry between the beginning of 1960 and the end of 2000. Five individuals were diagnosed with two cancers during the follow-up period, and these second cancers were included in the analysis. The Registry does not record basal or squamous cell carcinomas of the skin. Analyses are presented for the following outcomes:
(a) all cancers, as defined above;
(b) all cancers except melanoma of the skin and carcinoma of the external lip – the latter are considered to be strongly associated with exposure to sunlight, and are therefore expected to be more prevalent among divers than other military personnel;
(c) various subsets of cancers according to definitions given below.

The main outcome from which to draw conclusions is considered by us to be outcome (b).

(d) Following the findings in analysis (b), a further subdivision of the exposed cohort (E) according to estimated level of exposure was considered for that analysis, as follows:

group E1 – divers who did not finish their training course in the Kishon plus the "yechidat hasirot"; group E2 – combat divers; group E3 – professional divers. The estimated level of exposure rises from group E1, through E2, to the highest level among those in E3.

The main method of analysis is through the calculation of the Standardized Incidence Rate (SIR) for each of the cohorts (E, C1 and C2) and their subcohorts divided into pre and post-1975. The risks in the different cohorts and subcohorts are then compared via a ratio of these SIR's, which we call the Rate Ratio (RR). Statistical significance is conducted via the assumption that the numbers of cancer cases have a Poisson distribution. P-values are two-sided.

a) All cancers

All members of cohort

	Divers exposed (E)	Divers unexposed (C1)	Army controls (C2)
Person Years*	35,576	44,606	209,095
No. cases expected**	32.21	30.44	138.54
No. cases observed	39	37	111
SIR***	1.21	1.22	0.80
RR: E versus C (95%CI)#	-	0.99 (0.56,1.44)	1.51 (1.02,2.20)
P-value##	-	>0.9	0.04

* Calculated from time of recruitment to army until death or 31/12/2000
** Calculated by applying person years to Israel national cancer rates
*** Standardized Incidence Ratio = Cases observed/ Cases expected
# Rate ratio = SIR of exposed group (E) / SIR of control group (C1 or C2); 95% confidence interval in brackets
P-value based on Poisson distribution assumption

Recruitment before 1975

	Divers exposed (E)	Divers unexposed (C1)	Army controls (C2)
Person Years	21,791	17,082	78,959
No. cases expected	26.25	18.69	84.04
No. cases observed	27	25	63
SIR	1.03	1.34	0.75
RR: E versus C (95%CI)#	-	0.77 (0.43,1.38)	1.37 (0.84,2.19)
P-value	-	0.4	0.2

Recruitment from 1975 onwards

	Divers exposed	Divers unexposed	Army controls

	(E)	(C1)	(C2)
Person Years	13,785	27,524	130,136
No. cases expected	5.96	11.75	54.50
No. cases observed	12	12	48
SIR	2.01	1.02	0.88
RR: E versus C (95%CI)[#]	-	1.97 (0.81,4.80)	2.28 (1.10,4.37)
P-value	-	0.14	0.03

Summary of results in tables:
The results above indicate that there is a statistically significant excess risk of cancer among exposed divers compared to Army controls (P=0.04), but no excess risk compared to unexposed divers. Among those recruited after 1975, there is again a statistically significant excess risk among exposed divers compared to Army controls (P=0.03). The risk among exposed divers also appears elevated compared to unexposed divers, but the difference is not statistically significant (P=0.14).

b) All cancers excluding skin melanoma and carcinoma of the lip

All members of cohort

	Divers exposed (E)	Divers unexposed (C1)	Army controls (C2)
Person Years	35,618	44,642	209,270
No. cases expected	29.48	27.50	124.39
No. cases observed	31	28	91
SIR	1.05	1.02	0.73
RR: E versus C (95%CI)[#]	-	1.03 (0.60,1.79)	1.44 (0.96,2.16)
P-value	-	>0.9	0.11

Recruitment before 1975

	Divers exposed (E)	Divers unexposed (C1)	Army controls (C2)
Person Years	21,829	17,098	79,085
No. cases expected	24.17	17.02	75.71
No. cases observed	21	21	53
SIR	0.87	1.23	0.70
RR: E versus C (95%CI)[#]	-	0.71 (0.37,1.36)	1.24 (0.71,2.09)
P-value	-	0.3	0.5

Recruitment from 1975 onwards

	Divers exposed (E)	Divers unexposed (C1)	Army controls (C2)

Person Years	13,789	27,544	130,185
No. cases expected	5.31	10.48	48.68
No. cases observed	10	7	38
SIR	1.88	0.67	0.78
RR: E versus C (95%CI)[#]	-	2.82 (0.97,8.73)	2.41 (1.07,4.93)
P-value	-	0.06	0.03

Summary of results in tables:
The results above indicate that the apparent excess risk of "non-sunlight associated" cancer among exposed divers compared to Army controls is not statistically significant (P=0.11), and that there is no apparent excess risk compared to unexposed divers. Among those recruited after 1975, there is a statistically significant excess risk among exposed divers compared to Army controls (P=0.03). The risk among exposed divers also appears elevated compared to unexposed divers, but the difference does not reach statistical significance (P=0.06). Since the control group that is of greatest relevance to the assessment of the risk to divers is the group of members of the divers corps who did not dive in the Kishon (group C1), there is not sufficient evidence to conclude that the exposure to those diving in the Kishon River has caused an increase in cancer risk. At present, the evidence is simply suggestive and without the weight usually demanded for the epidemiological demonstration of a new risk factor.

c) Cancer subsites

Cancers were divided into subgroups according to their anatomical site and/or their histological type.
The 9 subsites chosen a priori were:
1. Central nervous system (CNS)
2. Gastrointestinal tract (GIT)
3. Genitourinary tract (GUT) (excluding testis)
4a. Leukemia
4b. Lymphoma
5. Respiratory tract
6. Sarcoma
7. Testis
8. Thyroid

Note that all SIR's and Relative Risk estimates are based on very small numbers and are subject to great uncertainty. Because of the small numbers the P-values in these analyses are generally large, and indicate the sparsity of evidence available. Even for the analyses in which when the P-values are smaller, because of the multiple analyses, the P-values should be interpreted very conservatively, and only P-values less than P=0.005 should be taken as impelling evidence of an effect of exposure. In fact there are no such extreme P-values in the analyses presented below, with the conclusion that these analyses do not

provide strong evidence of an increase in cancer risk in any particular sub-site among those divers exposed to the Kishon waters.

c1. Central nervous system

All members of cohort

	Divers exposed (E)	Divers unexposed (C1)	Army controls (C2)
Person Years	35,618	44,642	209,270
No. cases expected	2.49	2.53	11.99
No. cases observed	4	2	9
SIR	1.61	0.79	0.75
RR: E versus C	-	2.04	2.15
P-value	-	0.7	0.3

Recruitment before 1975

	Divers exposed (E)	Divers unexposed (C1)	Army controls (C2)
Person Years	21,829	17,098	79,085
No. cases expected	1.93	1.42	6.81
No. cases observed	2	0	3
SIR	1.04	--	0.44
RR: E versus C	-	--	2.36
P-value	-	0.7	0.6

Recruitment from 1975 onwards

	Divers exposed (E)	Divers unexposed (C1)	Army controls (C2)
Person Years	13,789	27,544	130,185
No. cases expected	0.56	1.11	5.19
No. cases observed	2	2	6
SIR	3.57	1.80	1.16
RR: E versus C	-	1.98	3.08
P-value	-	0.8	0.4

c2. Gastrointestinal tract

All members of cohort

	Divers exposed (E)	Divers unexposed (C1)	Army controls (C2)
Person Years	35,618	44,642	209,270
No. cases expected	6.46	5.13	22.37

No. cases observed	5	3	16
SIR	0.77	0.58	0.72
RR: E versus C	-	1.33	1.07
P-value	-	>0.9	>0.9

Recruitment before 1975

	Divers exposed (E)	Divers unexposed (C1)	Army controls (C2)
Person Years	21,829	17,098	79,085
No. cases expected	5.90	4.07	17.62
No. cases observed	2	3	13
SIR	0.34	0.74	0.74
RR: E versus C	-	0.46	0.46
P-value	-	0.7	0.5

Recruitment from 1975 onwards

	Divers exposed (E)	Divers unexposed (C1)	Army controls (C2)
Person Years	13,789	27,544	130,185
No. cases expected	0.56	1.06	4.76
No. cases observed	3	0	3
SIR	5.36	--	0.63
RR: E versus C	-	--	8.51
P-value	-	0.08	0.04

c3. Genitourinary tract (excluding testis)

All members of cohort

	Divers exposed (E)	Divers unexposed (C1)	Army controls (C2)
Person Years	35,618	44,642	209,270
No. cases expected	4.73	3.63	14.55
No. cases observed	5	4	11
SIR	1.06	1.10	0.76
RR: E versus C	-	0.96	1.39
P-value	-	>0.9	0.7

Recruitment before 1975

	Divers exposed (E)	Divers unexposed (C1)	Army controls (C2)
Person Years	21,829	17,098	79,085
No. cases expected	4.34	2.87	11.15
No. cases observed	4	4	8

SIR	0.92	1.39	0.72
RR: E versus C	-	0.66	1.28
P-value	-	0.8	0.9

Recruitment from 1975 onwards

	Divers exposed (E)	Divers unexposed (C1)	Army controls (C2)
Person Years	13,789	27,544	130,185
No. cases expected	0.39	0.76	3.41
No. cases observed	1	0	3
SIR	2.56	--	0.88
RR: E versus C	-	--	2.91
P-value	-	0.7	0.7

c4a. Leukemia (NB: there were no cases in the exposed group)

All members of cohort

	Divers exposed (E)	Divers unexposed (C1)	Army controls (C2)
Person Years	35,618	44,642	209,270
No. cases expected	1.29	1.37	6.22
No. cases observed	0	1	4
SIR	--	0.73	0.64
RR: E versus C	-	--	--
P-value	-	--	--

Recruitment before 1975

	Divers exposed (E)	Divers unexposed (C1)	Army controls (C2)
Person Years	21,829	17,098	79,085
No. cases expected	0.95	0.70	3.08
No. cases observed	0	0	1
SIR	--	--	0.32
RR: E versus C	-	--	--
P-value	-	--	--

Recruitment from 1975 onwards

	Divers exposed (E)	Divers unexposed (C1)	Army controls (C2)
Person Years	13,789	27,544	130,185
No. cases expected	0.34	0.67	3.14
No. cases observed	0	1	3
SIR	--	1.49	0.96

RR: E versus C	-	--	--
P-value	-	--	--

c4b. Lymphoma

All members of cohort

	Divers exposed (E)	Divers unexposed (C1)	Army controls (C2)
Person Years	35,618	44,642	209,270
No. cases expected	4.33	4.81	22.52
No. cases observed	5	4	20
SIR	1.15	0.83	0.89
RR: E versus C	-	1.39	1.29
P-value	-	0.9	0.8

Recruitment before 1975

	Divers exposed (E)	Divers unexposed (C1)	Army controls (C2)
Person Years	21,829	17,098	79,085
No. cases expected	3.07	2.32	10.75
No. cases observed	5	2	12
SIR	1.63	0.86	1.12
RR: E versus C	-	1.90	1.46
P-value	-	0.7	0.6

Recruitment from 1975 onwards

	Divers exposed (E)	Divers unexposed (C1)	Army controls (C2)
Person Years	13,789	27,544	130,185
No. cases expected	1.26	2.49	11.77
No. cases observed	0	2	8
SIR	--	0.80	0.68
RR: E versus C	-	--	--
P-value	-	0.9	0.9

c5. Respiratory tract

All members of cohort

	Divers exposed (E)	Divers unexposed (C1)	Army controls (C2)
Person Years	35,618	44,642	209,270

No. cases expected	3.10	2.28	9.36
No. cases observed	3	5	7
SIR	0.97	2.19	0.75
RR: E versus C	-	0.44	1.29
P-value	-	0.4	>0.9

Recruitment before 1975

	Divers exposed (E)	Divers unexposed (C1)	Army controls (C2)
Person Years	21,829	17,098	79,085
No. cases expected	2.93	1.96	7.87
No. cases observed	3	4	6
SIR	1.02	2.04	0.76
RR: E versus C	-	0.50	1.34
P-value	-	0.6	0.9

Recruitment from 1975 onwards

	Divers exposed (E)	Divers unexposed (C1)	Army controls (C2)
Person Years	13,789	27,544	130,185
No. cases expected	0.18	0.33	1.49
No. cases observed	0	1	1
SIR	--	3.03	0.67
RR: E versus C	-	--	--
P-value	-	>0.9	>0.9

c6. Sarcoma

All members of cohort

	Divers exposed (E)	Divers unexposed (C1)	Army controls (C2)
Person Years	35,618	44,642	209,270
No. cases expected	1.11	1.29	6.00
No. cases observed	5	2	5
SIR	4.50	1.55	0.83
RR: E versus C	-	2.90	5.42
P-value	-	0.3	0.02

Recruitment before 1975

	Divers exposed (E)	Divers unexposed (C1)	Army controls (C2)
Person Years	21,829	17,098	79,085
No. cases expected	0.75	0.57	2.69

No. cases observed	3	2	3
SIR	4.00	3.51	1.12
RR: E versus C	-	1.14	3.57
P-value	-	>0.9	0.2

Recruitment from 1975 onwards

	Divers exposed (E)	Divers unexposed (C1)	Army controls (C2)
Person Years	13,789	27,544	130,185
No. cases expected	0.36	0.71	3.31
No. cases observed	2	0	2
SIR	5.56	--	0.60
RR: E versus C	-	--	9.27
P-value	-	0.2	0.1

c7. Testis

All members of cohort

	Divers exposed (E)	Divers unexposed (C1)	Army controls (C2)
Person Years	35,618	44,642	209,270
No. cases expected	1.76	2.41	11.26
No. cases observed	2	3	8
SIR	1.14	1.24	0.71
RR: E versus C	-	0.92	1.61
P-value	-	>0.9	0.8

Recruitment before 1975

	Divers exposed (E)	Divers unexposed (C1)	Army controls (C2)
Person Years	21,829	17,098	79,085
No. cases expected	0.93	0.76	3.43
No. cases observed	1	2	2
SIR	1.08	2.63	0.58
RR: E versus C	-	0.41	1.86
P-value	-	0.9	>0.9

Recruitment from 1975 onwards

	Divers exposed (E)	Divers unexposed (C1)	Army controls (C2)
Person Years	13,789	27,544	130,185
No. cases expected	0.83	1.65	7.83
No. cases observed	1	1	6

SIR	1.20	0.61	0.77
RR: E versus C	-	1.97	1.56
P-value	-	>0.9	>0.9

c8. Thyroid

All members of cohort

	Divers exposed (E)	Divers unexposed (C1)	Army controls (C2)
Person Years	35,618	44,642	209,270
No. cases expected	1.08	1.12	5.50
No. cases observed	1	1	7
SIR	0.93	0.89	1.27
RR: E versus C	-	1.04	0.73
P-value	-	>0.9	>0.9

Recruitment before 1975

	Divers exposed (E)	Divers unexposed (C1)	Army controls (C2)
Person Years	21,829	17,098	79,085
No. cases expected	0.82	0.62	3.02
No. cases observed	0	1	2
SIR	--	1.61	0.66
RR: E versus C	-	--	--
P-value	-	0.9	>0.9

Recruitment from 1975 onwards

	Divers exposed (E)	Divers unexposed (C1)	Army controls (C2)
Person Years	13,789	27,544	130,185
No. cases expected	0.26	0.51	2.48
No. cases observed	1	0	5
SIR	3.85	--	2.02
RR: E versus C	-	--	1.91
P-value	-	0.7	>0.9

(d) Subdivision of the exposed cohort

As explained in the Introduction, we conducted a further exploratory analysis of the exposed cohort (E), according to a subdivision into three subgroups (E1, E2, E3) at increasing estimated levels of exposure. This was done particularly in the light of a suggested increased cancer risk among the exposed cohort who had started diving in the Kishon after 1975 (see analysis (b)).

The main interest in this analysis was to see if there was an increasing trend in the rates of cancer (without melanoma and cancer of the lip) over the four groups C1 (unexposed divers), E1, E2 and E3. The results are presented below:

All members of cohort

	Divers unexposed (C1)	Divers exposed at lowest level (E1)	Divers exposed at intermediate level (E2)	Divers exposed at highest level (E3)
Person Years	44,642	13,526	14,302	7,790
No. cases expected	27.50	11.57	10.79	7.11
No. cases observed	28	8	13	10
SIR	1.02	0.69	1.20	1.41
Test for trend*	-	z=0.91, P=0.3		

Recruitment before 1975

	Divers unexposed (C1)	Divers exposed at lowest level (E1)	Divers exposed at intermediate level (E2)	Divers exposed at highest level (E3)
Person Years	17,098	8,540	6,942	6,346
No. cases expected	17.02	9.60	8.01	6.56
No. cases observed	21	5	9	7
SIR	1.23	0.52	1.12	1.07
Test for trend*	-	z=0.30, P=0.7		

Recruitment from 1975 onwards

	Divers unexposed (C1)	Divers exposed at lowest level (E1)	Divers exposed at intermediate level (E2)	Divers exposed at highest level (E3)
Person Years	27,544	4,985	7,359	1,444
No. cases expected	10.47	1.98	2.78	0.55
No. cases observed	7	3	4	3
SIR	0.67	1.52	1.44	5.45
Test for trend*	-	z=2.60, P=0.006		

* Using a Poisson log-linear model Wald statistic (z) with a Monte-Carlo simulation test (for small numbers).

The statistically significant trend found for exposure in the Kishon from the year 1975 onwards appears to support the hypothesis of a raised risk of cancer from. However, the observed trend is:
(i) highly influenced by a very small number of cases (3) in the group of highest exposure (E3), and is therefore unstable to future follow-up data.
(ii) one of many trends that were tested in this project and should therefore be interpreted conservatively (see the comments on the number of different sub-analyses in section (c)).
Definitive conclusions cannot be based on this analysis.

(e) Overall conclusions

My overall summary of the results of this project is that the results are inconclusive and that scientific judgment should await further follow-up data on these cohorts. The data provide no evidence of an increased cancer risk among those who dove in the Kishon before 1975. The data do point to a possibly increased risk in those who dove in the Kishon after 1975, particularly among those exposed regularly (professional divers), but the observed increases are based on very small numbers and are not statistically convincing.