Effect of depleted uranium weapons used in the Balkan war on the incidence of cervical intraepithelial neoplasia (CIN) and invasive cancer of the cervix in Greece

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Summary

Objective: To compare the incidence rates of CIN and invasive cancer of the cervix in two district areas near the borders with the former Yugoslavia and an urban area away from these borders three years before and three years after the bombings in this country.

Material: Two peripheral hospitals (in Kilkis and Serres) which are near the border with the former Yugoslavia and one University hospital (Hippocratio hospital of Thessaloniki) in a rural area away from the borders, where routine Papanicolaou smear tests for screening of CIN and invasive cancer of the cervix are performed in the general female population.

Methods: Hospital records were searched for abnormal smear test results. Incidence rates of CIN and invasive cancer of the cervix three years before (1997-1999) and three years after (2000-2002) the bombings were calculated and compared in the three different settings. The relation between the mean age of the first occurrence of an abnormal smear test was also examined. The results were examined using the chi-square test.

Results: The incidence of CIN in the three-year period 1997-1999 was 0.68% and 0.9% for the two district hospitals of Kilkis and Serres, respectively. These figures rose to 1.11% and 1.13% in the three-year period 2000-2002 for the two district hospitals. The incidence of CIN in the three-year period 1997-1999 was 1.06% for the Hippokrateion University Hospital of Thessaloniki and 0.88% for the three-year period 2000-2002. There has been a small but not statistically significant increase in the incidence rates of CIN in the two district areas near the borders with the former Yugoslavia over the last few years ($p = 0.355$ for Kilkis and $p = 0.472$ for Serres), compared with the small but statistically significant decrease in the incidence of CIN in the urban area of Thessaloniki ($p = 0.0275$). The rates of invasive cancer of the cervix diagnosed from the routine smear tests were too small to make any conclusions.

Conclusion: The increase in the incidence of precancerous lesions of the cervix in areas near the borders with the former Yugoslavia during the last three years may be influenced by environmental factors such as exposure to depleted uranium due to the bombings of 1999. To comfirm this bigger epidemiological studies are needed.

Key words: Depleted Uranium; Cervical Intraepithelial Neoplasia (CIN); Cervical cancer.

Introduction

Cervical intraepithelial lesions typically arise from infection by oncogenic types of human papillomavirus (HPV). Infection by oncogenic HPV is a necessary but not sufficient cause of cervical cancer. It has been assumed that other factors, acting in conjunction with HPV, influence the risk of transition from cervical HPV infection to cervical cancer such as high parity, long-term oral contraceptive use and smoking. There is limited evidence for the role of other environmental factors in HPV carcinogenesis.

Depleted uranium (DU) is a by-product of the enrichment of uranium for the production of nuclear weapons. In recent years there has been increased concern about a possible link between the use of DU and increased number of cases of cancer (including leukaemia and solid tumours) among war veterans and civilians after the Gulf war and the bombings in Kosovo.

This paper covers six years of data from three different hospitals for Papanicolaou smear test results to determine the possible role of exposure to depleted uranium after the Balkan war on the incidence of CIN and invasive cancer of the cervix in Greece.

Material and Methods

We included in our search two peripheral hospitals (Kilkis and Serres) near the borders with the former Yugoslavia and one University hospital in Thessaloniki which is far away from these borders.

Analysis of all Papanicolaou smear test results from the three different settings was performed for the trienniums 1997-1999 and 2000-2002.

As there is no structured national screening programme for cervical cancer and precancerous lesions in Greece the majority of the general female population is screened annually in hospitals (through local screening programmes) or in the private sector. Every hospital keeps its own hard copy records.

Abnormal Pap smear results were considered those reported as CIN 1-3 or those reported as suspicious for invasive cancer of the cervix. Borderline smears and those reported as having

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only inflammatory changes were considered as "not abnormal". Most of the patients having an abnormal smear were referred for colposcopy and biopsies excluding those having a first smear test with CIN 1 who had a repeated smear test in six months time. Follow-up results after an already diagnosed and treated precancerous lesion of the cervix were excluded so only newly diagnosed cases were included in the analysis.

The results were analysed using the chi-square test (statistically significant when $p < 0.05$).

Results

The incidence rates of CIN 1-3 and invasive cancer for the trienniums 1997-1999 and 2000-2002 for the three different hospitals are shown in Table 1. The incidence of CIN 1-3 in the triennial period 1997-1999 was 0.68% and 0.9% for the two district hospitals near the borders, Kilkis and Serres, respectively. The incidence was 1.11% and 1.13% in the three-year period 2000-2002 for these same hospitals. The incidence of CIN in the three-year period 1997-1999 was 1.06% for the Hippocratio University Hospital of Thessaloniki and 0.88% for the three-year period 2000-2002. There was a small but not statistically significant increase in the incidence rates of CIN in the two district areas near the borders with the former Yugoslavia over the last few years ($p = 0.355$ for Kilkis and $p = 0.472$ for Serres) compared with the small but statistically significant decrease in the incidence of CIN in the urban area of Thessaloniki ($p = 0.0275$). The rates of invasive cancers of the cervix diagnosed from the routine smear test were too small to make any conclusions.

Table 1. — *Incidence rates of CIN 1-3 and invasive cancer for the trienniums 1997-1999 and 2000-2002 for the three different hospitals.*

		Kilkis	Serres	Thessaloniki
1997-1999	CIN 1-3	8 (0.68%)	34 (0.9%)	346 (1.06%)
	Cervical cancer	1	2	12 (0.03%)
	Total no. (smear tests)	1175	3685	32538
2000-2002	CIN 1-3	15 (1.11%)	46 (1.11%)	266 (0.88%)
	Cervical cancer	0	3	9 (0.02%)
	Total no. (smear tests)	1350	4135	30007

Table 2 shows the mean age of presentation of an abnormal smear test in the three different hospitals for the trienniums 1997-1999 and 2000-2002. It can be seen that there is a small but not statistically significant ($p = 0.121$) shift in the age presentation of cancer cases towards younger age groups.

Table 2. — *Mean age (years) of presentation of an abnormal smear test in the three different hospitals for the trienniums 1997-1999 and 2000-2002.*

		Kilkis	Serres	Thessaloniki
1997-1999	CIN I-III	39.8	38.2	39.2
2000-2002	CIN I-III	37.6	36.8	37.8

Discussion

Epidemiological and laboratory data suggest that cervical intraepithelial lesions typically arise from infection by oncogenic types of venereally transmissible human papillomavirus (HPV) [1]. However, oncogenic HPV infections are usually benign and usually resolve within one to two years [2]. Because infection by oncogenic HPV is a necessary but not a sufficient cause of cervical cancer it has been assumed that other factors, acting in conjunction with HPV, influence the risk of transition from cervical HPV infection to cervical malignancy [3]. The risk factors for progression are mainly unknown but include HPV type and intensity, cell mediated immunity and reproductive factors. Based on the evidence provided by the largest epidemiological studies, it can be concluded that among HPV positive woman, high parity, long-term oral contraceptive use, smoking and co-infection with other sexually transmitted agents are the most consistently identified epidemiological co-factors likely to influence the risk of progression from cervical HPV infection to high-grade cervical intraepithelial lesions and invasive cervical cancer. There is limited evidence for the role of dietary and other environmental factors in HPV carcinogenesis [3].

Depleted uranium (DU) is a by-product of the enrichment of uranium for the production of nuclear weapons and reactor fuel. When DU ammunition hits its target, it explodes and burns, forming chemically toxic and radioactive dust. Because the particles are very small they can travel up to 300 kilometres and contaminate the air and water. The uranium oxide compounds in this dust can enter the body by ingestion or inhalation [4]. During the 1999 Kosovo campaign 31,000 shells containing DU were fired. The main isotope in DU, U238, has a half-life of 4.5 billion years [4]. Although the US and European governments have sought to deny the connection between the use of DU weapons and cancer there has been increased concern about a possible link between the use of DU and increased number of cases of cancer (including leukaemia and solid tumours) among war veterans and Iraqi civilians after the Gulf war [4, 5]. A paper published in 1999 reported a 160% rise in the reported cases of cervical cancer in Basrah in 1997 compared with the year 1990 with a shift in the age distribution of cancer cases towards younger age groups [5].

The validity of our study depends on the accuracy of data entry and collection for the three different hospitals in the two different periods. Although there is no structured national screening programme for cervical screening in Greece there is no evidence that there has been a change in the methods used for screening and collecting data or any change in sexual behaviour, the other risk factors or the consistency of the population screened for cervical cancer in the three different settings between the triennials 1997-1999 and 2000-2002.

If that is the case the small but noticeable increase in the incidence rate of precancerous lesions of the cervix may be attributed to an exposure to a new risk factor that did not exist before 1999. Ionising radiation from

depleted uranium after the bombings in the nearby former Yugoslavia may have played its role in the increase in the incidence of precancerous lesions of the cervix after 1999 in the areas which are near the borders. An indirect mechanism of changes in cell mediated immunity because of the radiation that may have influenced the degree of clearing the infection with oncogenic HPVs in a proportion of the female population may be proposed.

If the hypothesis is correct it can be predicted that in the near future an increase in the incidence of cervical cancer in areas near the former Yugoslavia will be noticed, thus a more intense screening and intervention programme for cervical cancer is required.

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