The Janus serum bank and biomarkers of cancer

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ABSTRACT

The Janus serum bank, established in 1973, contains sera stored at –25 degrees collected from 330,000 originally healthy individuals. The number of cancer cases have increased from zero in 1973 to more than 50,000 in 2005, including invasive and non-invasive cancers. Information on cases have been obtained by coupling the Janus file against the Norwegian Cancer Registry. The sera have been used in over 70 different cancers research projects, usually in case-control studies and in collaboration with national and international research groups. The type of biomarker analysed include antibodies against Chlamydia, CMV, Epstein Barr virus, HPV and Helicobacter pylori. Leptin, long chain fatty acids, androgens and other hormones, vitamins as well as environmental toxins such as organochlorines are other types of cancer biomarkers investigated. Mutation analyses (BRCA-1 etc) have been possible using PCR and the trace amounts of DNA remaining in the sera.

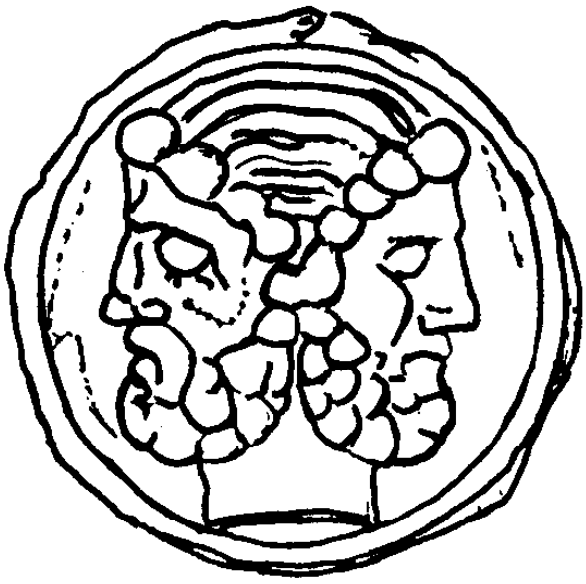
NORSK SAMMENDRAG

Janus serum bank ble etablert i 1973 og inneholder sera lagret ved –25 grader, innsamlet fra 330.000 opprinnelig friske personer. Antall krefttilfeller har steget fra null i 1973 til over 50.000 i år 2005, inkludert både invasiv og ikke-invasiv kreft. Informasjon om kasus er tilgjengelig ved å koble Janus-filene mot Kreftregisterets databaser. Serumprøvene er blitt benyttet i over 70 forskjellige kreftforskningsprosjekter, som oftest i kasus-kontroll studier og i samarbeide med en rekke nasjonale og internasjonale forskningsgrupper. Mange ulike biomarkører på kreft er blitt analysert, bl.a. antistoffer mot Chlamydia, CMV, Epstein Barr virus, HPV og Helicobacter pylori. Leptin, lange fettsyrer, androgener og andre hormoner, vitaminer såvel som miljøgifter av typen organiske klorforbindelser er eksempler på andre kreftbiomarkører som er undersøkt. Det har også vært mulig å gjøre mutasjonsanalyser (BRCA-1 etc) ved å bruke PCR til å amplifisere opp den spormengden DNA som finnes i serum.

BACKGROUND

The "Janus-idea" was proposed by O. Torgersen (1907-1978), a professor of pathology at Rikshospitalet, Oslo, in the late sixties. He suggested to commence collection of a few mL of serum from a large number of presumably healthy persons, and store the samples in a deep-freezer. As time passes he argued, some of the blood donors will inevitably develop some type of cancer. By coupling the information from the Norwegian Cancer Registry with the Janus-protocols, one could easily identify the cancer cases. These samples could then be used to search for changes in chemical, biochemical, immunological or other compounds that might indicate cancer development at early stages, or be indicative of increased risk of cancer.

Although the idea was rejected by many at first, funding was made available from the Norwegian Cancer Society in 1973, which was the year when the Janus serum bank was established.



THE JANUS SERUM BANK

The Janus serum bank is currently one of the oldest and largest biobanks available, containing sera from more than 330,000 individuals who have donated from 1 to 13 samples (average 2.2) each. About 30 per cent of the sera stem from Red Cross Blood Donors in Oslo, whereas the majority of the samples originate from persons undergoing regular health examinations in many counties in Norway. The number of cancer cases have increased from zero in 1973 to more than 50,000 in 2005, including invasive and non-invasive cancers.

One of the critisisms of the bank is the storage temperature, which is –25 degrees C. A number of stability experiments have, however, confirmed that many compounds are surprisingly stable at this temperature. Even if a compound is slowly degraded over the years, the use of age-, sex-, and storage-matched controls may compensate for this slow decomposition.

The Janus bank has been owned by the Norwegian Cancer Society up to May 1, 2005, after which date the responsibility was transferred to the Norwegian Cancer Registry.

A steering board has administered the use of the biobank in all these years, and has reviewed all the project proposals received from reseachers in Norway and abroad.

USE OF THE JANUS BANK IN CANCER RESEARCH

During the first 10-15 years of the Janus-bank, collection of sera was given the highest priority. Furthermore, during this period the number of cancers were too few to be able to carry out case-control studies with sufficient statistical power to draw safe conclusions.

The very first study was carried out in 1982 where an anti-tumor response in the preclinical period of lung cancer was reported. Some years later (1988/89) more typical cancer markers like CA-125 and Epstein Barr virus were examined in relation to ovarian cancer and Hodgkins disease, respectively. It was not until the late 1990's, however, that the scientific use of the biobank was clearly manifested. Collaboration with many groups, particularly in Scandinavia, but also in Europe and USA, were initiated, and a number of results were achieved and presented.

In general, a given biomarker is analysed in a number of cases (e.g. 500 breast cancers) and in 3 times as many matched controls (sera from Janus donors without cancer)

The cases and controls are retrieved from the large commercial storage freezer according to lists provided by the Cancer Registry. After thawing and aliquoting the samples are coded and shipped on dry-ice to the collaborating laboratory. After completion of the analyses, the code is broken and statistical analysis carried out. In this way bias is avoided and the anonymity of the Janus donor is always preserved.

BIOMARKERS OF CANCER STUDIED IN THE JANUS SERA

Up to now about 50 different projects have been completed and published and about fifteen more studies are currently under way. It is, however, outside the scope of this paper to discuss the indivual papers and results obtained. Clearly, in all these studies a number of different biomarkers have been examined in relation to different types of cancer. This is summarized in the table shown below. For further details the reader may consult the rerences given and the website: www.kreftsaken.no with links to Janus.

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Table 1. Cancer projects derived from the Janus bank.

Biomarkers	Type of Cancer	Reference no.
Breast cancer antigen-1 mutation	Breast	51, 52
Cancer Antigen-125	Ovarian	4
Chlamydia trachomatis antibody	Cervical	27, 31, 33, 40, 43
Chlamydia trachomatis antibody	Prostate	48
Cytomegalovirus antibody	Testis	29
Enterolactone	Prostate	42
Epstein Barr virus antibody	Hodgkin's disease	5
Epstein Barr virus antibody	Nasopharyngeal carcinoma	9
Epstein Barr virus antibody	Non Hodgkin's lymphoma	8
Epstein Barr virus antibody	Testis	29
Fatty acids in serum phospholipids	Prostate	21
Helicobacter pylori antibody	Cardia	30
Helicobacter pylori antibody	Gastric lymphoma	13, 22
Helicobacter pylori antibody	Non cardia gastric	30
Herpes simplex antibody	Cervical	38
Herpesvirus 8 antibody	Multiple myeloma	53
Human Papilloma virus antibody	Anal and perianal	34
Human Papilloma virus antibody	Cervical	18, 26, 31, 37, 40, 41
Human Papilloma virus antibody	Esophageal	23
Human Papilloma virus antibody	Head and neck	35
Human Papilloma virus antibody	Non cervical anogenital	19
Leptin	Colon	47
Leptin	Prostate	45
Long chain serum fatty acids	Thyroid	14
Lung cancer antibody	Lung	1
Methylene tetrahydrofolate reductase gene mutation	Colorectal	49
Polyunsaturated phospholipids	Breast	11
Prostate antigen	Prostate	12
Selenium	Thyroid	6
Serum androgens	Prostate	25
Serum dehydroepiandrosterone sulfate	Thyroid	28
Serum organoclorines	Breast	32
Serum proteins	Multiple myeloma	20
Testosterone	Prostate	46, 46
Thyroglobuline	Thyroid	3
Vitamin D	Prostate	39, 44