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Impact of vaccinations and infectious diseases on the risk of melanoma—evaluation of an EORTC case–control study

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Abstract

A significant correlation between a reduced risk of melanoma and BCG and vaccinia vaccination in early childhood or infectious diseases later in life has already been reported from the FEBrile Infections and Melanoma (FEBIM) multicentre case–control study. This correlation is further evaluated in this study based on 603 incident cases of malignant melanoma and 627 population controls in six European countries and Israel by means of a joint analysis of the influence of vaccinations and infectious diseases. In addition, the previously unconsidered impact of influenza vaccinations is evaluated for the whole study population. The strong effects of the frequently given BCG and vaccinia vaccinations in early childhood, as well as of uncommon previous severe infectious diseases, were apparently not cumulative. With the Odds Ratio (OR) being set at 1 in the absence of vaccinations and infectious diseases, the OR dropped to 0.37 (95% Confidence Interval (CI): 0.10–1.42) when subjects had experienced one or more severe infectious diseases, associated with a fever of $> 38.5\ ^{\circ}C$, and had not been vaccinated with BCG or vaccinia. The OR was 0.29 (CI: 0.15–0.57) in those who had had a severe infectious disease and were vaccinated with either BCG or vaccinia and 0.33 (CI: 0.17–0.65) for those with 1 or more severe infectious diseases and who had received both vaccinations. We conclude that both vaccinations as well as previous episodes of having a severe infectious disease induced the same protective mechanism with regards to the risk of melanoma. Because of a 'masking effect' by the vaccinia vaccination, the protective effect of the BCG vaccination and of certain infectious diseases against cancer has remained undetected. The vaccinations contributed more to the protection of the population than a previous episode of having an infectious disease. In view of the termination of vaccinations with vaccinia in all countries and of BCG in many of them, these findings call for a re-evaluation of vaccination strategies.

Keywords: Anticancer defence; Melanoma; Vaccination; Vaccinia; BCG; Innate immunity; Infection

''Was du ererbt von deinen Vätern hast, Erwirb es, um es zu besitzen''
(J.W. Goethe, Faust I)

1. Introduction

There is increasing evidence that various microbial stimuli are necessary for the normal maturation of the immune system [1]. This insight stems mainly from epidemiological data pointing to an inverse correlation between infectious diseases acquired early in childhood

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and atopic symptoms [2], and from old and recent observations that routine vaccinations with vaccinia, Bacille Calmette-Guérin (BCG) and measles have non-specific positive influences on infant survival, in contrast to vaccinations with polio, tetanus and diphtheria vaccines [3,4]. Moreover, there are epidemiological data suggesting that various infectious diseases experienced later on in life have inhibitory effects on the development of cancer [5,6]. Comparable findings had been described by us in a pilot study on melanoma of the skin [7]. The aim of the FEBIM (FEBrile Infections and Melanoma) study was to determine, by means of a multicentre population–based case–control study, whether infectious diseases and influenza vaccinations as well as vaccinations against tuberculosis with BCG and against smallpox with vaccinia within the first year of life can influence the subsequent risk of melanoma.

In a previous paper, a separate analysis of the influence of infections on the melanoma risk was described [8]. It was revealed that certain, predominantly severe and rare, infectious diseases, with fevers of > 38.5 °C, correlated significantly with a reduced melanoma risk, namely pulmonary tuberculosis, sepsis, pneumonia and infections due to *Staphylococcus aureus*. Certain less severe infectious diseases, also with fevers of >38.5 °C, for example influenza, were associated with only a moderately reduced melanoma risk, but with repeated episodes of such disease, this risk reduction attained statistical significance. Some additional infectious diseases had, when analysed separately as a single event, no impact on the melanoma risk; namely, hepatitis, erysipelas, urinary tract infections, endocarditis, meningitis, rheumatic fever, cholecystitis, bronchitis, herpes simplex with fevers above 38.5 °C, that had occurred within a 5-year period before surgical removal of the tumour (cases) or before the interview (controls). Infectious enteritis was the only infectious disease which had a significant melanoma risk-reducing effect, at least when the body temperature was elevated. Subsequently, we also observed that some vaccinations were associated with a reduced melanoma risk. Analysis of data from the Italian centres showed that the effect of the influenza vaccination was weak, but became significant when three or more vaccinations were given during the previous 5 years [9]. However, the effects with BCG and vaccinia in many centres were strong [10].

This paper presents the final and joint analysis of the data from all study centres concerning the vaccinations and episodes of infectious diseases. Attention is focused on the concomitant exposures to vaccinations and infectious diseases. Specifically, the following questions are raised, analysed and discussed: (1) How strong is the evidence for an interdependency between certain microbial challenges (vaccinations, natural infections) and melanoma protection? (2) Why do previous studies on BCG vaccination and cancer protection appear to yield highly conflicting results? (3) What is the relative importance of the vaccinations and infectious diseases and how may their changing influence, beneficially or detrimentally, alter the epidemiology of malignant melanoma?

2. Description of the study

2.1. Patients and methods

Under the auspices of the Melanoma Cooperative Group of the European Organisation for Research and Treatment of Cancer (EORTC), we conducted a population-based case–control study, named FEBIM involving 11 collaborating institutions in six European countries and Israel. From 1994 to 1997, we enrolled 603 incident cases (277 males, 326 females) with a histopathologically-verified diagnosis of malignant melanoma of the skin and 627 population controls without tumours (263 males, 364 females), as detailed in Ref. [8]. The participation rates among the eligible cases and controls were 81.2 and 85%, respectively. Controls had been frequency-matched to patients with respect to gender, age, and ethnic origin within each centre. Although frequency-matching for age was performed using only three broad categories (<40 years, 40–59 years, $>$ 59 years), the resulting age distributions among cases and controls were very similar (median age: 57 years for cases and 55 years for controls; interquartile range: 24 years for both groups). Detailed information on exposure to a variety of factors, including the history of previous infectious diseases, was obtained by a personal interview conducted by a trained person with a medical background. Specifically, interviewers asked study subjects for their personal history of BCG vaccinations against tuberculosis and vaccinia vaccinations against smallpox during childhood. Answers were verified, where possible, by the interviewers after inspection of the subject's vaccination cards.

For statistical analysis, logistic regression was used to determine the effect of the two different vaccinations on the melanoma risk. The combined effect of infections accompanied by a body temperature above 38.5 °C and of the two vaccinations was determined in logistic regression models. Confounding variables included in all models were study centre, gender, age, ethnic origin, skin type according to the classification of Fitzpatrick and colleagues [11], freckling index according to the charts described by Gallagher and colleagues [12], number of pigmented naevi and number of sunburns. The influence of the exposure variables in the different sub-groups of the study sample was examined with regard to the variables of study centre (eight regions), gender, and age (<50 years, $\geqslant 50$ years).

Results of the logistic regression analyses were expressed as the estimates of the adjusted Odds Ratios (ORs) for the corresponding exposure variables related to the vaccination status and their 95% Confidence Intervals (CIs). All statistical analyses were performed using the SAS software (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Melanoma risk in relation to vaccinations and infectious diseases

Basic characteristics of the two populations with respect to the distribution of a variety of socio-economic factors and clinical features of the tumour, as well as the relationship between known risk factors and melanoma occurrence have been described elsewhere in Refs. [8,10].

Table 1 presents the raw data for the BCG, vaccinia and influenza vaccinations. Data are given for the total case and control groups and also for the sub-groups from the different study regions. Because of small sample sizes in two of the three participating institutions from the former West Germany, we pooled the data from Berlin (West), Göttingen and Hamburg. The two Italian samples, from Padova and Verona, were likewise combined for this reason.

In the entire group, there was a comparable significant reduction in melanoma risk for vaccinations with BCG as well as with vaccinia (Table 1). In Dijon and Northern Italy, the BCG vaccination did not correlate with melanoma protection. No remarkable differences in risk reduction were observed with respect to gender. Thus, with the OR of non-vaccinated subjects being set at one, males and females vaccinated with both BCG and vaccinia had ORs of 0.38 (CI: 0.16–0.85) and 0.44 (CI: 0.22–0.85), respectively.

Single vaccinations with influenza within the past 5 years did not have a protective effect on the melanoma risk. This lack of an effect was also mirrored in the results for each study centre, irrespective of the frequency of vaccination (Table 1). Results showing such effects for more than two influenza vaccinations, as reported in a preliminary analysis of the Italian samples (OR = 0.43, CI: 0.19–1.00) [9], could not be confirmed for the whole study (OR = 0.79, CI: 0.52–1.20). Similarly, the data from Dresden, Germany, showed only non-significantly reduced effects (OR = 0.45, CI: 0.19–1.05). A calculation of the effect of repeated vaccinations was not possible for any centre outside of Italy because of sample size limitations.

3.2. Effects of vaccinations and infections

Table 2 shows the results of the joint analysis for BCG and vaccinia. Compared with subjects who had received neither of the two vaccinations, a significantly reduced melanoma risk was observed for those receiving only BCG, only vaccinia, and those who had received both vaccines. The effect was even more clearly seen in the sub-group of persons aged <50 years, with an OR of 0.23 (CI: 0.05–0.93) for those receiving BCG only, an OR of 0.33 (CI: 0.10–1.06) for those receiving vaccinia only, and an OR of 0.28 (CI: 0.09–0.84) for people who had been vaccinated with both vaccinia and BCG. These data also show that, in the entire sample, the risk-lowering effect of the BCG vaccination was not augmented by an additional vaccinia vaccination.

Table 1
Melanoma risk and vaccination against tuberculosis (BCG) of new-borns or, in those centres marked with asterisks, of older children or adults, against smallpox (vaccinia) within the first year of life, and against influenza of adults within the last 5 years

Study region	Cases				Controls				BCG		Vaccinia		Influenza	
	Positive history of vaccination				Positive history of vaccination				OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
	n	BCG	vaccinia	influenza	*n*	BCG	vaccinia	influenza						
Vienna, Austria	45	23	37	10	45	32	37	7	0.43	(0.17–1.00)	1.00	(0.33–2.99)	0.79	(0.18–3.39)
Sofia, Bulgaria	115	85	104	8	115	100	111	8	0.43	(0.21–0.84)	0.34	(0.09–1.03)	0.74	(0.19–2.62)
Tallinn, Estonia	101	59	95	6	101	68	100	3	0.67	(0.38–1.21)	0.16	(0.01–0.95)	1.77	(0.40–9.37)
Dijon, France	55	29	42	22	59	25	45	16	1.52	(0.72–3.18)	1.01	(0.42–2.41)	2.13	(0.60–8.24)
Berlin, Göttingen, Hamburg, Germany	70	23	50	9	69	37	64	11	0.42	(0.21–0.84)	0.20	(0.06–0.52)	0.91	(0.28–2.89)
Dresden, Germany	71	25	66	20	80	45	74	29	0.42	(0.22–0.81)	1.07	(0.31–3.87)	0.45	(0.19–1.05)
Tel Aviv, Israel	47	24	29	12	54	40	31	9	0.37	(0.16–0.83)	1.20	(0.54–2.67)	0.83	(0.13–5.25)
Padova, Verona, Italy	99	22	98	18	104	20	102	27	1.20	(0.61–2.37)	1.92	(0.17–2.15)	0.71	(0.33–1.51)
Total	603	290	521	105	627	367	564	110	0.69	(0.52–0.92)	0.65	(0.44–0.98)	0.91	(0.65–1.28)

BCG, Bacille Calmette-Guérin.
Descriptive data are given for the total sample and the sub-samples in the study regions as well as Odds Ratios (OR) and accompanying 95% Confidence Intervals (CI) for the association between vaccination and melanoma occurrence. The reference group consists of persons not vaccinated, with the OR set at 1. Observations are significant when the CI does not contain the value 1.

Table 2
Melanoma risk in relation to the vaccination patterns with BCG and/or vaccinia determined by a joint analysis of the two vaccinations

	Neither vaccine	BCG and vaccinia	Only BCG	Only vaccinia	All
Adjusted OR[a] (95% CI)	1.0 (reference)	0.41 (0.25–0.67)	0.40 (0.18–0.85)	0.60 (0.36–0.99)	
Mean age of patients (standard deviation)	65.9 (17.7)	52.2 (15.0)	53.3 (19.5)	63.0 (13.6)	
Number of cases	63	271	19	250	603
Number of controls	37	341	26	223	627

BCG, Bacille Calmette-Guérin.
[a] Odds Ratios (OR) adjusted for centre, age, gender, ethnic origin, skin type, freckling index, number of naevi and number of sunburns are given together with the 95% Confidence Interval (CI). Also given are the number of cases and controls (note that the OR reference value, set at 1, is for people vaccinated with neither vaccine).

Table 3
Combined effect of (a) severe infections (b) less severe infections with a body temperature above 38.5 °C and the two vaccinations (BCG and vaccinia) on the melanoma risk

Vaccinations		(a) Number of severe infections		(b) Number of less severe infections	
		0	$\geqslant 1$	0	$\geqslant 1$
No	No. of cases/controls	57/31	6/6	46/26	17/11
	Adjusted OR[a] (95% CI)	1.00 (reference)	0.37 (0.10–1.42)	1.00 (reference)	0.81 (0.31–2.13)
BCG or vaccinia	No. of cases/controls	229/191	40/58	200/169	69/80
	adjusted OR[a] (95% CI)	0.57 (0.33–0.96)	0.29 (0.15–0.57)	0.61 (0.34–1.08)	0.37 (0.19–0.70)
BCG and vaccinia	No. of cases/controls	231/285	40/56	174/188	97/153
	adjusted OR[a] (95% CI)	0.40 (0.23–0.68)	0.33 (0.17–0.65)	0.47 (0.26–0.84)	0.31 (0.17–0.57)

BCG, Bacille Calmette-Guérin. OR, Odds Ratio; CI, Confidence Interval. The reference groups consisted of people who had not received either vaccine and had not been afflicted with past severe respectively less severe infectious diseases, with a fever of > 38.5 °C.
[a] Adjusted for centre, gender, age, ethnic origin, skin type, freckling index, number of naevi and number of sunburns.

In the separate analysis of the individual centres, the less pronounced effect for the vaccinia vaccine was found to be due to the Italian centres where nearly all subjects had been vaccinated with vaccinia, so that no valid testing could be performed. After removal of the data from the Italian centres, the protective effects of vaccinia and BCG were equally strong and not additive: again compared with those subjects who had not received either of the two vaccinations and, as could be most clearly seen in the sub-group of persons aged <50 years, a significantly reduced risk of melanoma was observed for those who had received only the BCG vaccine with an OR = 0.13 (CI: 0.03–0.58), for those receiving only vaccinia (OR = 0.18, CI: 0.04–0.71), and for those receiving both vaccines (OR = 0.18, CI: 0.04–0.63).

Joint analysis of the effect of vaccinations and infectious diseases on the risk of melanoma showed that the effect of a single vaccination or episode of an infectious disease on this risk was, under some circumstances, dependent on the other vaccinations or infectious diseases studied, whereas under other circumstances it was not. Cumulative effects were only observed with weak influences, such as repeated episodes of less severe infectious diseases, childhood vaccinations with vaccinia and BCG in the age group of $\geqslant 50$ years, or, for all age groups, vaccination with vaccinia or BCG *and* one or more episode of less severe infectious diseases. However, quasi non-additive effects were observed in combinations of strong influences, such as a single episode of a severe infectious disease and another episode or another kind of severe infectious disease, childhood vaccinations with vaccinia and BCG in the age group of <50 years, for all age groups vaccination with vaccinia and BCG *and* one or more episodes of a severe or less severe infectious disease. Thus, for those who had $\geqslant 1$ severe infectious diseases and no vaccinations, the OR (0.37) was only slightly higher compared with cases who had had $\geqslant 1$ severe infectious disease episode and received one or both vaccinations (0.29 and 0.33, respectively) (Table 3).

Melanoma patients vaccinated with BCG and vaccinia were significantly younger compared with those who were not vaccinated (Table 2, $P < 0.0001$, t-test).

4. Discussion

We show here, in the framework of a large population-based case–control study, that challenge of the immune system by vaccinations with vaccinia or BCG and by certain microbial infections correlates significantly with a reduced risk of melanoma. Repeated influenza vaccinations were not found to protect against melanoma in contrast to episodes of influenza itself and some other less severe infectious diseases.

4.1. Joint analyses and differences among the study centres

Cumulative effects of vaccinations and infectious diseases were observed when immune stimulation was suboptimal. With maximal protection by either a vaccination or an infectious disease, an additional challenge by a vaccination or infection hardly afforded any further protection. The 'quasi' non-additive findings suggest that the two quite different vaccines as well as a range of very divergent infections induce a protection which has an upper limit (Table 3a and b).

The interdependencies of the influences of the vaccinations and infectious diseases were helpful in understanding the differences between the various study centres. The failure to demonstrate protection by vaccination with vaccinia in some regions may be due to the fact that, since such vaccination was once compulsory in some countries, there were hardly any unvaccinated persons in these study regions. Thus, in Italy, only 3 of 201 persons had not been vaccinated. For the whole study, the vaccination coverage was lower for the BCG vaccination compared with vaccinia. This seems to be the reason why the CIs of the ORs are more convincing for a protection from the BCG vaccine compared with vaccinia, although both show significance.

Since in Italy, almost all patients and controls had been vaccinated against smallpox, everyone was probably protected against melanoma by this vaccination. Under these circumstances, it was not possible to show a protective effect for the vaccinia or BCG vaccinations. Similarly, multiple episodes of less severe infections might, at least in some regions, induce protection. A high frequency of such non-identified infections would make it impossible to show the protective effect of vaccinia vaccinations in these regions. In the former East Germany, unidentified environmental factors and infections have also been suggested as the reason for the reduced incidence of atopy relative to the former West Germany, on the basis of specific social conditions and, accordingly, an increased number of infections [13].

The protective effect of the influenza vaccination, as observed only in the Italian population, may have been an artefact, but it may also have been due to vaccinations with the influenza vaccine (or due to the influence of infectious diseases) at a relatively old age, when the protective effects of the BCG and vaccinia vaccinations were already weak. Another possibility is that there are variations in the types of vaccines used in this country compared with the other countries, particularly in view of the fact that it is only within the last few decades that the molecular determinants of different strains of vaccines in current use have been identified [14]. Unfortunately, the strains of vaccinia supplied to the birth cohorts from 1915 to 1945 cannot be retrospectively characterised. Finally, the age of the vaccinees seems to be important (see below).

4.2. Evidence for an influence of vaccinations and infections on melanoma development

The long-standing protective effect of BCG vaccination against cancer, as described first by Rosenthal and colleagues [15], was confirmed with respect to melanoma in this study. Likewise, the vaccinia-induced protection appears to be long-lasting. At a first glance, our data are striking for BCG, less impressive for vaccinia, and comparably weak for infectious diseases. However, the 'quasi' non-cumulative optimal influences of the two vaccinations and of single and repeated episodes of certain severe and less severe infectious diseases favour another view: all three of the related influences induce protection against melanoma.

The possibility that the findings of this study have been influenced by confounding factors cannot be ruled out definitively. This problem has already been discussed at length in previous reports arising from this project [8,10], as well as questions related to the validity of the vaccination history by vaccination records from birth, and the validity of self-reported severe infections. Furthermore, the possibility of selection bias arising from the recruitment methods for cases and controls has also been previously addressed in detail in Ref. [10]. However, several factors would have opposing effects on the likelihood of developing infections and receiving vaccinations. Thus, for example, immune deficiency would be a reason not to vaccinate and would predispose to serious infectious diseases. However, contraindications to vaccination with vaccinia had apparently little effect on the vaccination programmes since in our study the vaccination coverage for vaccinia ranged from 47 to 99% in the different study centres. Thus, contraindications of vaccination are unlikely to explain why both vaccinations and certain infectious diseases are associated with protection against melanoma. The protective effect was as strong for an uncommon disease, such as pulmonary tuberculosis, as for frequent vaccinations. It therefore seems unnecessary to seek a third factor to explain our observations.

In our experience, there are substantial differences between vaccination policies of different regions resulting

from the different attitudes of public health authorities in these specific regions. Despite these differences, we found a consistent pattern of results with regard to the relationship between the melanoma risk and BCG vaccinations in the various centres. This supports the concept that the strong protective effect against melanoma in association with the vaccinations reflects a true causative relationship.

4.3. Anticancer defence by BCG—why did it take so long to be revealed by epidemiology?

We suggest four reasons why earlier epidemiological studies on BCG vaccination and cancer, reviewed by Grange and Stanford [16], gave results which seemed highly contradictory: BCG revaccination or vaccination of older children and adults is counter-productive, vaccination with vaccinia induces the same upper-limit effect as BCG, infectious diseases also induce the same upper-limit effect and, finally, differences in the BCG vaccine daughter strains may be of importance. The negative results, as well as those that appear contradictory, may also be attributed to the different study designs used.

Several studies have indicated that BCG vaccination of new-borns confers protection against cancer, whereas vaccination of older children or adults tends to be counterproductive [17]. With the exception of one study [18], protection against cancer was only demonstrated in studies involving neonatal BCG vaccination [16]. This holds also for our present study. In Italy and France, BCG was, in contrast to the other studied regions, given to older children and adults and was found not to protect against melanoma. The tuberculin skin test reverts to negative in many who have been vaccinated [19,20]. As a consequence, misclassifications were probably made in cohort studies in which subjects were classified as not protected or not vaccinated on the basis of negative skin tests [17,21]. Since vaccinia induces the same degree of protection against melanoma and probably some other cancers as BCG, coverage with vaccinia in the population would limit the protective effect of BCG vaccination. For example, in the study of Salonen [22], Finland was compared with other Scandinavian countries, where the BCG vaccination was given much less frequently, but the fact that, in contrast to Finland, smallpox vaccination had been compulsory in Denmark, Norway and Sweden [23], was not taken into account. The frequently given vaccinia also exerts a 'masking effect' for studies on the protective effects of infectious diseases on cancer. This explains difficulties in reproducibility and in showing the significance of the findings.

As early as 1863, Virchow, followed later on by Thomas and Burnet, put forward some hypotheses relating to the immune surveillance of cancer [24]. However, epidemiological studies have so far failed to demonstrate convincingly the effect described here. Because influences of different vaccinations, as well as infectious diseases, were only additive when they were weak, it was necessary to address all of these factors simultaneously in a single epidemiological study and to perform joint analyses. As a result of the conflicting reports and subsequent controversy in the 1970s, the general viewpoint was that BCG vaccination did not protect humans against cancer. This viewpoint now becomes untenable because the important influence of vaccinia had not previously been taken into account. Besides our data, there is only one previous study where vaccination with vaccinia had been studied and shown to be correlated with a reduced risk of rhabdomyosarcoma [25].

Diverse appropriate microbial stimuli induce a defence against melanoma. We suspect that it is most likely a part of innate immunity. No specific antigens need to be involved. Heat shock proteins [26] might herald cell damage, paving the way to malignancy. Moreover, the risk-reducing effect of the vaccinations on thicker melanomas was stronger compared with its effects on thinner ones [10]. Thus, the defence also seems to slow down tumour growth. We suspect that the defence induces a dormant tumour stage during which tumour cells are destroyed by apoptosis. A delayed onset of melanoma might be another aspect of the protection (Age-related effects (Table 2 and Ref. [6]) were not observed in line with the study design and may well be meaningless. They seem to be paradoxical.).

4.4. How may the epidemiology of malignant melanoma change beneficially or detrimentally under the influence of vaccinations and infectious diseases?

When vaccinia vaccination programmes were stopped in the 1970s and BCG vaccination around 1990 in many countries, two essential microbial stimuli correlating strongly with a reduced melanoma risk were removed. However, this is unlikely to explain the increased rate of melanoma. Since melanoma is a tumour of older age, termination of the vaccination programmes would only be expected to begin to exert an effect around 2010 and with the full effect only becoming apparent some decades later. Instead, in Europe, we would still be benefiting from the augmented vaccination coverage after World War II, compared with the previous decades. Today, most older Europeans probably have a reduced protection because the effects of the vaccinations given in childhood are waning with time.

Remaining factors which may contribute to protection of the not—or no longer—vaccinated European population are certain documented and non-documented infections [8]. These diseases are most likely responsible for the comparably weak residual protective effect seen in our study in the non-vaccinated persons.

Infectious diseases correlating strongly with melanoma protection were uncommon and, therefore, their impact was apparently low. The only frequent infectious diseases shown in the FEBIM study to correlate significantly with a reduced melanoma risk were influenza and infectious enteritis.

On the one hand, the protective effect of the vaccinations seems sufficiently strong to be useful in the prophylaxis of melanoma. On the other hand, there is ample literature showing that stimuli such as the BCG vaccination rarely, if ever, lead to a complete cure of an already established melanoma. Thus, there is a need to develop vaccines or immunotherapeutic agents that can induce the destruction of all latent and active cancer cells and several possible candidates have recently been reported [27–29]. Vaccinia and neonatal BCG vaccinations seem to have saved many people from developing melanoma in the past and, on this basis, their re-introduction might even be justifiable. Although their modes of action appear not to be specific, neither of the two vaccinations could, at present, be replaced by other available ones for this purpose. Future epidemiological studies should also provide answers regarding the relative importance of immunostimulation in antitumour defence in general. On this basis, recommendations for future vaccination programmes for neonates and, perhaps, even older age groups may, hopefully, soon be possible.

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