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Prior immunisation of patients with malignant melanoma with vaccinia or BCG is associated with better survival. An European Organization for Research and Treatment of Cancer cohort study on 542 patients

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Abstract

There is increasing evidence that infections and vaccinations play an important role in the normal maturation of the immune system. It was therefore of interest to determine whether these immune events also affect the prognosis of melanoma patients. A cohort study of 542 melanoma patients in six European countries and Israel was conducted. Patients were followed up for a mean of 5 years and overall survival was recorded. Biometric evaluations included Kaplan–Meier estimates of survival over time and Hazard Ratios (HRs), taking into account all known prognostic factors. During the follow-up between 1993 and 2002, 182 of the 542 patients (34%) died. Survival curves, related to Breslow's thickness as the most important prognostic marker, were in accordance with those observed in previous studies where the cause of death was known to be due to disseminated melanoma. In a separate analysis of patients, vaccinated with vaccinia or Bacille Calmette-Guérin (BCG), HRs and the corresponding 95% Confidence Intervals (CIs) were 0.52 (0.34–0.79) and 0.69 (0.49–0.98), respectively. Joint analyses yielded HRs (and 95% CIs) of 0.55 (0.34–0.89) for patients vaccinated with vaccinia, 0.75 (0.30–1.86) with BCG, and 0.41 (0.25–0.69) with both vaccines. In contrast, infectious diseases occurring before the excision of the tumour had little, or, at the most, a minor influence on the outcome of the melanoma patients. These data reveal, for the first time, that vaccination with vaccinia in early life significantly prolongs the survival of patients

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with a malignant tumour after initial surgical management. BCG vaccination seems to have a similar, although weaker, effect. The underlying immune mechanisms involved remain to be determined.

Keywords: Melanoma; Survival; Immunisation; Vaccinia; BCG

1. Introduction

There is increasing evidence that vaccinations and infections in early childhood, and possibly also in adult life, play an important role in the normal processes of maturation of and development of regulatory pathways in the immune system [1,2]. Infections and certain vaccinations in early childhood reduce the occurrence of immunoregulatory disorders over the ensuing decades, particularly those mediated by Th2-cells [3–5]. In this context, since the beginning of the 20th century, there have been a number of reports of an inverse association between the incidence of cancer and the frequency of infections [6]. Two recent detailed studies have revealed a significant relationship between protection against childhood leukaemia and the incidence of common infections acquired by exposure to other children in day-care facilities [7,8].

Two case-control studies on cutaneous melanoma, one of the most aggressive of all human tumours, have revealed that various infectious diseases and/or immunisation with vaccinia, Bacille Calmette-Guérin (BCG) or both in childhood strongly reduced the risk of developing melanoma [9–11]. It was also observed that this prophylactic effect has an upper limit so that not all those infected or vaccinated are protected [12]. This raises the question as to whether similar protective effects affect the prognosis of patients who have actually developed a melanoma.

The aim of this cohort study was to determine whether prior immunisation with vaccinia and/or BCG and various infectious diseases occurring before the surgical removal of the primary melanoma affect the long-term survival, in relation to those prognostic factors already known.

2. Description of the study

2.1. Patients and methods

The investigation was designed as an ambidirectional cohort study [13], using the framework of the Melanoma Cooperative Group of the European Organisation for Research and Treatment of Cancer (EORTC). The cohort was composed of the case arm of the FEBIM (febrile infection in melanoma) case-control study. For this study, cases were enrolled immediately after excision of the primary tumour and histopathological confirmation of diagnosis [10,11]. The period for inclusion in the cohort dated from March 1994 until August 1997. Data were collected both forwards and backwards in time. Patients were prospectively examined at regular intervals until death or end of follow-up (December 2002). As information on the development of metastases or other malignancies could not be obtained reliably, the primary end-point of the study was death, irrespective of the cause. Retrospective information on exposure to putative protective factors was obtained from the melanoma patients by use of a questionnaire and their clinical records (see below). Exposed and unexposed cases, all inside the same cohort, are here compared for the frequency of outcome. Initially, 603 patients from 11 centres in six European countries and Israel were recruited for the study, but 30 patients were classified as having melanoma *in situ* and were omitted from the follow-up. Thus, 573 patients were entered into the study, but as 31 (5%) were lost during the follow-up, the outcome of 542 patients was evaluated. Numbers of recruited patients, completeness of follow-up and deaths occurring at the centres are shown in Table 1.

2.2. Assessment of exposure

Data on Breslow's thickness and presence or absence of ulceration as well as the type and location of the primary tumour were obtained from clinical records. Patients were interviewed about their personal history of vaccinations and infectious diseases. Vaccinia vaccination against smallpox and BCG vaccination against tuberculosis during childhood were verified, where possible, by the interviewers by examination of the patients' vaccination cards. The relationship between vaccination status and other prognostic variables is given in Table 2.

Infectious diseases occurring before the diagnosis of melanoma were divided into two groups. Group I comprised severe diseases irrespective of elevated temperatures, including hepatitis (all types), pulmonary tuberculosis, erysipelas, abscesses, wound infections, furunculosis, urinary tract infection, sepsis, endocarditis, meningitis, osteomyelitis, rheumatic fever and cholecystitis. Group II comprised less severe infections occurring during the 5 years before the removal of the primary tumour. To avoid the inclusion of trivial illnesses, an elevated body temperature was an inclusion criterion in this group. Among those included were influenza, infectious enteritis (summer diarrhoea), acute

Table 1
Completeness of follow-up by centre

Centre	Total number of patients	Participants		Death of participants	
		Number	(%)	Number	(%)
Tallin	101	94	(93.1)	36	(38.3)
Vienna	43	43	(100)	13	(30.2)
Sofia	115	115	(100)	56	(48.7)
Tel Aviv	42	28	(66.7)	15	(53.6)
Dijon	52	50	(96.2)	14	(28.0)
Dresden	69	68	(98.6)	17	(25.0)
Göttingen, Berlin, Hamburg	68	62	(91.2)	16	(25.8)
Verona, Padua	83	82	(98.8)	15	(18.3)
Total	573	542	(94.6)	182	(33.6)

bronchitis and pneumonia and herpes simplex. Since changes in body temperature influence host defence, an attempt was made to assess the level of body temperature for any indicated disease using three categories in group I diseases (A: not elevated; B: elevated, but below 38.5 °C; C: elevated above 38.5 °C) and two categories in group II diseases (elevated, but below 38.5 °C and elevated above 38.5 °C). All interviews were conducted by trained personnel with medical backgrounds at the patients' homes and lasted approximately 30–40 min.

2.3. Statistical analysis

In a first step, established prognostic factors for patients with melanoma were analysed to check whether our data are consistent with current concepts of melanoma prognosis. Next, the immune events (infections and vaccinations) of primary interest were considered. Results of a crude analysis – ignoring the impact of confounding in this observational study – are presented as Kaplan–Meier estimates of the survival function over time. In a final step, proportional hazard models including known prognostic factors (restricted to time-independent factors) and the immune events of interest were analysed. The prognostic factors taken into account included centre, gender (female vs. male), age (in years), adjuvant therapy (yes vs. no), anatomical site (four categories: trunk, head/neck, arms/hands, legs/feet), type of primary tumour (five categories: superficial spreading melanoma (SSM), nodular melanoma (NM), lentigo maligna melanoma (LM), acral lentiginous melanoma (AL), other), Breslow's thickness (in mm) and ulceration (yes vs. no). Since different types of adjuvant therapies were administered, and since some patients received more than one type, the only information considered was whether or not adjuvant therapy had been given. Adjusted Hazard Ratios (HRs) with 95% Confidence Intervals (CIs) were calculated. The widths of

Table 2
Relationship between vaccination status and other prognostic variables

Variable		Vaccination status											
		No vaccination			BCG, no vaccinia			No BCG, vaccinia			BCG, vaccinia		
Gender	Male (*n*,%)	27		10.6	8		3.2	112		44.1	107		42.1
	Female (*n*,%)	28		9.7	8		2.8	112		38.9	140		48.6
Age (median, mean, std. dev.)		70.0	64.2	18.1	56.5	55.8	19.7	63.0	60.7	13.4	52.0	52.7	14.7
Breslow's thickness (median, mean, std. dev.)		1.4	2.4	2.5	1.1	1.5	1.3	1.2	2.2	2.5	1.6	2.5	2.5
Ulceration	Yes (*n*,%)	8		6.7	2		1.7	54		45.4	55		46.2
	No (*n*,%)	47		11.1	14		3.3	170		40.2	192		45.4
Type of tumour	SSM (*n*,%)	27		8.5	9		2.8	140		44.0	142		44.7
	NM (*n*,%)	14		10.6	2		1.5	47		35.6	69		52.3
	LM (*n*,%)	2		8.7	2		8.7	8		34.8	11		47.8
	AL (*n*,%)	3		10.7	1		3.6	15		53.6	9		32.1
	Other	9		22.0	2		4.9	14		34.2	16		39.0
Location of tumour	Head, neck (*n*,%)	8		9.8	5		6.1	30		36.6	39		47.6
	Trunk (*n*,%)	19		9.1	6		2.9	88		42.1	96		45.9
	Arms, hands (*n*,%)	8		11.3	2		2.8	35		49.3	26		36.6
	Legs, feet (*n*,%)	19		11.0	3		1.7	68		39.3	83		48.0

BCG: Bacille Calmette-Guérin; std. dev.: standard deviation; SSM:superficial spreading melanoma; NM:nodular melanoma; LM:lentigo maligna melanoma; AL: acral lentiginous melanoma.

the excision margins were not considered since they have been shown not to influence the overall survival of melanoma patients [14].

The vaccinations were analysed using a two-step-strategy [11]. First, the effects of the different vaccinations in two separate proportional hazard models, each of which comprised a dichotomous exposure variable for the specific vaccination under study, were analysed. Second, to address the combined effect of the two vaccinations, a joint proportional hazard model was utilised in which all combinations of both exposure variables as well as all of the confounders were incorporated. In this model, four categories of vaccination history were considered: neither vaccinated with vaccinia nor with BCG (reference category), vaccinated with vaccinia, but not with BCG, vaccinated with BCG, but not with vaccinia, and vaccinated with both vaccinia and BCG. This parametrisation of the vaccination status is equivalent to one that includes the main effects of BCG and vaccinia vaccination and an interaction effect of the two vaccinations. However, it does give adjusted HRs for the different subgroups of the study population instead of focusing on the breakdown of the observed effect into independent main effects and combined interaction effects of the two vaccinations.

For analysis of the effect of infections, the previously described strategy [10], in which the data on the infections were considered separately for the three body temperature categories in both disease groups, was used. Additionally, this strategy was used to determine whether there was a cumulative effect of several infections, i.e. separately for group I and group II, and the temperature categories.

For all calculations, the statistical software package SAS (SAS Version 8.2, SAS Institute Inc. Cary, NC, USA) was used.

3. Results

3.1. Characteristics of the patients

Table 3 gives the characteristics of the 542 statistically evaluated patients. The number of males and females were fairly evenly balanced and the median age at the time of diagnosis was 58 years (range 18–90 years). Breslow's thickness varied between 0.1 and 20.5 mm thickness (median 1.39 mm, mean 2.36 mm).

Between 1993 and 2002 (mean observation time 68 [median 73] months) 182 (34%) of the 542 patients died

Table 3
Characteristics of the patients

Variable		Number	(%)	Death	Sum of person-time (years)
Gender	Male	254	(46.9)	99	1373
	Female	288	(53.1)	83	1677
Age (years)	18–39	71	(13.1)	13	441
	40–49	107	(19.7)	22	646
	50–59	109	(20.1)	25	683
	60–69	112	(20.7)	39	616
	⩾70	143	(26.4)	83	664
Breslow's thickness[a] (mm)	<0.75	147	(29.4)	18	945
	0.75–1.5	116	(23.2)	32	674
	1.5–3	106	(21.2)	36	632
	3–4	35	(7.0)	16	181
	>4	96	(19.2)	67	391
Ulceration	Yes	119	(22.0)	71	545
	No	423	(78.0)	111	2505
Type of tumour	Superficial spreading	318	(58.7)	79	1883
	Nodular	132	(24.4)	65	691
	Lentigo maligna	23	(4.2)	6	140
	Acral lentiginous	28	(5.2)	15	132
	Others	41	(7.6)	17	205
Location of tumour[a]	Head, neck	82	(15.3)	38	409
	Trunk	209	(39.1)	73	1165
	Arms, hands	71	(13.3)	27	392
	Legs, feet	173	(32.3)	41	1054
Observation time (months)	Range	110.9			
	Mean	67.5			
	Median	73.1			

[a] Some data are missing.

Table 4
Separate and joint analyses of the influence of BCG and/or vaccinia on melanoma survival

	HR	(95% CI)		HR	(95% CI)
Separate analysis					
Smallpox (vaccinia)	0.52[a]	(0.34–0.79)	Tuberculosis (BCG)	0.69[a]	(0.49–0.98)
Yes (n = 471) vs. no (n = 71)			Yes (n = 263) vs. no (n = 279)		
Age (10 years)	1.42	(1.25–1.61)		1.43	(1.26–1.63)
Gender (female vs. male)	0.99	(0.72–1.37)		1.00	(0.72–1.39)
Breslow's thickness (mm)	1.17	(1.10–1.24)		1.17	(1.10–1.24)
Ulceration	1.75	(1.21–2.53)		1.55	(1.07–2.22)
Adjuvant Ther. (yes vs. no)	1.25	(0.87–1.80)		1.33	(0.92–1.92)
Type of tumour					
NM vs. SSM	1.36	(0.93–1.99)		1.44	(0.99–2.11)
LM vs. SSM	0.73	(0.30–1.79)		0.80	(0.33–1.96)
AL vs. SSM	2.67	(1.39–5.14)		2.72	(1.41–5.22)
Other vs. SSM	1.15	(0.56–2.36)		1.29	(0.63–2.65)
Location of tumour					
Head/neck vs. trunk	1.22	(0.77–1.91)		1.18	(0.75–1.86)
Arms/hands vs. trunk	1.21	(0.75–1.94)		1.12	(0.69–1.80)
Legs/feet vs. trunk	0.49	(0.31–0.77)		0.47	(0.30–0.74)
Joint analysis					
No vaccinia, no BCG (n = 55)	1.00[a]	Reference	No vaccinia, no BCG (n = 55)	1.00[a]	Reference
BCG, no vaccinia (n = 16)	0.75[a]	(0.30–1.86)	Vaccinia and/or BCG (n = 487)	0.50[a]	(0.32–0.78)
Vaccinia, no BCG (n = 224)	0.55[a]	(0.34–0.89)			
Vaccinia and BCG (n = 247)	0.41[a]	(0.25–0.69)			
Age (10 years)	1.39	(1.22–1.59)		1.41	(1.24–1.61)
Gender (female vs. male)	1.00	(0.72–1.38)		0.99	(0.72–1.37)
Breslow's thickness (mm)	1.17	(1.11–1.25)		1.17	(1.11–1.24)
Ulceration	1.71	(1.18–2.47)		1.71	(1.18–2.47)
Adjuvant Ther. (yes vs. no)	1.29	(0.89–1.87)		1.25	(0.87–1.81)
Type of tumour					
NM vs. SSM	1.41	(0.96–2.07)		1.35	(0.92–1.97)
LM vs. SSM	0.76	(0.31–1.86)		0.79	(0.33–1.93)
AL vs. SSM	2.71	(1.41–5.22)		2.73	(1.42–5.25)
Other vs. SSM	1.16	(0.56–2.37)		1.18	(0.58–2.43)
Location of tumour					
Head/neck vs. trunk	1.24	(0.79–1.95)		1.23	(0.78–1.93)
Arms/hands vs. trunk	1.16	(0.72–1.87)		1.21	(0.75–1.94)
Legs/feet vs. trunk	0.48	(0.30–0.76)		0.48	(0.31–0.76)

Confounding factors used for adjustment are also given.
BCG: Bacille Calmette-Guérin; HR: Hazard Ratio; CI: Confidence Interval; SSM: superficial spreading melanoma; NM: nodular melanoma; LM: lentigo maligna melanoma; AL: acral lentiginous melanoma.
[a] Adjusted.

(99 males, 83 females). The mean time between initial treatment and death was 40 [median 35] months.

The Kaplan–Meier estimates for survival in relation to Breslow's thickness of the primary tumour are in accordance with the recognised worse prognosis of patients with thick tumours and differ only minimally from those whose cause of death was disseminated melanoma disease. Moreover, patients with ulcerated tumours also had a worse prognosis (data not shown), probably because ulceration is linked to tumour thickness [15].

Besides prognostic markers of minor importance such as age, gender and site of the primary tumour, the item 'adjuvant therapy' was included in the proportional hazard model calculations. This term covers a plethora of therapeutic interventions ranging from immunotherapy with cytokines of various types and dosage schedules to complementary or alternative remedies. In some cases, a patient received more than one therapy. Accordingly, and as at the present time there is no adjuvant therapy with proven efficacy for malignant melanoma, it was decided to simply group patients into those who had received any adjuvant therapy and those who had not. Using this approach, survival was slightly reduced in those who had received adjuvant therapy (Table 4).

3.2. Effect of vaccinations

Two vaccinations were considered: vaccinia and BCG. Fig. 1 shows that survival of the melanoma patients vaccinated with vaccinia and/or BCG is far better than that of the unvaccinated patients. Since Kaplan–Meier estimates do not take into account potential confounding by other prognostic factors the interpretation

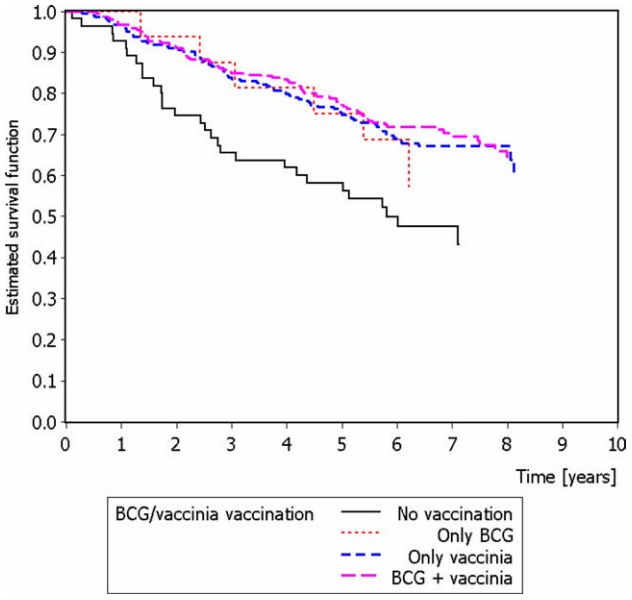

Fig. 1. Kaplan–Meier estimates for overall survival in relation to BCG and vaccinia vaccination.

of the curve is compromised. In particular, there is a different age distribution between the vaccinated and unvaccinated subgroups, with unvaccinated patients being roughly 10 years older [12].

Age and all other abovementioned confounders were incorporated in the proportional hazard calculations. The top part of Table 4 shows the adjusted HRs for both vaccinations based on separate analyses. In this case, patients receiving one vaccine may or may not have received the other vaccine. For patients vaccinated with vaccinia, the risk of death is approximately halved and, on the basis of the 95% CI, reaches significance; in patients who had received BCG, the risk of death was reduced by approximately one fourth, but this reduction reaches statistical significance in the separate analysis only. The lower part of Table 4 shows the joint analysis, with the reference group consisting of those patients who had received neither vaccinia nor BCG vaccine. This again reveals different effects on the HR: vaccinia reduces the risk of death by approximately one half, and BCG reduced it by one fourth, although the latter did not achieve significance, probably due to the small sample size. No remarkable cumulative effect was evident in those who had been given both vaccinations and the HR for those who had received vaccinia and/or BCG was 0.50 (95% CI = 0.32–0.78).

3.3. Effect of infections

The adjusted HRs and the corresponding 95% CIs for the individual infectious diseases were also analysed (data not shown). Only those infectious diseases that were observed in numbers sufficient for statistical analysis were taken into consideration. For this reason, diseases caused mainly by *Staphylococcus aureus* (osteomyelitis, mastitis, abscess, furuncle) were grouped together in one category. For severe infections (group I), data for categories 'irrespective of body temperature' (category A), 'an elevated temperature, but below 38.5 °C' (category B) and 'temperature above 38.5 °C' (category C) were analysed. A significantly reduced HR was not detected for any infectious disease in any of the categories. In the case of the less severe infections suffered by individuals during the 5 years preceding the removal of the primary tumour (group II), the HRs remained more or less unchanged for all types of infections and temperature categories.

Table 5
Cumulative effect of repeated infections of more severe (group I) infectious diseases irrespective of elevated temperature: adjusted HRs, 95% CIs

No. of infections	Category A (irrespective of elevated temperature)	
	Adjusted HR	(95% CI)
Group I		
0	1.00	Reference
1	0.66	(0.45–0.96)
2–3	0.63	(0.43–0.94)
⩾4	0.32	(0.13–0.82)
Trend test (*P*-value)	0.004	

Table 5 shows the results of the analysis of the cumulative effect of repeated infectious diseases on the HR. The number of infectious diseases experienced by each patient was computed separately for the different body temperature categories as well as for group I and group II diseases from their complete histories of infectious diseases (including certain rare diseases that are not listed in Section 2.1). A reduced risk was detected only for category A (irrespective of elevated body temperature) of group I diseases: for the other categories of both disease groups there was no influence on survival (data not shown). Thus, only relatively uncommon serious infectious diseases were associated, in a cumulative manner, with a reduced HR.

4. Discussion

To the best of our knowledge, this is the first report showing that certain vaccinations given in childhood with the aim of preventing specific infectious diseases can prolong the survival of patients developing cancer, in this case malignant melanoma, in adult life. In contrast, infectious diseases, apart from a somewhat dubious cumulative effect of certain ones defined as severe, occurring before the surgical removal of the primary tumour, did not appear to have an effect on prognosis.

Due to the heterogeneity of the participating centres, we restricted the primary end-point, or outcome event, to death regardless of the cause. The approach is used when reliable information on death, but not always on the exact cause of death, is available. This may, of course, lead to biased results, especially if there are differences in the age distribution between the study groups. Nevertheless, there was a close association between survival and Breslow's thickness of the tumour which is currently regarded as the most important prognostic marker in melanoma. Survival was also strongly associated with ulceration of the primary tumour. It therefore seems unlikely that the difference in HRs observed in the various vaccination groups are unduly biased by age or other factors. The recently described metallothionein overexpression as a prognostic factor [16] was unknown at the beginning of the study.

With respect to any single specific infection studied, a negligible influence on prognosis was found. The mild infectious diseases of childhood were not considered since previous studies have shown that they do not affect the risk of developing melanoma and other malignancies [6,9]. It therefore seems improbable that they would affect the prognosis of an established tumour. The influence of infectious diseases occurring after removal of the primary tumour was beyond the scope of this investigation, although there is historical evidence that severe infections have on occasions led to regression or even remission of various established tumours [17]. Although further studies on a possible cumulative effect of certain severe infectious diseases on the prognosis of melanoma are needed, the data provided by this study suggests that such events are rare. Their contribution to a protection against melanoma in the European population would in all probability be a very small one.

In contrast to the impact of infections, the improvement in prognosis in those patients previously vaccinated with vaccinia and/or with BCG was remarkable and calls for further studies in relation to melanoma and other cancers. The improvement in prognosis in patients vaccinated with vaccinia alone exceeds that conferred by BCG alone, whereas previous investigations showed that the two vaccines had an almost equal ability to prevent the development of melanoma [11]. This difference, and the varying impact of infectious disease on the risk of developing melanoma and on the prognosis of established tumours [9,10], leads to the tentative suggestion that the immunological mechanisms behind the two related phenomena are not completely identical. It is possible that prevention of melanoma requires a form of immune surveillance which suppresses tumour-promoting factors or causes either apoptosis or repair of a single cell that is in the process of malignant transformation. By contrast, prognosis of an established tumour might be more dependent on massive tissue necrosis mediated, perhaps, by tumour necrosis factor, lymphocyte-mediated cytotoxicity, or by effects on the microvasculature of the tumour. However, it is noteworthy that, although the vaccinations do not afford protection against melanoma in all cases, they nevertheless beneficially affect the prognosis in many who do develop the disease.

Most patients presenting with melanoma today would have received compulsory vaccinia vaccinations, which ended in 1979 following the global eradication of smallpox. Accordingly, the immune systems of most inhabitants of the Western hemisphere born before this date have been affected by vaccination against smallpox. By contrast, coverage of the population with BCG vaccination has always been sporadic due to the different vaccination policies of the various European countries. In Germany, the BCG programme ended in 1970 (West) and 1989 (East). The full impact of the cessation of both vaccinations on the incidence and prognosis of malignant melanoma will not be seen until the year 2010 or later. The results of this study, especially if similar beneficial effects are demonstrable with other cancers, should lead to a serious re-evaluation of vaccination strategies. A reintroduction of mass vaccinia vaccination is unlikely owing to its occasional severe adverse effects, whereas BCG might be reconsidered on account of the global rise in the incidence of tuberculosis, including multidrug-resistant forms. Alternatively, a determination of the underlying immunological mechanisms could lead to the development of a 'designer vaccine', possibly a subunit vaccine with few or no harmful side-effects, specifically against melanoma and eventually, hopefully, other cancers.

Conflict of interest statement

None declared.

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