The Moscow smokebuster

Peter McIntyre

There are smokers in Russia alive today thanks to **David Zaridze** and the lead he took in halving tar levels 20 years ago. He has a long history in cancer prevention, but believes the biggest gains may lie in early detection. Will the country that discovered the first liver cancer marker give the world the first proteomic marker for lung cancer?

Lung cancer deaths have been in decline in Russia since the mid 1990s, which is perhaps surprising given that 35 million Russians smoke and show few signs of giving up the habit (70% of young men and 25–30% of young women are current smokers).

Mortality from all cancers in Russia is still higher than in the US and other Western countries. Lung cancer deaths in Russian men are a third higher than in Western Europe.

Yet after rising steadily between 1965 and the early 1990s, the age-standardised death rates from lung cancer levelled out and then began to fall. David Zaridze, Deputy Director of the N N Blokhin Cancer Research Centre in Moscow and Director of the Institute of Carcinogenesis, traces the turning point to the first meeting on smoking prevention in what was then the Soviet Union, in 1985.

Zaridze organised the meeting in conjunction with the International Agency for Research on Cancer (IARC) and the renowned Oxford University epidemiologists Richard Doll and Richard Peto. The meeting was attended by influential Russian doctors and senior officials from the Ministry of Public Health and other agencies.

Behind the scenes, there was a dispute. Zaridze and Peto both saw the high levels of tar in Russian cigarettes as being the priority. Lorenzo Tomatis, then director of IARC, believed that this should be secondary to a "stop smoking" message.

The Moscow–Oxford alliance held. The conference adopted a resolution which said: "although elimination of tobacco consumption should be the final goal, an upper limit such as, perhaps, 15 mg, on cigarette tar deliveries should be introduced as quickly as possible."

Zaridze believes that was right. "At that time Soviet cigarettes had tar levels of 30 plus, so this was a proposal to reduce the tar levels by half. We have seen since the middle of the 1990s a reduction in the incidence and mortality of lung cancer. The only explanation of this decline is that measure we took in the middle of the 1980s, because smoking levels in Russia have not changed."

The Soviet Union introduced tobacco regulations within three years of the meeting. Since the state had a monopoly on cigarette production,

putting it into effect was easy. The reduction in lung cancer mortality will continue for many years because of the effect on lifetime smokers. More recently, the International Cigarette Variation Group compared packets of Camel, Lucky Strike, and Marlboro cigarettes purchased in 29 countries. The cigarettes were analysed in Moscow where they found similar amounts of tar and nicotine, but great variations in the amounts of two nitrosamines, NNK and NNN, carcinogens which are probably responsible for the increase in adenocarcinoma of the lung.

Zaridze has written to the chief physician at the Ministry of Public Health to call for regulations to reduce the level of these carcinogens in cigarettes on the market. But he recognises that in the market economy of modern Russia, this time there will be a fight with the tobacco companies.

"The high content of nitrosamines in these tobaccos has different causes, but the tobacco companies don't care and they don't want to invest."

Some campaigners fear that if cigarettes become "safer" that will dilute the "stop smoking" message. Zaridze does not see these policies as mutually exclusive. "The main slogan of anti-smoking campaigners, myself included, is that there are no safe cigarettes. Safe cigarettes don't exist and never will be produced. But if we can make cigarettes less carcinogenic, less harmful, less noxious, we have to do this."

Zaridze does not seem perturbed at the prospect of having to take on the tobacco companies while keeping anti-tobacco campaigners united. In the course of his career, he has promoted public health within a variety of political systems and social policies, while keeping strong international contacts. He has learned to respect the data, rather than the current orthodoxy.

In 1969, Zaridze was accepted as a postgraduate fellow in pathology at what was then the Institute of Experimental and Clinical Oncology, headed by Nicolai Krayevsky. As chief pathologist of the Soviet Army during World War 2, Krayevsky had been responsible for identifying the remains of Hitler and Eva Braun in Berlin. Zaridze says he was "a very nice man and a first class pathologist".

And this was what Zaridze himself wanted to be. Over the next decade, he carried out hundreds of autopsies and biopsies on all kinds of tumours, with a special interest in thyroid cancers and morphological peculiarities. This hands-on approach, examining tumours

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Lighting up. Zaridze and his assistant Olga Gorbacheva at the tobacco smoke analysis kit in the Institute of Carcinogenesis in Moscow. This machine can 'smoke' 20 cigarettes at once – and it doesn't like what it finds in any of them

physically, gave Zaridze a grounding. "Knowledge of the body is essential and I had ten years of very valuable experience. I do not want to insult modern pathologists, but in recent years there are fewer and fewer autopsies. And some molecular biologists for example have no idea what happens above molecular level."

Nikolai Blokhin, a former wartime surgeon and a leading traumatologist, became the first Director of the Cancer Research Centre in Moscow. "He was really a brilliant personality. The cancer institute was just a hospital before he took over and the research part was really his child, based on his interests. He was interested in basic science, and understood and took part in discussions and arguments in this field. He was fascinated by basic research into cancer and by epidemiology which was a very new, young discipline for chronic disease."

When Blokhin met Richard Doll – the pioneer on work relating smoking to lung cancer – something clicked. He was determined that his centre would base research and treatment on the best epidemiological evidence. He looked for someone to train in this new art. Of his team, Zaridze had the best English.

Zaridze went to Oxford in 1977 on a fellowship from IARC. "I joined the department where Richard Doll was Regis Professor. This was a brilliant team. Doll himself, Richard Peto (today Professor of Medical Statistics & Epidemiology at Oxford University), and his brother Julian Peto (now Cancer Research UK Chair of Epidemiology) and many other brilliant people."

He was only in Oxford for 10 months but his collaboration and friendship with Doll and Richard Peto has been lifelong. After a crash-course in epidemiology and statistics at the London School of Hygiene and Tropical Medicine, Zaridze was appointed to work at IARC in Lyon.

For six years, he headed the group on diet and cancer. He also worked on colorectal and prostate cancer. In the early 1980s Zaridze and Peter Boyle (now Director of IARC) published the first paper that explained the rise in incidence of prostate cancer in the US.

"Today, what we said is commonplace. PSA screening was discovering a lot of indolent carcinomas which, thank god, the urologists have now understood should be followed, not treated. Urologists in the United States pushed this test into the screening programmes without testing it as an instrument for screening. It was misused."

In 1985, Blokhin invited Zaridze back to Moscow to head the unit of epidemiology, a small group who did not then even have a computer.

One of his early efforts was on diet and cancer. It was becoming obvious that diets rich in green vegetables are protective against cancer. Zaridze had been instrumental in setting up an intervention trial in Uzbekistan, where a study group was encouraged to take vitamin supplements in the form of pills – beta-carotene for vitamin A, riboflavin (vitamin B2) and vitamin E. However, the results were disappointing, as were trials in other parts of the world. Vitamin supplements appear to offer no protection.

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effects of beta-carotene, vitamins B, C & E and ascorbic acid, but we do not know their complex interactions. Twenty years ago, we were sure about the story of diet and cancer; we knew more then than we know now! Today, we know the beneficial role of a diet low in calories and high in fruit and vegetables, but it is a complex interaction."

By the time Zaridze returned to Russia, Gorbachev was President and social and political life was beginning to loosen up. However, a party apparatchik from the central committee was still in charge of the Institute of Carcinogenesis.

Zaridze says: "People started to say what they thought and they were fed up with this guy. Finally, he was sacked. Then the staff met and everybody voted – not a scientific council but all 350 people who worked here. I was probably the first and the last director of a research institute who was elected by popular vote."

Zaridze was a member of the executive board of the Organization of European Cancer Institutes, and he helped its chairman, Walter Bodmer, to plan a meeting in Moscow on Cancer Prevention in Central and Eastern Europe. The date was set for 2 September, 1991. On 19 August, a group calling itself the State Emergency Committee launched a coup, holding Gorbachev in the Crimea and surrounding the Parliament with tanks.

Zaridze recalls how nervous they all felt that the old guard would return. His staff took their photocopiers and paper to the Parliament, so that the anti-coup forces could print out their own leaflets and orders. After a week, the coup collapsed and Gorbachev was back, although now Yeltsin was effectively in power.

Despite the crisis, Zaridze decided to go ahead with the meeting, warning those coming that they had better bring their own paper. "We had a beautiful meeting here – a historic meeting. Everybody arrived with a pack of paper. The day was devoted to visiting the barricades in Moscow, and we worked at night-time. I have a lot of memories of this meeting because people who were coming from the West were delighted to visit barricades in central Moscow."

The economic crisis in the former Soviet Union coincided with a fall in life expectancy. From 1991 to 1995, premature mortality rose steadily. In 1998 a further economic crisis saw the death rate climb again.

Zaridze and his colleagues worked on a hypothesis that the high background mortality rate in Russia was mainly to do with smoking, while fluctuations in the 1990s were mainly to do with high levels of alcohol consumption.

At the close of the decade the Institute of Carcinogenesis in cooperation with Oxford University and IARC set up a huge two-part study in three Russian cities – Tomsk, Barnaul and Novgorod – a retrospective mortality study and a longitudinal study, following the lifestyle and health status of 200,000 healthy people.

Results from the mortality study are not yet published, but will show a much greater than expected role of alcohol. In Barnaul, researchers examined records of 25,000 forensic autopsies carried out on those who died outside hospital or the home. They found that an incredibly high proportion of men had high levels of alcohol in their blood.

"About 20% of those people who had a post-mortem diagnosis of cardiovascular disease in fact died from alcohol poisoning. Russia in general is a very heavy drinking country and all negative situations are washed down by vodka. There is also a lot of spirit that people make themselves. With the fake product on the market, even lower levels of alcohol may be lethal."

Alcohol and smoking together multiply the risk of cancers of the pharynx, larynx, oesophagus and stomach. Surveys show an interrelation between habits that can damage the health of young people. A teenager who smokes has a

The famous 1991 meeting in Moscow that took place amidst the barricades. Amongst the audience are (*foreground from left*), Maurice Tubiana from Paris, Richard Peto from Oxford, IARC editor Elizabeth Heseltine and Rodolfo Saracci, director of epidemiology in Pisa

greater chance of drinking alcohol, taking drugs and becoming involved in crime.

Zaridze believes there should be stronger public policy to alert the public to the dangers of hard drinking and illegal spirits, but policy is currently poorly related to evidence. In April 2006, Russia banned imports of wine from two neighbouring republics, Georgia and Moldavia, with whom it is having political disputes, on "health grounds". No action was taken against home-brewed vodka.

The Institute of Carcinogenesis is responsible for basic research as well as population-based studies. Its current focus is on the need for early detection of lung cancer.

Zaridze points out that even countries with screening programmes really only succeed in preventing cervical cancer, while mammography prevents only 25% – 30% of deaths in the screening group. He believes they can do better and that the most urgent need is for early detection of lung cancer.

"Screening means that you discover the disease before symptoms, before clinical manifestation of cancer. Lung cancer is different because people who smoke have a lot of problems like coughing, bronchitis, emphysema and so on. We need early biological markers that can help us to detect disease at an early stage, because disease detected at early stage is curable."

"I am working for the development of highly sensitive and highly specific cancer markers. We have collected a huge database, epidemiological database and blood serum bank for about 1,000 cases of lung cancer and 1,000 controls. All these cases are very well documented. We know the type of cancer, squamous, adenocarcinoma, small cell and so on.

"Using mass spectrometry, we are looking for proteomic patterns in blood which distinguish the plasma serum of lung cancer patients from the plasma of healthy individuals. When these proteins are discovered and characterised we will produce diagnostic chips that can be used for early detection of lung cancer, and for monitoring, before and after an operation.

"We have seen four or five peaks which distinguish the blood from lung cancer from the blood of healthy people. We don't know what these proteins are; we have not characterised them yet, but sensitivity is about 96% and specificity is about 94% and this is already quite good. We are going to try to make them more sensitive and more specific, and to identify the proteins.

"The next step will be to test it in epidemiological studies as a screening tool for lung cancer. You screen heavy smokers – those who smoke one

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pack plus, because you know that in this high-risk group, 17% develop lung cancer in their lifetime.

"We have only a small group interested in proteomic patterns but I don't think that we are much behind internationally. They started earlier in the US, but they made a lot of mistakes which we learned from."

Keeping up with cutting edge research is difficult when so much talent is lost.

"A lot of young people go to the US. We lose a terrible amount both in molecular biology and in epidemiology. We just cannot keep the best young people. This is not a question of personal income, but mainly of being able to do something good. When you are young, you have to work and have facilities. I don't know if I would come back myself, if I were their age.

"Frankly if I did not have a lot of grants from different parts of the world I would not be able to do anything.

"Now, like the Americans, I spend half of my working time writing up grant applications. I hope from next year we will have quite reasonable grants for different bits of research."

One research gap he would like to plug is to investigate what makes some cancers indolent while others progress rapidly. "That has fascinated me for several years. Prostate cancer is probably the best example, but breast cancer incidence is increasing partly because indolent breast cancers are discovered by mammography. They are probably different. If not discovered on screening, they would not manifest themselves clinically during the person's life span."

Perhaps it would help the research programme if Russian researchers could exploit their developments as their US and European counterparts do. But there is no tradition of taking their work to market. The liver cancer marker, alpha-feto protein, was discovered in the Institute of Carcinogenesis by Gary Abelev 35-years ago. Abelev still works at the Institute. Neither he nor Russian science ever made a penny out of their discovery.

Nor is there a tradition in Russia of those who have made money putting something back into research. Zaridze compares unfavourably the Russian billionaires who made their money by taking over the assets of the old Soviet state, with Bill Gates, whose foundation now funds research all over the world.

As President of the Russian Cancer Society, Zaridze sees how the money trickles in. "Contributions are mainly very small sums offered by old people from their pensions, 10, 20, or 30 roubles – less than US$ 1. These people feel something and want to do something. They are different from those billionaires."

In all the changes in Russia there have been gains and losses – wealth for some, poverty for others. Few want to turn back the clock, but some services have been abandoned in a rather shocking manner. The former screening system for cervical cancer (based on check-ups every two years) was cancelled in the early 1990s, since when deaths of young and middle-aged women from cervical cancer have been on the increase.

The role of Zaridze's institute is partly to provide evidence to help policy makers protect the population – by curbing smoking, reducing alcohol intake and appropriate screening. But Zaridze is frustrated that cancer is still not being given the priority it deserves. AIDS and avian 'flu, he says, are the subject of intense debate at high-level political meetings, while cancer, which kills 300,000 people a year in Russia, is scarcely mentioned.

"Our duty is to inform people that if cancer is discovered at an early stage you are saved. For example if breast cancer is discovered at an early stage, a small operation is done which is not mutilating. The main message should be that cancer, if discovered at an early stage, is a curable disease."