

Cancer patients report a history of fewer fevers during infections than healthy controls

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Abstract: Fever is one of the pathophysiological symptoms accompanying the response of the host to infection and inflammation. Although the adaptive value of the fever response has been well documented in laboratory studies, its role in clinical medicine is still under debate. Two of the hypotheses studied state that endogenous mediators of fever may be involved in establishing the Th1 immunologic phenotype of the host and in improving general immunologic surveillance. It is known that these factors play a significant role in defence against tumour cells. Therefore, in the present study we tested the hypothesis that patients diagnosed with cancer reveal a history of fewer fevers during the disease than control, healthy volunteers. 18 questions were asked concerning the history of fever prior to diagnosis from 355 persons suffering from cancer, and 244 healthy controls, matched for age and living in Poland. Cancer patients reported a lower incidence of fever during illness than controls. The percentage of cancer patients and controls who reported no fever during infections was 83.10% and 56.97%, respectively. Similarly, 16.90% of cancer patients and 43.03% of controls reported always experiencing fever during infections. The results of our study support the hypothesis that during their lifetime cancer patients experience less fever during infection than healthy controls.

Key words: fever, infection, cancer, allergy, spontaneous regression

INTRODUCTION

Fever is a specific and well-coordinated pathophysiological phenomenon associated with infections and trauma, and manifested by an increase of body core temperature above normal. It is a part of an acute phase response (APR) – an early inflammatory response consisting of a host of immunologic, endocrinologic and neurologic alterations. APR results in metabolic and behavioural changes collectively called ‘sickness behaviour’ [1, 2]. Thus, fever has a significant diagnostic value which, however, is mostly regarded as an unpleasant and preventable weakening phase of disorder. In spite of the overwhelming antipyretic therapy and widespread use of the fever-preventing drugs, there is ample evidence demonstrating that fever correlates with increased survival and better prognosis during microbial infections [3, 4, 5].

Studies into the mechanism and phylogeny of fever indicate that fever evolved as a constituent of the innate immune response [4, 6]. Thus, from the biological point of view, fever is an adaptive response in interactions between the host and the pathogenic microorganisms. The key steps of the mechanism of fever have been thoroughly investigated during the last decades. Briefly, fever is triggered by microbial factors and products known as ‘exogenous pyrogens’ or ‘pathogen associated molecular patterns’ (PAMPs). Structures such as lipopolysaccharides (LPS), peptidoglycans, porin complexes, lipoteichoic acid, lipoarabinomannans, bacterial DNA,

mycoplasma lipoproteins, staphylococcal and streptococcal proteinaceous superantigens constitute a major group of the pyrogens of gram-negative, gram-positive and mycobacterial origin [7-12]. In response to the PAMPs, the immune cells of an infected organism generate a host of mediators called ‘endogenous pyrogens’. Among them are cytokines such as IL-1, IL-6 and TNF- α [14]. Endogenous pyrogens stimulate the production of prostaglandins of the E series (PGE₂) which, in turn, act on the fever-mediating thermoregulatory region of the preoptic area of the anterior hypothalamus to shift upward a thermoregulatory set-point. The presented scheme of molecular events leads to the stimulation of thermoregulatory effectors to gain body heat and to drive body core temperature. Although the net benefit of elevated temperature is still under debate, it has been demonstrated that fever stimulates number of key mechanisms of the defence against infections; among others, it stimulates T cells proliferation and differentiation, B cells proliferation and the production of antibodies, secretion of interferons, phagocytosis, and the migration of macrophages and neutrophils [15, 16, 5].

Despite the well documented ubiquity of fever, there are clinical reports suggesting a decreased frequency of fever, or even the lack of capability of generating fever within certain groups of patients. Fewer fevers have long been recognized, especially amongst cancer patients. As early as 1855, the English surgeon John Laurence acknowledged the fact that cancer patients have a “remarkable disease-free history” [17]. Since then, clinical oncologists have often reported that in their history cancer patients stressed that they were almost never ill, and had never been feverish before the onset of cancer. Consequently, it has been postulated that a prolonged lack of fever can be considered as a threat of cancer [18]. Also,

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the more recent studies of Witzel (1970), Newhouse et al. (1977), Remy et al. (1983), Grufferman et al. (1982), Ronne (1985), Van Stensel-Moll et al. (1986), Grossarth-Maticek et al. (1987), Abel et al. (1991), and Kolmel et al. (1992) [19-27], among others, have supported the conclusion that deficiency of fever in the medical history of the patient corresponds with high risk of cancer. In the present paper we also report a lower frequency of fever in the population of tumour patients compared to healthy volunteers.

MATERIALS AND METHODS

The study was conducted during a relatively short period, from January 2005 – June 2006. Retrospective information on fever and fever disorders was obtained from 355 cancer patients and 244 healthy volunteers by use of a questionnaire. To collect the information we cooperated with the following health care institutions: The Polish Amazons Club, The House of Social Assistance in Toruń, and the Academy for Fighting with Cancer and Public Hospital in Inowrocław. Each patient had a documented tissue diagnosis of cancer from pathology records. The majority of the examined patients were from the Kujawsko-Pomorskie province, and the healthy control volunteers were randomly selected from the same area. The respondent cohort consisted of 350 women and 249 men. The average age was 52 (ranging from 16-96 years old) and 57 (ranging from 17-95 years old) for women and men, respectively. All participants signed the consent for taking part in the questionnaire studies. Only completely filled in questionnaire forms were analyzed. The collected forms were entered into the Access Database for evaluation and statistical analyses. The chi-square test was used to compare rates of occurrence between patients with cancer and healthy people.

RESULTS AND DISCUSSION

Nowadays, it is well documented that fever directly activates defence against various dangers (including cancer cells) [28, 29]. It is also well known that various microbial stimuli are necessary for the normal maturation of the immune system [30]. This discovery places in an unfavourable light the situation of cancer patients, who very often stress that before diagnosis they could be considerate as examples of health. They had never been ill, and even if they had, they almost never been feverish. Moreover, the observation that cancer patients who experienced a feverish period after surgery survived significantly longer than patients without fever, and the fact that spontaneous tumour remission was observed mostly after a fever, confirms the significant meaning of this mechanism for a patient's recovery [31]. For this reason we performed an epidemiological study. Our aim was to discover whether there is a difference in the frequency of fever episodes between healthy people and cancer patients, and to check peoples' attitude to fever. We compared 355 forms filled out by cancer patients, with another 244 forms from healthy people (Table 1).

It was observed that the frequency of feverish events during a whole life significantly differed between the 2 groups: 83.1% of cancer patients, compared to 56.97% of control group, declared that they never or almost never have been feverish (Table 1,

Table 1 Epidemiological studies examining the association between febrile tendencies and subsequent development of cancer.

Question	Cancer patients	Healthy volunteers	P
Lack of fever	83.1%	56.97%	p<0.001
Average, highest temperature during whole life	39.5 C ± 0.8	39.2 C ± 0.9.	
Fever during last year	30.14%	47%	p<0.001
Rate of allergy disease	5.92%	22.14%	p<0.0001
Percentage of people who feel uncomfortable after rise of body temperature to 37.5°C	31.55%	38.94%	p=0.1
Temperature regarded as fever	37.82 °C ± 0,4	37.83 °C ± 0.5	
Responders who need to use medicines against fever after rise of body temperature	87.80%	91.40%	p=0.2
People using NSAIDs before Tb rises to 38°C	74.6%	67.96%	p=0.02
People always using NSAIDs after a small rise of body temperature	51.42%	60.89%	p=0.03

Fig. 1). Among the cancer patients only 16.9% did recall of getting fever in compare to 43.03% of control people. This data are in accordance with Engel's results, who compared 300 cancer patients with 300 patients not suffering from cancer. People who had never experienced febrile infectious disease were 46 times more likely to have developed cancer than those who had had febrile infections [32]. More recent studies also confirm these earlier results. In 1987, Grossarth-Maticek et al., after questioning 1,353 people, indicated that: "episodes of high fever during the entire life span in the case of an acute illness as a typical reaction are inversely related to later cancer incidence" [25]. In 1991, Abel et al., in a case-control study with 255 cancer patients compared with 230 controls, showed that patients who had the highest risk for cancer were those with a low "infectious index" [33]. Kolmel demonstrated the essential meaning of the number of febrile illnesses, their length and level concerning the risk of melanoma incidence. The undergoing of a minimum of 3 fevers above 38.5°C decreased the risk of melanoma incidence by approximately 40% [34].

The surprising result of our research was that above 56% of healthy volunteers have never been feverish (Fig. 1). During 17 months of our research we found a few cases from the control group who were subsequently diagnosed as cancer patients. It is possible that such cases were or will be more frequent. This could be the cause of erasing the difference between two groups of our responders.

We observed that there were no significant differences between cancer patients and healthy control volunteers in the highest temperature value they recalled having during their lives. The average, highest temperature during whole life for the control group was 39.5 C ± 0.8, and for cancer patients 39.2 C ± 0.9. We conclude that this part of cancer patients who had been feverish (16.9% of cancer patients) can develop the same level of fever as healthy people. This suggests that carcinogenesis of some cancers may be indirectly connected with inefficient generation of fever.

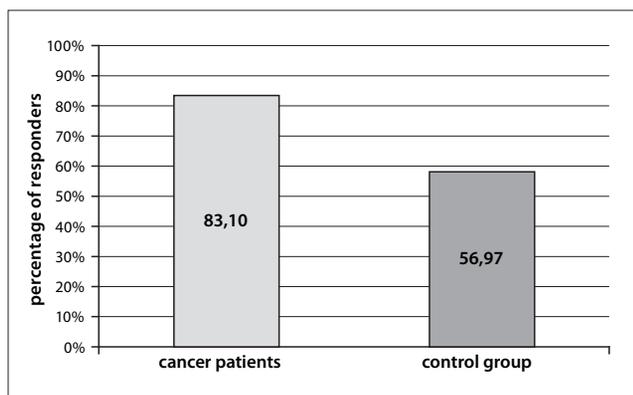


Figure 1 Infections associated with lack of fever.

We also found that during the past year (therefore after cancer diagnosis), 30.14% of cancer patients were ill and had fever, compared to 47% of control) (Table 1, Fig.2). Fever of cancer patients was mainly a result of the immunosuppressive property of chemotherapy and radiotherapy.

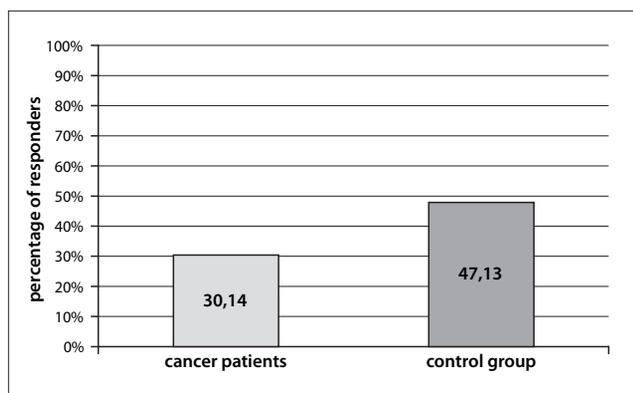


Figure 2 Fever during the last year.

There exist epidemiological studies supporting the hypothesis that there is an association between febrile infectious childhood diseases and subsequent cancer risk. Kolmel *et al.* demonstrated an inverse relation between the number of children's febrile infections and the incidence of malignant melanoma in 271 controls versus 139 melanoma patients [27]. Exposures to such infections were also associated with a reduced risk for ovarian cancer [35, 20] and multiple cancers combined [33, 36]. We investigated whether the assertion that children's contagious illnesses have a preventive effect on cancer is true or not. After our respondent cohort examination, significant differences were observed in the incidences of children's contagious illnesses such as: mumps, rubella and chicken pox (Tab. 2, Fig.3).

The study by Hoffman *et al.* suggests that chickenpox and mumps were associated with an increased risk of cancer [37]. We demonstrate that healthy volunteers suffered from such disease more often than cancer patients. Our results are in accordance with Newhouse data who found lower incidence of mumps, measles and rubella in the cancer group [20]. Hoffman *et al.* suggested that no significant reduced risk is seen between cancer and rubella [37], whereas our data and data by Newhouse showed a lower frequency of rubella for cancer patients, compared to healthy people. Only data concerning measles are in accordance – we did not observe any

Table 2 Morbidity in children's contagious illnesses.

Illness	Cancer patients	Healthy volunteers	P
*mumps	34.66%	51.55%	p<0.001
Scarlatina	9%	9.78%	p<0.1
*rubella	18%	35.10%	p<0.001
*chicken pox	51.70%	65%	p=0.001
Measles	44.60%	37.77%	p=0.12

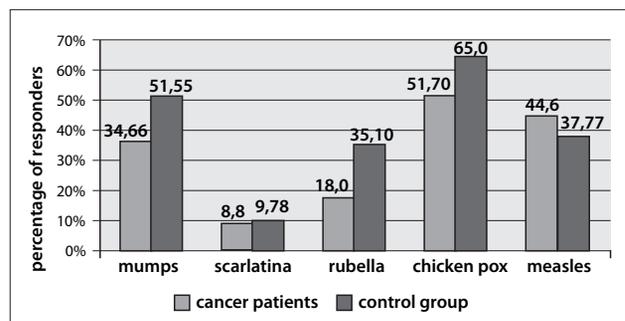


Figure 3 Morbidity in children's contagious illnesses.

statistically significant difference in the mortality between cancer patients and healthy people. We conclude that because of divergent results, no final statement on the association between childhood disease and cancer may be made. However, taking into consideration our results and published data we must stress that febrile contagious illnesses during early life are probably not sufficient to protect against cancer because many of our cancer patients had suffered from such diseases. We can therefore suppose that not only infection is important for the stimulation of the immune system against cancer. We would like to emphasize that infection connected with fever, which occurs directly before or at the beginning of cell transformation, is probably of the greatest significance. Our stance is in accordance with results of Kolmel *et al.* who also stressed that febrile infectious childhood diseases were less protective against cancer than adult febrile infections [27].

It is known that endogenous mediators of fever play a significant role in defence against tumour cells [38, 39]. We hypothesize that these factors may be involved in establishing the Th1 immunologic phenotype of the host. We suppose that cancer patients who had never been feverish, prefer Th2 phenotype. Similarly, allergy is an immunological disorder with a predominant Th2 inflammatory response [40]. The debate about the relationship between allergy and cancer is not recent [41]. The "hygiene hypothesis" proposes that lack of early life infections may up-regulate allergic disorders [42]. We found an appreciable difference in the incidence of allergy between cancer patients and healthy volunteers (Table 1, Fig. 4). If a decrease in the number of infections is essential for allergic disorders and for cancer, it is surprising that only 5.92% of cancer patients, compared to 22.13% of the control group, suffered from allergy. Moreover we have data which suggest that cancer and allergy exclude one another (data not published). The question whether allergy really is a protective factor for cancer, remains unanswered. However, efficient redirecting the Th2 response in favour of Th1 will probably be most essential for both disorders.

The second part of our questionnaire form contained questions to check people's general attitude to fever (Table 1). We discovered that people regard the 2 notions – fever and

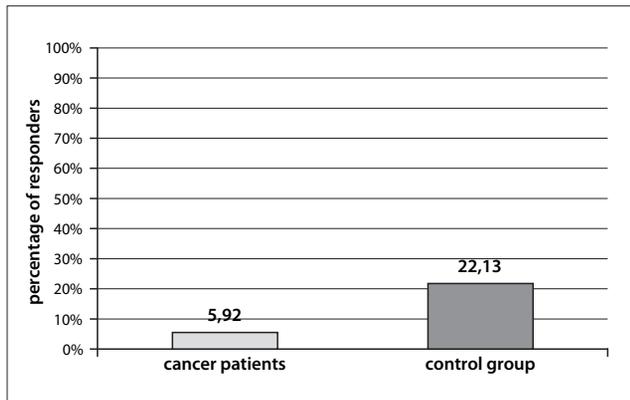


Figure 4 Rate of allergy disease.

illness – as being identical. A small rise of temperature from 36.6°C to 37.5°C by both groups was treated as an uncomfortable symptom (Table 1, Fig. 5). The temperature regarded as fever by cancer patients was 37.82°C ± 0.4; by control 37.83°C ± 0.5. People tried to eliminate this disparate state, in spite of the fact that it is a symptom which informs the body of the danger related to infections. As mentioned earlier, on the one hand fever may directly debilitate the pathogen, on the other hand it induces a cascade of host defence mechanism that increases the action of the immune system [15, 16].

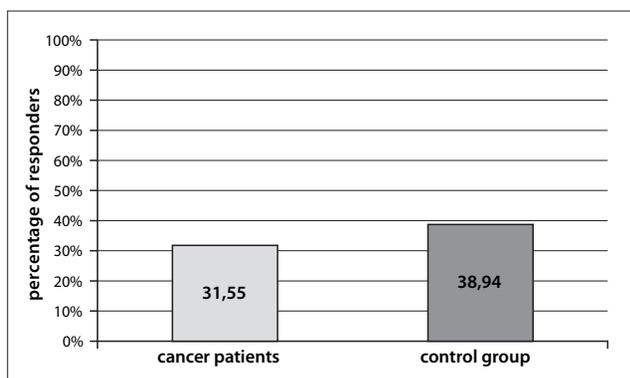


Figure 5 Percentage of people who feel uncomfortable after rise in body temperature to 37.5°C.

The rise in body temperature is closely related to the ability to increase cyclooxygenase (Cox) products of arachidonic acid (especially prostaglandin PGE₂). There are actually 2 Cox enzymes – Cox-1 and Cox-2 – both of which produce prostaglandins that promote inflammation, pain, and fever. Nonsteroidal anti-inflammatory drugs (NSAIDs) block the Cox enzymes and reduce prostaglandins throughout the body. In consequence, ongoing inflammation, pain, and fever are reduced [43]. Because of easy access, nonsteroidal anti-inflammatory drugs are very popular. Nowadays almost everybody can reduce or block fever. The necessity for using medicines against fever because of the rise in body temperature was declared by 91.4% of people in the control group, and 87.8% of the cancer patients (Fig. 6). We found that 67.96% of the control group and 74.6% of cancer patients take these medications before their temperature reaches 38°C (Table 1). Moreover, 60.89% of the control group and 51.42% of cancer patients take medicines against fever always, or almost always, even after a small rise in body temperature (Fig. 7). For this reason we can suppose that episodes of really high and long-

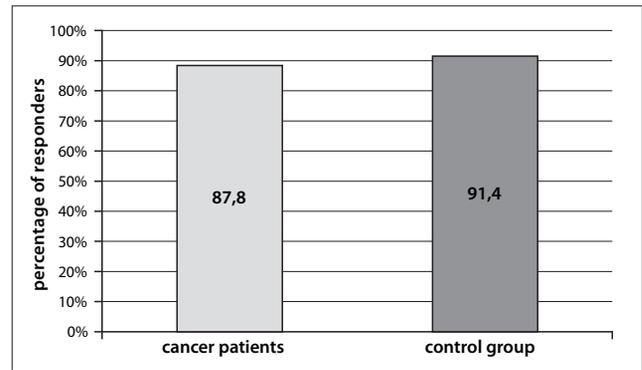


Figure 6 Respondents who need NSAIDs after rise in body temperature.

lasting fever actually do not happen. There are a number of prospective and retrospective studies indicating that febrile infections lower the risk of cancer, and can be associated with the spontaneous remission of various tumours [44, 28]. Early use of NSAIDs may deprive us of this chance. In 1998, Mastrangelo *et al.* revealed that a reduction of infections in the second half of 20th century caused an increase in cancer cases. They discovered that a 2% decrease of febrile illnesses in one year correlated with a 2% increase in tumors after 10 years [45]. This reduction of infections is undoubtedly connected with so-called “increase in life hygiene” and with the use of NSAIDs and antibiotics. Taking into consideration the influence of fever on the immune system, we consider that the use of NSAIDs should be more prudent.

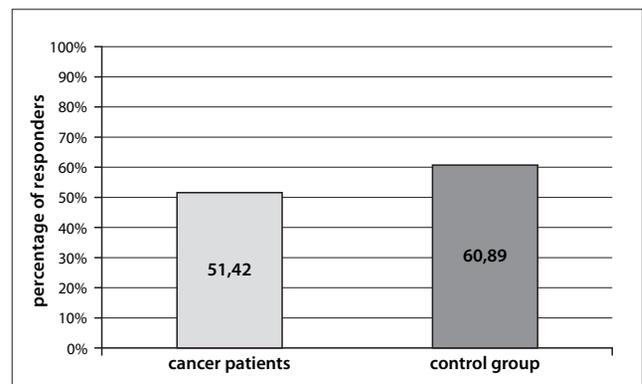


Figure 7 People always using NSAIDs after rise in body temperature.

Fever is a very important mechanism that supports our immunological system. Some disorders (cancer, allergy) seem to be preceded by a lack of fever. Our study confirmed this notion, despite the fact that it was performed during a relative short period (17 months). Whether this lack of fever starts before carcinogenesis or is a consequence of a long-term process which leads to cell transformation, remains unresolved. Moreover, we found that more than 72% of all respondents had never been feverish. It is an open question whether or not the rare fever episodes evolved naturally, or are the results of frequent switching off of this mechanism using NSAIDs which, as we established, people often take unquestioningly. It is possible that with the passing of time the immune system ceases developing fever at all and we would be totally dependent on medicine.

The increase of life hygiene and using NSAIDs is also connected with the high incidence of allergy. In our study,

we discovered that only small part of cancer patients who had never been ill and had never been feverish, suffer from allergy, even though some data suggest that infections are very essential for protection against cancer, as well as allergy. This problem should be meticulously examined. It is possible that artificial induction of fever will be helpful in therapies against both disorders, and research on this subject has already been started [46, 47]. However, nowadays we do not have an answer to the question: which part of the mechanism of fever is involved in decreasing risk of cancer and allergy, and which part participates in the induction of tumour prevention and remission.

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