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Cancer incidence among the NATO peacekeeping forces in Bosnia and Kosovo: a systematic review and metanalysis

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Keywords: Cancer incidence; military medicine; cohort study; environmental exposure

Abstract

Background: *A few cohort studies of the NATO peacekeepers in the Bosnia and Kosovo war reported inconclusive results on cancer risk. A systematic review and metanalysis of such studies might help to resolve the interpretative limitations.* **Methods:** *Relevant publications were retrieved through a PubMed search and from the list of references of the selected reports. Five epidemiological studies, one each from Denmark, Italy, the Netherlands, Norway, and Sweden, satisfied the selection criteria. Random and fixed effect estimators were calculated. Heterogeneity across studies was formally tested for all cancer outcomes.* **Results:** *Incidence of all cancers was below the expectation, as was the case for lung cancer and cancer at most other organs. The incidence of Hodgkin's lymphoma exceeded expectation in the first years after deployment in the Italian cohort but not in the subsequent years of follow-up. The risk of colorectal cancer and bone cancer was increased in the Danish cohort, and so was the risk of leukaemia in the Swedish cohort. Bladder cancer cases were non significantly more than expected in the three Scandinavian studies. The Cochrane's Q-test was indicative of significant heterogeneity across studies for total cancer, colorectal cancer, melanoma, and leukaemia. The meta-estimate of risk of bladder cancer was increased two-fold (fixed effect summary [FES] = 2.16 (95% CI 1.35 – 2.97), based on three studies.* **Discussion:** *Exposure to depleted uranium, metals, and ultrafine particles has been claimed as responsible for the cancer cases observed among peacekeepers. None of these would account for the excess of bladder cancer. The hypothesis of viral epidemics around the deployment area of the Italian military as contributing to the temporary excess of Hodgkin's Lymphoma cases would be worth exploring.*

Introduction

The twentieth anniversary of the publication of the "Preliminary Report of the Ministry of Defence Commission on the incidence of malignant neoplasms among the military deployed in Bosnia and Kosovo" on 19 March 2001 [1] has passed in complete silence. The current pandemic might have obscured the event in sharp contrast with the broad coverage in the national and international media, from the year 2000 onwards, that focussed mainly on the cases of lymphatic cancer among the NATO peacekeeping military forces deployed in the Balkans. A parallel with the Gulf war syndrome pointed at the never documented exposure to depleted uranium (DU) from the ammunition used in the NATO bombing as responsible for the excess.

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Veterans who developed cancers and the families of those who succumbed submitted numerous applications for compensation, claiming that the exposure to a wide range of plausible and implausible factors was the cause of their diseases. Most claims pointed at the use of DU ammunition by the NATO forces in Bosnia, and Kosovo. However, in the worst-case scenario [2], the effective dose of absorbed radiation might have reached around 0.15 mSv, 15% of the effective dose limit in one year for the general population [3] and between 1-7.5% of the absorbed dose during a CT scan, depending on the site and the type of exam [4]. Besides, the environmental monitoring program conducted by the United Nation Environmental Program (UNEP) in 11 Bosniak sites, seven years after the end of the Balkan war, did not detect significant contamination of the soil, water, foodstuffs, crops, and vegetables [5, 6]. However, the search was restricted to a few spots, due to unexploded land mines [7]. Also, the average urinary total uranium in Italian, German, and Canadian veterans deployed in Bosnia and Kosovo, was comparable to the respective general population [1, 8, 9], and the ratios between ^{235}U, ^{236}U, and ^{238}U isotopes were similar to that of natural uranium [8, 9]. Therefore, the unproven exposure to DU would be an unlikely explanation for the excess incidence of bladder cancer, thyroid cancer, and Hodgkin lymphoma among the NATO peacekeeping forces reported by individual studies.

Once the evidence ruled out the DU hypothesis, exposure to nanoparticles and metals took the stage. However, the few studies conducted so far in military settings have shown a rapid dilution of nanoparticle concentration up to 400 metres in the wind direction from the source of emission [10], and deaths did not exceed the expectation in a small military cohort with potential exposure to nanoparticles [11]. Inhaling fine and ultrafine *a*-emitting DU particles might be a plausible risk factor for cancer at the site of contact (the lung) and deposit (bone and kidney), but not those most frequently claimed as associated. Post-deployment biomonitoring of metallic elements showed concentrations always within the reference values for the general population [12, 13].

Although various scientific commissions concluded that the environmental health consequences of using DU ammunition were negligible, the NATO Command of Military Medicine Services (COMEDS) recommended conducting epidemiological investigations on the long-term health outcomes among the military who participated in the peacekeeping operations [1]. The Commission of the Italian Ministry of Defence acknowledged that the yet unproven exposure of the Italian soldiers to DU had to be considered extremely low. However, it did not exclude a possible link with Hodgkin's lymphoma [1], based on a positive association reported in a study of U.S. uranium refiners and smelters (4 observed cases *vs* 1.6 expected) [14], despite opposite findings of a metanalysis of similar studies [15]. Claims about the side effects of the vaccination protocols have also been raised. However, an Italian study did not find any association between vaccination and micronuclei frequency in lymphocytes of Italian troops deployed in Iraq [12], and a follow-up study of a small military cohort did not observe any effect of multiple vaccinations on the cause-specific mortality [11].

Thirty-four countries, 24 affiliated and 10 non-affiliated with NATO, intervened in Bosnia and Kosovo at different stages between 1989 and 2011 with a total of over 100,000 men and women. A few countries complied with the NATO COMEDS recommendations and conducted studies on cancer incidence or mortality among the respective peacekeeping cohorts in Kosovo e Bosnia. A systematic review and a meta-analysis of these studies were conducted to explore with adequate statistical power the observed associations with different cancer sites that emerged from the individual studies.

Methods

This systematic review followed the principles of the PRISMA Statement for Systematic Reviews and Meta-Analyses and the related check-list [16].

Search strategy

A bibliographic search was conducted on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) up to 8 July 2021 with the following search string: "(Balkan war OR Bosnia OR Kosovo) AND (veterans OR military OR soldiers OR peacekeepers OR peacekeeping forces OR troops) AND (mortality OR incidence OR epidemiology OR cohort study)". The list of references of each article detected through the automatic search was double-checked to identify further publications. Relevant studies were identified through the title, the abstract, and the text, in case of ambiguity.

Study selection and inclusion criteria

The inclusion criteria for the studies contributing to this review were the following: cohort studies of NATO peacekeeping military forces, deployed in Bosnia and Kosovo during and/or in the aftermath of the Balkan conflict, with cancer incidence data, written in English or any European Language. Figure 1 describes the selection process. Overall, we retrieved nine cohort studies of cancer incidence among peacekeeping forces; after excluding the original report of the Commission of the Italian Ministry of Defence, two other Italian studies with methodological issues, and a further Italian cohort study with unidentifed site of the mission, five studies were retained for metanalysis. Three mortality studies, one each from Finland, Italy, and the United States, were excluded from further analysis as only the study conducted in Italy had results by specific

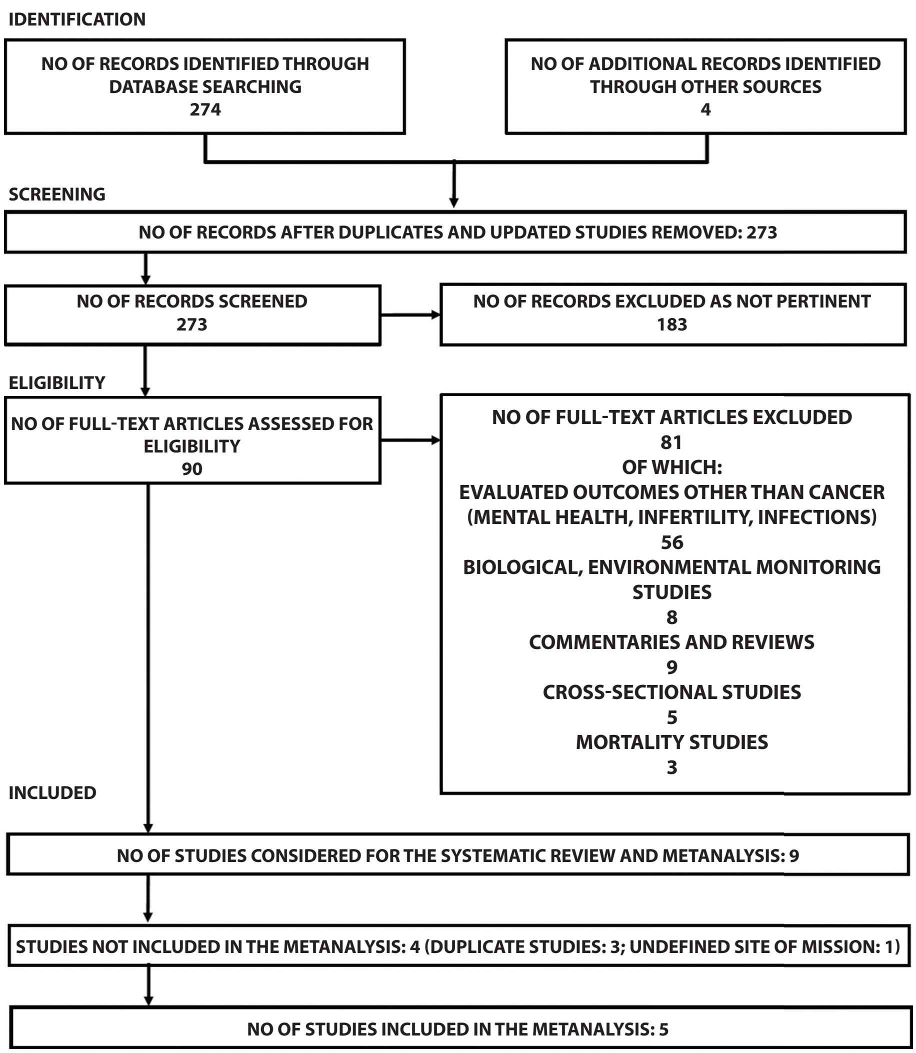

Figure 1. Flow diagram of the selection process for the studies retained in the meta-analysis

cancer site. All the cohorts included a minority of women separately analyzed in a few studies; however, overall, a female cohort would have been too small for any useful inference to be drawn about gender-specific findings. The retained Italian study, by Grandolfo et al., was an update of the final report of the Commission of the Italian Ministry of Defence [1], which extended the follow-up for another seven months, up to 31 December 2001, and detected nine more incident cancer cases [2]. Both analyses reported the absolute numbers of all the incident cancer cases but presented standardized incidence rates and risk estimates only for cancer of the lymphatic organs, solid tumours combined, and all cancers. Grandolfo et al. did not provide the person-years count by age groups. However, the 1995-2001 incidence rates of 8 Italian Cancer Registries were available from the IARC CI5 website [17]. Besides, the age-specific number of cases and incidence rates of all cancers reported in the final report of the Commission of the Ministry of Defence allowed us to estimate the person-years up to December 2001. The expected events for each solid cancer occurring in the cohort were calculated by applying the incidence rates from the southern Italy Cancer Registries, specific by 5-year age group in the 20-59 years age range, gender and calendar-year to the respective person-years count. The choice of re-calculating the expected events in the Grandolfo et al. study using the incidence data from the Southern Italy Cancer registries as the reference was based on the fact that two-thirds of the Italian soldiers were from those regions, and because of the large differences in cancer incidence between North and South of Italy [18]. Table 1 shows selected features of the five cancer incidence studies, one each from Italy [2], the Netherlands [19], Sweden [20], Denmark [21], and Norway [22].

Data abstracted from each study were the cohort size, the total person-years, year of starting and ending the follow-up, number of observed events for all cancers and for specific cancer sites, and the respective expected events from the age-and sex-specific rates of the reference population. While being aware that the healthy worker effect would be much more likely to occur among severely selected populations, such as the military, the expected from general population rates were selected first because all the studies calculated them, and secondly as the healthy worker effect would be less relevant for neoplastic diseases than respiratory or cardiovascular diseases [23]. Fixed and random effect meta-estimates, and heterogeneity have been calculated with Comprehensive Metanalysis® [24].

Results

Overall, the selected studies covered 28-years of follow-up of 88 655 men and identified 470 incident cases. Table 2 shows further details. Most studies reported the average duration of the mission, but not its range. There was also some imprecision about the deployment area: in the Dutch study it was generically indicated as the Balkans, and 42% of the

Table 1. Selected characteristics of the five cohort studies of cancer incidence among the NATO peacekeeping forces in Bosnia and Kosovo

Cohort	Date served	Years of follow-up	Cohort size	Person-years	Observed/expected total cancer cases	Risk estimate
Italy [2]	12-1995-11-2001	1996-2001	42 697	115 037	44/81*	SIR
Netherlands [19]	01-1993-03-2001	1993-2008	18 175	Not available	175/205	SIR
Sweden [20]	1989-1999	1989-1999	8 347	39 816	26/22	SIR
Denmark [21]	01-1992-12-2001	1992-2002	13 552	Not available	84/92	SIR
Norway [22]	1999-2016	1999-2016	5 884	88 941	141/127	SIR
Total	1989-2001	1989-2016	88 655	-	470/527	

*Notes: *The expected events in the Grandolfo et al. are calculated by applying the incidence rates of the southern Italy Cancer registries active in the respective years of follow-up*

Table 2. Details of the five cohort studies of cancer incidence among the NATO peacekeeping forces in Bosnia and Kosovo

First author, year [ref]	Country	Minimum length of deployment	Reference population	Detail on cancer events	Detail on lymphatic cancer	Trend	Deployed in…
Grandolfo M, 2003 [2]	Italy	One mission (2 months)	Southern Italy Cancer Registries	Limited	Yes	No	Bosnia, Kosovo
Bogers RP, 2013 [19]	Netherlands	28 days	Dutch Population Non deployed cohort	Limited (only lung ca & leukaemia)	Only leukaemia	No	Unspecified Balkan area
Storm HH, 2006 [21]	Denmark	Less than six months	Danish Population	Yes	Yes	No	Bosnia (45%), Kosovo (12%), Croatia (38%), other (5%)
Gustavsson P, 2004 [20]	Sweden	Six months (regular duration of the mission)	Swedish Population	Yes	Yes	No	Bosnia, Kosovo
Strand LA, 2019 [22]	Norway	(<1 year)	Norwegian Population	Yes	Yes (partial)	Yes	Kosovo

Danish cohort had been deployed in countries not hit by DU ammunition (Albania 1%, Croatia 38%, Macedonia 3%), and 2% in generic Balkan locations.

Systematic review

Table 3 summarises the results of the individual studies. The results of the Italian study updated by Grandolfo et al. showed a 2.3-fold excess of Hodgkin's lymphoma (SIR = 2.26, 95% CI 1.31 –3.93), based on 12 observed cases against 5.3 expected [2]. The risk of NHL was not elevated (8 observed *vs* 7 expected cases; SIR = 1.14, 95% CI 0.57 – 2.29), and there were two cases of leukaemia *vs* 3.1 expected (SIR = 0.64, 95% CI 0.16 – 2.52). The other cancer cases were three thyroid tumours (5 expected), four cases of testicular cancer (11.1 expected), four colorectal cancer cases (4.6 expected), two brain cancers (4.3 expected), three cases of melanoma (2.8 expected), two cases of lung cancer (7.6 expected), and one of kidney cancer (2.2 expected). There were also one case each of cancer of the pharynx, larynx and stomach, of which only stomach cancer was represented in another study, the Denmark cohort study (2 observed vs 1.6 expected); therefore, the expected events were not estimated for these cancers. The overall 22 observed solid tumours were much less than the 64.7 expected estimated from the incidence data of the southern Italy Cancer Registries (SIR = 0.34, 95% CI 0.23 – 0.51), as it was the case for total cancers (SIR = 0.54, 95% CI 0.41 – 0.73).

The same Italian cohort was included in another three studies. Peragallo et al. took profit from the implementation of the Cancer Surveillance Program of the Army personnel, which was initiated in January 2001, to extend the follow-up to 31 December 2007 [25]. Their cohort included 58,413 troops who participated in at least one mission in Bosnia or Kosovo (a minimum of two months) from 1996-2007 [25], about 16,000 more than the cohort assembled by the Commission of the Ministry of Defence. In respect to the Grandolfo et al. update of the report by the Commission of the Italian Ministry of Defence, there were two main differences: 1) the excess risk of Hodgkin's lymphoma vanished (20 observed cases *vs* 19.86 expected for the Bosnia and Kosovo subsohorts combined; SIR = 1.01, 95% CI 0.54 – 1.88). An analysis by year of diagnosis showed that these cases clustered in the year 2000 in Bosnia and 2001 in Kosovo, and subsequently declined; and 2) a significant excess of thyroid cancer (24 cases *vs* 15.42 expected SIR = 1.56, 95% CI 1.05 – 2.32) showed up, equally shared by the soldiers deployed in Bosnia and Kosovo. The figures for the rest of the cancer

Table 3. Results of the individual cohort studies of cancer incidence among the NATO peacekeeping forces in Bosnia and Kosovo

Cancer site	Grandolfo M, [2] O E SIR 95%CI	Bogers RP, [19] O E SIR 95%CI	Gustavsson P, [20] O E SIR 95%CI	Storm HH, [21] O E SIR 95%CI	Strand LA, [22] O E SIR 95%CI
All cancers	44 80.9 0.54 0.41-0.73	175 205 3 0.85 0.73-0.99	26 21.8 1.19 0.80-1.80	84 92.0 0.90 0.70-1.10	141 127 1.11 0.93-1.31
Colorectal cancer	4 4.6 0.87 0.33-2.32	-	2 1.0 2.00 0.51-7.78	9 4.0 2.25 1.19-4.25	6 11.5 0.52 0.24-1.15
Lung cancer	2 7.6 0.26 0.07-0.95	10 20.8 0.48 0.23-0.89	1 0.8 1.25 0.18-7.08	2 5.0 0.40 0.10-1.52	5 5.7 0.87 0.28-2.04
Melanoma	3 2.8 1.07 0.35-3.32	-	2 2.2 0.90 0.10-3.30	5 7.1 0.70 0.20-1.70	16 11.7 1.36 0.78-2.22
Bone cancer	-	-	-	4 2.5 6.00 1.60-15.3	-
Thyroid cancer	3 5.0 0.60 0.20-1.84	-	-	1 0.9 1.10 0.19-5.89	4 2.5 1.60 0.43-4.09
Bladder cancer	-	-	2 0.7 2.90 0.40 -11.0	7 3.2 2.20 0.90-4.50	8 4.1 1.98 0.85-3.90
Kidney cancer	1 2.2 0.46 0.07-3.13	-	-	2 1.8 1.10 0.10-4.10	3 5.3 0.57 0.12-1.66
Testicular cancer	4 11.1 0.36 0.14-0.92	-	8 4.3 1.90 0.80-3.70	24 20.0 1.20 0.80-1.80	25 24.6 1.02 0.66-1.50
Brain cancer	2 4.3 0.47 0.12-1.82	-	3 2.6 1.20 0.20-3.40	9 7.5 1.20 0.50-2.20	8 10.9 0.73 0.32-1.44
Haemolymphatic	22 16.2 1.36 0.80–1.91	28 29.3 0.95 0.63-1.28	5 3.5 1.40 0.50-3.30	11 10.2 1.08 0.61-1.90	18 16.1 1.16 0.66-1.77
Hodgkin & non-Hodgkin Lymphoma)	20 12.3 1.63 1.05-2.51	-	3 2.3 1.30 0.43-3.95	6 6.8 0.89 0.40-1.96	10 9.7 1.03 0.49–1.89
H. lymphoma	12 5.3 2.26 1.31-3.93	-	2 1.1 1.90 0.20-6.70	3 3.0 1.00 0.20-2.90	-
Non-H. lymphoma	8 7.0 1.14 0.57-2.29	-	1 1.2 0.83 0.11-6.14	3 3.8 0.80 0.20-2.30	-
Leukaemia	2 3.1 0.64 0.16–2.52	5 8.0 0.63 0.20–1.46	2 0.5 4.00 1.28-14.3	4 2.9 1.40 0.40-3.50	8 6.4 1.25 0.54 -2. 46

sites were also largely below the expectation, confirming the Grandolfo et al. observation.

A major concern in the Peragallo study, acknowledged by the authors, was the likely incomplete retrieval of the incident cases, because of a substantial proportion of retirements among the soldiers deployed in the Balkans (24.9% up to 2003), who might have referred to the National Health System. Indeed, only the fraction of the retired who applied for compensation, assuming that exposures during the service had caused their disease, could be identified, which sheds uncertainty about the size of the lost incident cases. In a second paper [26], Peragallo et al. used a capture-recapture technique with two estimates of the incident cancer cases in 2001-2007 among the whole Italian military, whether deployed or not. The two methods yielded substantially different estimates of the total incident cases, ranging 571- 688 cases *vs* 371 detected through the Army Cancer Surveillance Program, corresponding to a loss between 35-46%. While it is conceivable that the loss of cases might have been greater among the non-deployed, there is no evidence that it was so. Besides, the denominator Peragallo et al. used to calculate the standardized incidence ratios was based on the number of soldiers deployed annually for the first time in Bosnia and in Kosovo, instead of the standard person-years count. About 42% of the cohort participated in multiple missions. Thirty-eight per cent of those first deployed in Kosovo and 41% of those first deployed in Bosnia were also deployed in the alternate intervention site during the subsequent missions. Whether these always counted once was not clarified. Still, these drawbacks would not explain the excess of thyroid cancer, which would stand as significant.

Another paper was published more recently on the overall cases recorded by the Army Cancer Surveillance Program up to 2012 [27]. The authors compared two sub-cohorts, one including the never-deployed soldiers, and another including all those who participated in any mission anywhere in the world, with no possible identification of the deployment site. The results of this paper highlighted associations with the condition of deployment abroad, which, in most instances, were specific by corps subgroup. Also, the use of 90% confidence intervals instead of the traditional 95%, along with the large number of comparisons made and the small number of events for some specific cancer sites, doubled the area to reject the null hypothesis; such strategy might have generated a substantial number of spurious positive findings.

As it concerns the rest of the studies (Table 3), the Dutch study did not detect an excess of incidence of all cancers and specifically of haemolymphatic cancer [19]. Among the Swedish military, there were 26 cases of cancer against 21.8 expected [20]. Eight cases were testicular cancer, twice the expected (SIR = 1.9, 95% CI 0.8 – 3.7), six of which occurred among the deployed in outdoor missions (6 observed vs 2.7 expected, SIR = 2.2, 95% CI 0.8 – 4.9). Cancer of the haemolymphatic organs were five against 3.5 expected (SIR = 1.4, 95% CI 0.5 – 3.3) and mainly occurred in indoor occupations. Other cancer sites were represented by more than one case: lung cancer (1 observed vs 0.8 expected), rectum cancer (2 *vs* 1.0 expected for colorectal cancer), bladder cancer (2 *vs* 0.7), melanoma (2 *vs* 2.2), brain cancer (3 *vs* 2.6), and leukaemia (2 *vs* 0.5) [20]. Among the Danish cohort, seven bladder cancer cases and four bone cancers were observed, more than twice and six-fold the expected (95% CI 0.9 – 4.5, and 1.6 – 15.3, respectively) [21]. However, three of the six cases of bone cancer were diagnosed within one year from deployment, which would exclude an association with exposure to *x* and *γ* radiation, the only risk factor for such cancer reported by IARC [28], at the mission site. No cases of bone cancer were observed in the other four studies. Haemolymphatic cancer cases were consistent with the expectation (11 observed vs 10.2 expected; SIR = 1.08, 95% CI 0.61 – 1.90), and there were three cases of Hodgkin's lymphoma, corresponding exactly to the expectation (95% CI 0.2 – 2.9), and four cases of leukaemia (SIR = 1.4, 95% CI 0.4 – 3.5). Cases of testicular cancer were 24, close to the expectation from the Danish Cancer Registry data (SIR = 1.2, 95% CI 0.8 – 1.8). Other cancer sites represented by two or more cases included the the colon-rectum (9 vs 4.0, SIR = 2.25, 95% CI 1.19 – 4.25), the lung (2 observed *vs* 5 expected), the kidney (2 *vs* 1.8), melanoma (5 *vs* 7.1), the brain (9 *vs* 7.5), and the stomach (2 vs 1.6, nor shown in Table 3) [21].

In the Norwegian study, the incident cancer cases observed up to 2016 slightly exceeded the expectation (SIR = 1.11, 95% CI 0.93 – 1.31), as it was the case for melanoma (16 *vs* 11.7; SIR = 1.36, 95% CI 0.78 – 2.22) [22], which had shown a 90% excess (95% CI 0.95 – 3.40) in a previous report on the 1999-2011 follow-up results [28]. There was no excess of testicular cancer (25 cases observed *vs* 24.6 expected; SIR = 1.02, 95% CI 0.66 – 1.50), thyroid cancers (4 *vs* 2.5, SIR = 1.60, 95% CI 0.43 – 4.09), and haemolymphatic cancer (18 vs 16.1, SIR = 1.16, 95% CI 0.66 – 1.77), with 8 cases of leukaemia vs 6.4 expected, and 10 vs 9.7 cases of lymphoma, Hodgkin's and non-Hodgkin combined. A list of other cancer sites with two cases or more included the following: oral cavity and pharynx (5 *vs* 3.1), oesophagus (2 *vs* 1.1), colon-rectum (6 *vs* 11.5), pancreas (4 *vs* 1.6), lung (5 *vs* 5.7), prostate (17 *vs* 14.9), kidney (3 *vs* 5.3), bladder (8 *vs* 4.1 expected), brain (8 *vs* 10.9), and soft tissue (2 *vs* 0.9) [22].

Metanalysis of cancer incidence

Table 4 shows the results of the metanalysis of the follow-up studies of the peacekeeping cohorts deployed in Bosnia and Kosovo for all cancers, the most prevalent specific cancer sites, and all those showing an increase in risk in at least one study and occurring in at least three studies, namely colorectal cancer, lung cancer, skin melanoma, thyroid cancer, bladder cancer, kidney cancer, testicular cancer, brain cancer, all haemolymphatic cancers, all lymphomas combined, Hodgkin's lymphoma, non-Hodgkin lymphoma, and leukaemia.

The results of the Dutch study were only available for all cancers, lung cancer, all haemolymphatic cancer, and leukaemia [19].

Overall, the meta-estimates suggest a reduction in cancer incidence among the peacekeeping forces in Bosnia and Kosovo. Significant heterogeneity in risk of total cancers was detected, with more than 90% of the variance explained by heterogeneity, as well as for for colorectal cancer and melanoma, while the Q-value was elevated but not significant for testicular cancer, and leukaemia. A significant two-fold meta-estimate of bladder cancer risk was based on the three Scandinavian studies only. The Grandolfo et al. study did not observe any case of bladder cancer, while the expected were 5.3. Assuming 0.5 observed cases, the SIR was 0.10, with a lower 95%

Table 4. Metanalysis of studies on cancer incidence among the peacekeeping forces deployed in Bosnia and Kosovo

Cancer	N. studies	N. cases	FES (95 % CI)	RES (95% CI)	Q-value (df)	p-value	I^2
All cancers	5	470	0.78 (0.71-0.85)	0.88 (0.63-1.14)	40. 96 (4)	< 0.0001	90.2
Colorectal cancer	4	21	0.74 (0.514-0.98)	1.25 (0.49-2.01)	15.97 (3)	0.001	81.2
Lung cancer	5	20	0.57 (0.40-0.74)	0.63 (0.39-0.86)	6.65 (4)	0.156	39.8
Thyroid cancer	3	8	0.94 (0.51-1.38)	0.94 (0.51-1.38)	1.82 (2)	0.403	0
Melanoma	4	26	0.64 (0.42-0.86)	0.79 (0.36-1.23)	8.80 (3)	0.032	65.9
Bladder cancer*	3	17	2.16 (1.35-2.97)	2.16 (1.35-2.97)	0.44 (2)	0.803	0
Kidney cancer	3	6	0.55 (0.27-0.84)	0.55 (0.27-0.84)	1.37 (2)	0.503	0
Testicular cancer	4	61	1.00 (0.78-1.21)	1.03 (0.68-1.38)	6.66 (3)	0.084	54.9
Brain cancer	4	22	0.69 (0.45-0.93)	0.75 (0.42-1.08)	4.59 (3)	0.204	34.7
Cancer of the Lymphatic system	5	84	1.09 (0.89-1.29)	1.09 (0.89-1.29)	1.80 (4)	0.773	0
Leukaemia	5	20	0.96 (0.63-1.28)	1.24 (0.61-1.87)	9.36 (4)	0.053	57.3
Lymphoma (any)	4	39	1.14 (0.86-1.42)	1.14 (0.86-1.42)	2.84 (3)	0.418	0
Hodgkin Lymphoma	3	17	1.29 (0.60-1.97)	1.29 (0.60-1.97)	1.96 (2)	0.375	0
Non-Hodgkin Lymphoma	3	12	0.87 (0.52-1.22)	0.87 (0.52-1.22)	0.13 (2)	0.938	0

Note: FES= Fixed Effect Estimate; RES=Randon Effect Estimate confidence interval of 0.01; the resulting Q-value became 25.17, highly suggestive of heterogeneity with the rest of the studies ($p < 0.0001$). Lack of an association and homogeneity across findings was observed for thyroid cancer, kidney cancer, brain cancer, cancer of the haemolymphatic system, and particularly Hodgkin and non-Hodgkin lymphoma.

Trends by surrogates for exposure were explored using different strategies. The Norwegian study explored the effect of duration of the peacekeeping mission on the risk of specific cancers: the risk of bladder cancer was more elevated among the Norwegian military whose mission lasted one year or more (SIR = 2.70, 95% CI 0.74 – 6.92, based on four observed cases vs 1.48 expected); testicular cancer and lymphomas were also moderately more frequent than expected in this group. In this study, however, length of exposure was not a good surrogate for cumulative exposure, as the average time spent in Bosnia and Kosovo was 10.2 months (95% CI 10.09 – 10.31) and only 6% of the Norwegian troops participated in three or more missions [22]. The number of deployments did not affect cancer incidence among the Dutch cohort [19]. The Swedish study explored sub-cohorts of indoor or outdoor activities, with the last further divided in participation in convoys or in destroying ammunition. Total cancer was in excess among those involved in convoy operations (5 observed, 1.7 expected, SIR = 3.0, 95% CI 1.0 – 7.0); testicular cancer (6 out of 10 cases) concentrated among those engaged in outdoor operations (2.7 expected, SIR = 2.2, 95% CI 0.8 – 4.9); melanoma, thyroid cancer, brain cancer, and haemolymphatic cancer were in excess among those involved in indoor operations. The two Hodgkin's lymphoma cases were equally shared between the indoor and ourdoor operations subcohorts [20].

Discussion

This systematic review and metanalysis of the epidemiological studies conducted among the peacekeeping troops deployed in Bosnia and Kosovo suggests an excess of bladder cancer incidence limited to the Scandinavian cohorts. When considering the Peragallo et al. results, instead of those by Grandolfo et al., there was also a marginal excess risk of thyroid cancer (FES = RES = 1.47, 95% CI 1.00 – 1.98). Total cancer incidence was below the expected figures, and no other cancer site showed an excess. There were isolated excesses of colorectal cancer and bone cancer in the Danish cohort, and of leukaemia (based on two cases, one defined as myelomatosis and one case of chronic myeloid leukaemia) in the Swedish cohort. These were most likely chance findings. The excess of Hodgkin's lymphoma in the Italian cohort was limited to the first period of observation, and reached its peak in the year 2000, when six cases occurred, generating the alarm in the media and in the public [1, 2, 25]. The observed excess was statistically robust in the first years of follow-up, and it eventually flattened down to match the expectation. This might have been a very rare chance event. Still, based on the first report of the Commission of the Italian Ministry of Defence, eight out 11 cases of Hodgkin's lymphoma occurred among the 25,083 deployed in Sarajevo and surroundings (135,866.25 person-years, incidence rate 5.89 x 10-5), while the remaining three HL cases had been deployed in Pec, Kosovo (51,526.67 person-years, incidence rate 5,82 x 10-5), and no cases occurred among the 21,348 soldiers deployed elsewhere in Bosnia and Kosovo. These eight HL cases occurred among the military who started their mission between 1996-1999, one year after the last NATO airstrike, 8 – 51 months after initiating their mission, which lasted a median of 167 days (range 80-388), similar to the median duration of the rest of the Italian contingent (161,5 rays, range 1-995). Such features suggest that two Hodgkin's lymphoma clusters occurred, one more robust in Sarajevo and another in Pec, involving three cases only. The rest of the Italian troops were not affected.

The healthy worker effect has been called as an explanation for the low cancer incidence among the Italian military cohorts [18, 26]. No such effect was visible in the Scandinavian cohorts, which would raise doubts about the incomplete retrieval of the incident cases affecting the Italian cohort studies [18]. Alternatively, the selection criteria for recruitment in the army might have been more severe in Italy, compared to the Scandinavian countries. A criticism against the analysis conducted by

Peragallo et al. was that the population covered by the Southern Italy Cancer Registries would have been the proper reference, as two-thirds of the Italian cohort originated from southern Italy and the islands, while the expected cases were derived from the incidence data of the Italian Cancer Registries operating at that time, that were mostly in northern Italy [18]. For instance, the incidence rate of haematological malignancies (HM) and HL prevailed among the Italian soldiers from the northern regions (crude rate: HM = 11.1 x 10-5; HL = 7.4 x 10-5) in respect to those from the southern regions (crude rate: HM = 8.5 x 10-5; HL = 5.7 x 10-5) [1, 26]. Therefore, for the purposes of this metanalysis, the expected events in the Italian cohort were re-calculated using the age-, gender-, and year-specific incidence rates from the Southern Italy Cancer Registries combined. The only substantial change in respect to the original results was a decrease in the expected cases of melanoma (7.3 based on all the Italian Cancer Registries *vs* 2.8 based on the Southern Italy Cancer Registries), which was reflected by an increase in the melanoma SIR (from SIR = 0.41, 95% CI 0.12 – 1.08, to SIR = 1.07, 95% CI 0.35 – 3.32). There were no substantial changes in the risk estimates for the other cancer sites. A third plausible explanation might be the different age ranges of the cohorts, as the healthy worker effect tends to be more evident at younger ages. If so, a younger Italian cohort might account at least in part for the observed heterogeneity in the results. This explanation might be valid in comparison with the Danish cohort, which included subjects up to 65-year-old. However, the age range of the Norwegian cohort was similar to that among the Italians; only 13% of the Dutch cohort were older than 20 at the end of their mission, and the Swedish study did not provide information on the age range of cohort members. Therefore, it seems implausible that different age ranges among the cohorts might have generated the observed heterogeneity in the results.

Lagorio et al. reviewed the results of the three studies that analysed HL incidence among the peacekeeping forces in Bosnia and Kosovo and the studies conducted among the U.S. and U.K. military who were engaged in the first Gulf War, under the hypothesis that a shared exposure to depleted uranium occurred in both events [18]. In their conclusion, the authors stated lack of evidence of an increase in the risk of tumours associated with radiation, lack of evidence of exposure to DU in the operating theatres, apart from internal exposure due to the retained shrapnel, and sporadic associations with specific cancer sites in individual studies.

According to IARC, twenty-seven agents or working processes, including smoking, working in aluminium smelting plants, aromatic amines, polycyclic aromatic hydrocarbons, painting, dry cleaning, diesel exhausts, and infection by schistosoma haematobium, are certain or probable causes of bladder cancer [29]. There are no clues that any such exposures might have occurred at biologically relevant levels among the military deployed one year or less on average. Also, the significant excess was based on three Scandinavian studies only with 17 observed cases overall.

As for thyroid cancer, IARC lists only radiation as a certain causative agent [29]. None of the other conditions which have been associated with thyroid cancer might have credibly contributed to increasing incidence among the peacekeeping forces deployed in Bosnia and Kosovo. As a result, chance is the most likely explanation of the significant excess mortality by this cancer.

As it concerns the excess of Hodgkin's lymphoma observed in the first follow-up of the Italian cohort, there might be plausible explanations, not previously considered. Viral infections, including the Epstein-Barr virus (EBV), the hepatitis B and C viruses, the human immunodeficiency virus type 1 (HIV-1), and the human T-lymphotrophic virus type 1 (HTLV-1) infections, have been identified as Group 1, human carcinogens with lymphomas, and specifically Hodgkin lymphoma, as the main target [30]. The Sarajevo siege, which lasted from April 1992 through February 1996, was the longest in modern history. Stress, sleep loss, the precarious hygiene conditions, the scarcity of water, frequent shortages of electric power, the dust, the difficulty in maintaining a regular and sufficient food intake, not to mention the unavailability and the high cost of medical supplies, all such conditions and others might have favoured abnormal responses to infectious agents, so contributing to the observed increase in incidence of a few cancers among the local population and the interposition forces as well. Besides, a seroprevalence survey of hantavirus detected the highest prevalence in the population of some areas of Bosnia and Herzegovina [31], where epidemics of haemorrhagic fever with renal syndrome (HFRS) caused by rodent-borne hantaviruses occurred. In the Swedish population, the risk of Lymphoma (including Hodgkin's Lymphoma) was elevated among HFRS patients, which was highest within one year from the diagnosis, and tended to decrease afterwards [32]. Other viral infections were documented among peacekeeping forces in the Balkans [33-36], including phlebovirus infections which in some cases might mimic multiple myeloma [37]. Therefore, the hypothesis of an abnormal response to an undefined infectious agent among the Italian military deployed in Sarajevo and Pec would be worth considering.

If any adverse health effect followed the environmental exposures consequent to the war operations, likely it would have most severely hit the local population. However, as the UNEP report pointed out, problems related to the massive migration from the war areas, the lack of Cancer Registries, and the disruption of administrative services, including death registries, created difficult circumstances for epidemiological investigations on the general population of the Balkan war areas [7]. To the best of the available knowledge, only one study explored cancer incidence among the Sarajevo population in 1998-2004 and compared it to the expected cases from the regional and World population rates [38]. The results suggested that the incidences of lung cancer, breast cancer, liver cancer, and thyroid cancer were similar to that of other eastern European countries. On the other hand, laryngeal cancer, bladder cancer, brain cancer, sarcomas of the bone and cartilage, and malignant lymphomas, including Hodgkin's and non-Hodgkin's lymphomas, were significantly increased [38]. The author acknowledged limitations, including the possibility of duplicates in the reported cases. Anyhow, it is difficult to discriminate between direct emissions from war operations and their side effects, previously discussed, as possible determinants. High mortality rates directly or indirectly related to the war were also observed among the Serbian population [39], and the Albanian population of Kosovo [40], although neither report explored cancer mortality.

Limitations in this metanalysis include the small number of studies, as only a few countries complied with the NATO COMEDS recommendation, aggravated by the fact that the Italian study by Grandolfo et al. and the Dutch study restricted the analysis to cancer of the lymphatic organs. Although estimates of the expected events for other cancers were possible for the Italian study, several meta-estimates were based on fewer studies and were, therefore, less reliable. Three studies conducted subgroup analyses in the attempt of detecting higher exposure levels to whatever environmental agents might have been associated with the deployment in Bosnia and Kosovo; mission duration, indoor/outdoor tasks, and first deployment in Bosnia or Kosovo were considered in one study each. These analyses did not add further information, and, being different from one study to another, there was no possibility of calculating summary risk estimates.

Conclusions

This systematic review and metanalysis of the epidemiological studies of the NATO peacekeeping forces in Bosnia and Kosovo confirms that cancer incidence overall was not increased. Instead, in most instances, specific cancer cases were significantly below the expectation, while bladder cancer showed an excess, based on the three Scandinavian studies only; thyroid cancer exceeded the expectation when considering the Peragallo et al. study, which results might have been affected by incomplete retrieval of the relevant events; and the elevated risk of Hodgkin's lymphoma was limited to the first years after deployment, However, interpretation of such findings is weakened by the above-highlighted limitations, the lack of evidence that the claimed exposures occurred, and the lack of evidence of a link between those exposures and the observed cancer outcomes. Among the hypothetical exposures examined, only inhaled ultrafine particles might be plausibly associated with the observed access of bladder cancer among the Scandinavian peacekeepers [41]. However, lung cancer risk, the most likely outcome of exposure to inhaled particles, was strongly decreased in all cohorts, which would raise reasonable doubts about whether such exposure might have played a role. It is unclear what determinants, apart from chance, might explain the excess of thyroid cancer. Among the group 1-2A human carcinogens, the IARC lists radioiodine, *x* and *γ* radiation as determinants of thyroid cancer [28]. It is unknown whether such exposures or others of aetiological relevance occurred among the cases of thyroid cancer diagnosed in the NATO peacekeepers. As it concerns Hodgkin's lymphoma, the excess among the Italian military was statistically robust, but it did not occur in the other cohorts nor it did persist beyond the first years after deployment. Such observations would suggest a link with infectious agents, such as those which were observed in the local population. After twenty years of legal trials and public controversy, the vague definition of the exposures claimed as responsible, the small number of events, the small size of some cohorts, and the incomplete retrieval of the incident cases in the extended follow-up of the Italian cohort, along with the short period of follow-up in some studies [18], contribute to shed persisting uncertainty on the origin of the increased incidence of a few tumours among the NATO military operating as peacekeeping forces in Bosnia and Kosovo.

Although the specific causes remain unknown, the Italian soldiers who suffered from Hodgkin's lymphoma upon returning from their mission to Bosnia and Kosovo and their families obtained just compensation. The temporal sequence was enough to acknowledge the link with their occupation. Still, it is possible to rule out the unproven and unlikely exposure to depleted uranium or metals or inhaled particles.

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