Original Article

# Ascertainment of Cancer Cases in the German National Cohort (NAKO)

## Methods and Initial Results

Verena A. Katzke, Volker Arndt, [...]* Rudolf Kaaks

Division of Cancer Epidemiology, German Cancer Research Center, (DKFZ), Heidelberg: Dr. Verena Katzke, Prof. Dr. Rudolf Kaaks

Cancer Survivorship Outcomes and Epidemiology, Epidemiological Cancer Registry Baden-Württemberg, Heidelberg: Prof. Dr. Volker Arndt

*The remaining authors of this publication are listed in the citation and at the end of the article, where their affiliations can be found.

## Summary

**Background:** The German National Cohort (*NAKO Gesundheitsstudie*) is a prospective cohort study with 205 053 participants. Its goal is to investigate risk factors for chronic diseases, including cancer.

**Methods:** We describe the methods of ascertaining cancer cases in NAKO (linkage with cancer registries and self-reporting), the incidence and prevalence figures obtained so far, and the ratio of observed to expected (O/E) case numbers.

**Results:** Altogether, 2774 prevalent (diagnosed within the 5 years prior to study enrollment) and 4295 incident (diagnosed up to 5 years after enrollment) cancer cases were identified. Breast, prostate, lung, and colorectal cancers made up 55% of the incident cases. Fewer incident cases were found than would have been expected on the basis of incidence rates in the general population (O/E ratio 0.80, 95% confidence interval [0.76;0.83] for the first 2 years of prospective follow-up). The O/E ratio varied, however, across tumor sites (breast 1.02, prostate 1.12, lung 0.38, colorectal 0.62). Possible explanations include bias caused by the fact that most study participants were healthy, delayed tumor reporting, incomplete data linkage, and incomplete self-reporting.

**Conclusion:** Rising case numbers for the most commonly occurring types of cancer are expected in the next few years. This will enable comprehensive epidemiological analysis of the risk factors for cancer.

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Prospective population-based cohorts provide an optimal observational epidemiological study design to investigate risk factors and mechanisms underlying the development of common chronic diseases. The German National Cohort (*NAKO Gesundheitsstudie*) aims to provide the epidemiological resources needed to elucidate causes and courses of chronic disease development, including cancer, cardiovascular disease, rheumatic disease, chronic infectious diseases, diabetes, and dementia (1–3). For the NAKO study, 205 053 participants randomly drawn from German population registries were recruited between 2014 and 2019. They were examined and interviewed across 18 study centers. In epidemiological analyses, it is important to achieve high validity and completeness in prospective disease ascertainment. Depending on disease type, case documentation can be achieved by record linkage with specialized disease registries, mortality registries, health insurance data, and medical rehabilitation data, or by self-reports from study participants. Such self-reports are subsequently verified by the treating physicians and the medical records reviewed.

For cancer, NAKO uses a combination of ascertainment strategies, with linkage to cancer registries as the primary approach. Several studies have demonstrated the feasibility of linking external cohorts with cancer registries in Germany (4–6); NAKO is, however, the first epidemiological study that requires individual-record linkages for a large number of individuals across nearly all German federal states.

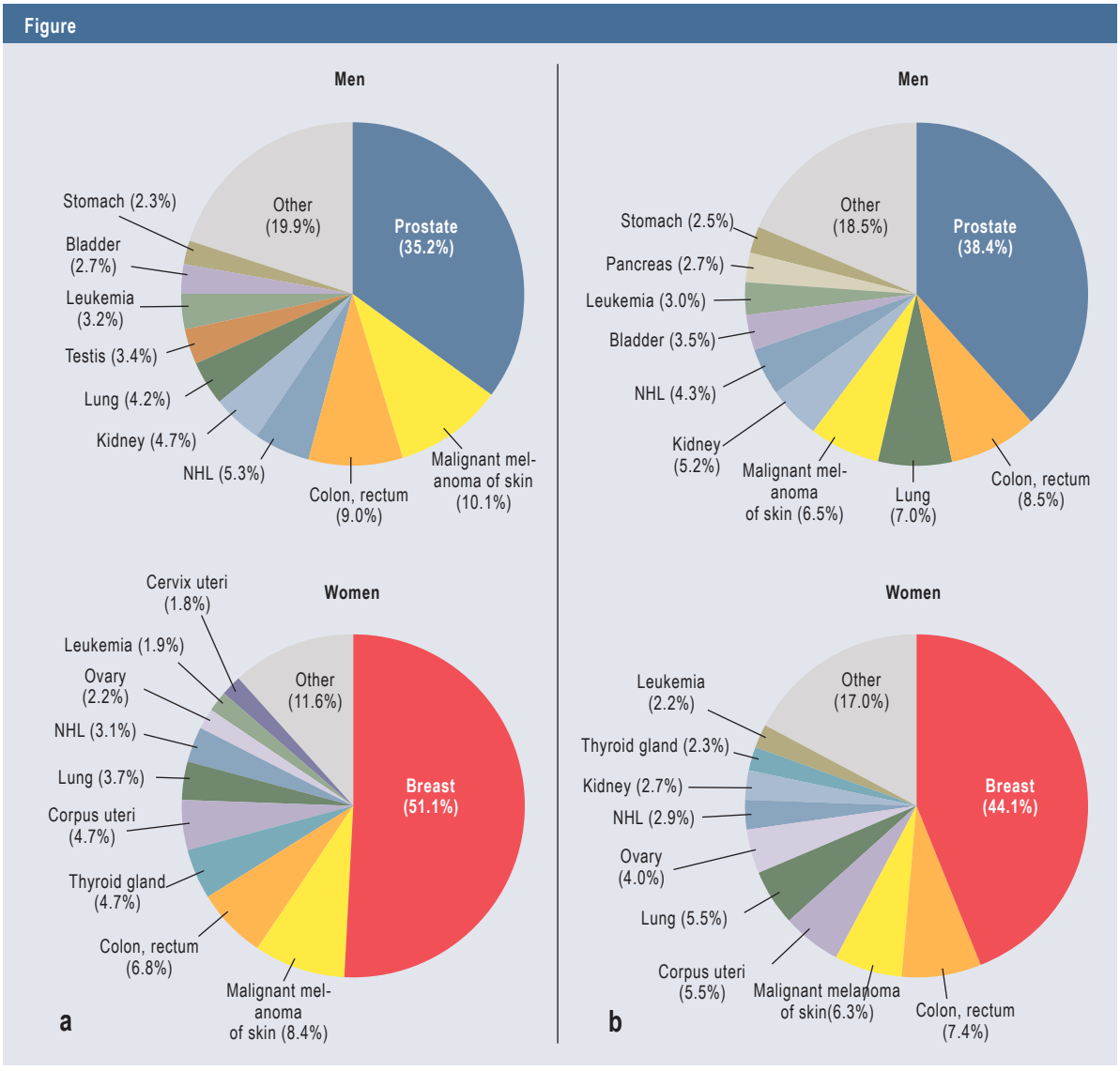
**Table 1**

**Frequencies of selected incident cancers (C00–C96 without C44)*1 in men and women of the German National Cohort (NAKO)**

| Incident malignant neoplasm | | Observed cases by years after baseline, n | | | | | Men | | Women | |
|---|---|---|---|---|---|---|---|---|---|---|
| ICD-10 code | Oncological diagnosis | 0 – <1 | 1 – <2 | 2 – <3 | 3 – <4 | 4 – <5 | N | Age at diagnosis, years*2 | N | Age at diagnosis, years*2 |
| **C00–C14** | Lip, oral cavity, pharynx | 32 | 26 | 30 | 15 | 17 | 94 | 62.0 | 26 | 60.3 |
| **C15–C26** | Digestive organs | 150 | 145 | 153 | 129 | 106 | 399 | 64.4 | 284 | 63.5 |
| C16 | Stomach | 18 | 20 | 18 | 16 | 14 | 57 | 68.1 | 29 | 64.3 |
| C18–C20 | Colon, rectum | 79 | 70 | 87 | 56 | 51 | 194 | 64.0 | 149 | 62.8 |
| C25 | Pancreas | 20 | 18 | 20 | 25 | 18 | 63 | 64.2 | 38 | 63.8 |
| **C30–C39** | Respiratory organs, other intrathoracic organs | 62 | 62 | 67 | 55 | 60 | 190 | 64.6 | 116 | 65.3 |
| C33–C34 | Trachea, bronchi, lung | 56 | 54 | 58 | 48 | 55 | 161 | 65.5 | 110 | 65.4 |
| **C43** | Malignant melanoma of skin | 70 | 65 | 64 | 44 | 31 | 148 | 63.1 | 126 | 61.3 |
| **C50** | Breast | 216 | 188 | 187 | 169 | 127 | 5 | 62.8 | 882 | 58.9 |
| **C51–C58** | Female genital organs | 44 | 62 | 53 | 57 | 40 | — | — | 256 | 61.8 |
| C54–C55 | Corpus uteri | 16 | 26 | 22 | 20 | 27 | — | — | 111 | 63.9 |
| C56 | Ovary | 14 | 23 | 18 | 18 | 8 | — | — | 81 | 62.6 |
| **C60–C63** | Male genital organs | 172 | 206 | 203 | 182 | 169 | 932 | 66.6 | — | — |
| C61 | Prostate | 158 | 195 | 194 | 171 | 162 | 880 | 66.9 | — | — |
| **C64–C68** | Urinary organs | 67 | 60 | 56 | 54 | 44 | 204 | 65.8 | 77 | 64.8 |
| C64 | Kidney, except renal pelvis | 46 | 41 | 33 | 27 | 27 | 120 | 65.2 | 54 | 64.0 |
| C67 | Urinary bladder | 21 | 18 | 22 | 25 | 15 | 80 | 66.8 | 21 | 67.5 |
| **C70–C72** | Brain, other parts of central nervous system | 15 | 11 | 7 | 12 | 7 | 33 | 60.0 | 19 | 60.1 |
| **C73–C75** | Thyroid gland, other endocrine glands | 18 | 12 | 13 | 20 | 7 | 24 | 57.9 | 46 | 51.4 |
| C73 | Thyroid gland | 17 | 12 | 13 | 19 | 7 | 22 | 59.5 | 46 | 51.4 |
| **C81–C96** | Lymphoid/hematopoetic/related tissue | 90 | 76 | 65 | 65 | 46 | 206 | 63.3 | 136 | 63.8 |
| C82–C88 | Non-Hodgkin lymphoma | 44 | 35 | 28 | 28 | 22 | 98 | 63.6 | 59 | 64.5 |
| C90 | Multiple myeloma | 9 | 16 | 12 | 14 | 7 | 29 | 62.4 | 29 | 64.7 |
| C91–C95 | Leukemia | 33 | 22 | 23 | 20 | 14 | 68 | 63.5 | 44 | 60.9 |
| **Other** | Other, unspecified, unknown sites | 25 | 16 | 12 | 20 | 19 | 58 | 61.5 | 34 | 58.8 |
| **Total (4295)** | | **961** | **929** | **910** | **822** | **673** | **2293** | **65.3** | **2002** | **61.1** |

*1 Diagnosed within 5 years after recruitment and reported through cancer registries
*2 Expressed as median

Figure




**The 10 most frequently occurring prevalent (a) and incident (b) cancers** (C00–C96 without C44) in the German National Cohort (NAKO) according to cancer registry linkage. The diagnoses presented are those established in the 5 years immediately before NAKO recruitment in the period 2014–2019 (prevalent) and in the 5 years thereafter (incident).
NHL, Non-Hodgkin lymphoma

Here, we describe the processes for cancer ascertainment among NAKO participants, with a focus on cancer registry linkage. We explain the linkage and matching procedures of NAKO data with registry data and report preliminary data on the incidence and prevalence of cancers within NAKO, ascertained up to October 2024. Further, we compare the incidence rates observed in NAKO with those expected, based on age- and sex-specific incidence rates from the German population. Finally, we provide an outlook on the future availability of data for scientific analyses.

## Methods

### NAKO examinations and follow-up

A total of 103 471 women and 101 582 men aged 19–74 years were recruited to NAKO between 2014 and 2019. The participants were examined at 18 study centers across Germany, using a standardized protocol for baseline assessments of exposures and functional health examinations. Further details on the NAKO cohort have been published previously (1–3, 7, 8), and a summary can be found in the *eMethods*. Participants were and are invited for re-examination approximately every 5 years. Additionally, questionnaires are sent out to reassess exposures and collect information on incident disease occurrence, including cancer. Additionally, passive record linkages to cancer registries, health insurance funds, and German pension funds are conducted every 2 years.

### Cancer diagnoses: cancer registry linkage and self-reports

Cancer ascertainment in NAKO relies primarily on linkage to cancer registry data. In Germany, the registration of all incident cancer cases is mandatory by law and organized at federal state level through population-based cancer

**Table 2**

**Incident cancers (ICD-10 diagnoses C00–C96 without C44) and ratios of observed to expected cases among NAKO participants in the first 2 years of follow-up*1**

| Incident cancers | | Observed cases by source n (%) | | | Expected cases*2, n | Ratio of observed to expected cases [95% CI] | |
|---|---|---|---|---|---|---|---|
| ICD-10 code | Diagnosis | Cancer registry | Additional cases: self-reports | Additional cases: DCO | ZfKD | Cancer registry | All sources |
| **C00–C14** | Lip, oral cavity, pharynx | 58 (87.9%) | 8 (12.1%) | 0 (0.0%) | 82 | 0.71 [0.54; 0.91] | 0.80 [0.62;1.02] |
| **C15–C26** | Digestive organs | 295 (83.1%) | 47 (13.2%) | 13 (3.7%) | 504 | 0.59 [0.52; 0.66] | 0.70 [0.63; 0.78] |
| C16 | Stomach | 38 (86.4%) | 4 (9.1%) | 2 (4.5%) | 63 | 0.60 [0.43; 0.83] | 0.70 [0.51; 0.94] |
| C18–C20 | Colon, rectum | 149 (90.3%) | 14 (8.5%) | 2 (1.2%) | 241 | 0.62 [0.52; 0.73] | 0.68 [0.58; 0.80] |
| C25 | Pancreas | 38 (76.0%) | 6 (12.0%) | 6 (12.0%) | 73 | 0.52 [0.37; 0.71] | 0.68 [0.51; 0.90] |
| **C30–C39** | Respiratory organs, other intrathoracic organs | 124 (86.1%) | 13 (9.0%) | 7 (4.9%) | 321 | 0.39 [0.32; 0.46] | 0.45 [0.38; 0.53] |
| C33–C34 | Trachea, bronchi, lung | 110 (86.6%) | 10 (7.9%) | 7 (5.5%) | 291 | 0.38 [0.31; 0.46] | 0.44 [0.36; 0.52] |
| **C43** | Malignant melanoma of skin | 135 (72.2%) | 52 (27.8%) | 0 (0.0%) | 122 | 1.11 [0.93; 1.31] | 1.53 [1.32; 1.77] |
| **C50** | Breast | 404 (92.2%) | 34 (7.8%) | 0 (0.0%) | 395 | 1.02 [0.93; 1.13] | 1.11 [1.01; 1.22] |
| **C51–C58** | Female genital organs | 106 (75.7%) | 31 (22.1%) | 3 (2.1%) | 138 | 0.77 [0.63; 0.93] | 1.01 [0.85; 1.20] |
| C54–C55 | Corpus uteri | 42 (85.7%) | 7 (14.3%) | 0 (0.0%) | 57 | 0.74 [0.53; 1.00] | 0.86 [0.64; 1.14] |
| C56 | Ovary | 37 (86.0%) | 5 (11.6%) | 1 (2.3%) | 35 | 1.06 [0.74; 1.46] | 1.23 [0.89; 1.65] |
| **C60–C63** | Male genital organs | 378 (86.7%) | 57 (13.1%) | 1 (0.2%) | 341 | 1.11 [1.00; 1.23] | 1.28 [1.16; 1.40] |
| C61 | Prostate | 353 (86.1%) | 56 (13.7%) | 1 (0.2%) | 314 | 1.12 [1.01; 1.25] | 1.31 [1.18; 1.44] |
| **C64–C68** | Urinary organs | 127 (74.3%) | 40 (23.4%) | 4 (2.3%) | 146 | 0.87 [0.73; 1.03] | 1.17 [1.00; 1.36] |
| C64 | Kidney, except renal pelvis | 87 (81.3%) | 19 (17.8%) | 1 (0.9%) | 74 | 1.18 [0.94; 1.45] | 1.45 [1.18; 1.75] |
| C67 | Urinary bladder | 39 (65.0%) | 21 (35.0%) | 0 (0.0%) | 62 | 0.63 [0.45; 0.86] | 0.97 [0.74; 1.25] |
| **C70–C72** | Brain, other parts of central nervous system | 26 (83.9%) | 2 (6.5%) | 3 (9.7%) | 37 | 0.70 [0.46; 1.03] | 0.84 [0.57; 1.19] |
| **C73–C75** | Thyroid gland, other endocrine glands | 30 (78.9%) | 7 (18.4%) | 1 (2.6%) | 41 | 0.73 [0.49; 1.04] | 0.93 [0.66; 1.27] |
| C73 | Thyroid gland | 29 (82.9%) | 5 (14.3%) | 1 (2.9%) | 39 | 0.74 [0.50; 1.07] | 0.90 [0.63; 1.25] |
| **C81–C96** | Lymphoid/hematopoetic/related tissue | 166 (84.3%) | 28 (14.2%) | 3 (1.5%) | 177 | 0.94 [0.80; 1.09] | 1.11 [0.96; 1.28] |
| C82–C88 | Non-Hodgkin lymphoma | 79 (81.4%) | 15 (15.5%) | 3 (3.1%) | 79 | 1.00 [0.79; 1.25] | 1.23 [1.00; 1.50] |
| C90 | Multiple myeloma | 25 (92.6%) | 2 (7.4%) | 0 (0.0%) | 30 | 0.83 [0.54; 1.23] | 0.90 [0.59; 1.31] |
| C91–C95 | Leukemia | 55 (83.3%) | 11 (16.7%) | 0 (0.0%) | 55 | 1.00 [0.75; 1.30] | 1.20 [0.93; 1.53] |
| **Other** | Other, unspecified, unknown sites | 41 (49.4%) | 38 (45.8%) | 4 (4.8%) | 72 | 0.57 [0.41; 0.77] | 1.15 [0.92; 1.43] |
| **Total** | | **1890 (82.7%)** | **357 (15.6%)** | **39 (1.7%)** | **2377** | **0.80 [0.76; 0.83]** | **0.96 [0.92; 1.00]** |

*1 Based on cancer registry data, self-reports, and DCO data; *2 based on age- and sex-specific incidence rates for the years 2014–2021 from the Center for Cancer Registry Data (ZfKD); DCO, death certificate only

**Table 3**

**Completeness of selected tumor characteristics captured in the cancer registry data for the 5 years before (prevalent) and the 5 years after (incident) NAKO recruitment**

| | Prevalent cancer (%) | | Incident cancer (%) | |
|---|---|---|---|---|
| | Total | Median (IQR) across registries | Total | Median (IQR) across registries |
| Tumor diagnosis (except ICD-10 codes C26.0, C26.9, C39.0, C39.9, C76, C80.9) | 99.7 | 99.9 (99.6–100.0) | 99.7 | 100.0 (99.5–100.0) |
| Year and month of diagnosis | 99.8 | 100.0 (99.8–100.0) | 100.0 | 100.0 (100.0–100.0) |
| Laterality (in the case of paired organs) | 88.9 | 95.2 (90.4–98.0) | 94.1 | 95.8 (93.7–98.0) |
| Diagnosis confirmed by histology/cytology | 94.2 | 97.6 (96.0–98.7) | 94.0 | 98.4 (91.7–98.8) |
| Morphology (except 8000/3, 8005/3) | 97.9 | 99.1 (98.6–99.6) | 95.9 | 98.9 (96.8–99.1) |
| TNM, tumor (for solid tumors) | 78.4 | 85.0 (76.9–90.8) | 78.3 | 80.9 (66.1–90.1) |
| TNM, node (for solid tumors) | 68.9 | 73.6 (61.5–88.4) | 70.1 | 73.8 (59.3–80.9) |
| TNM, metastases (for solid tumors) | 65.8 | 64.8 (51.3–92.2) | 73.0 | 70.9 (56.6–88.2) |

IQR, Interquartile range; TNM, tumor, (lymph) node, metastases

registries (9–11). For NAKO, procedures for separate cohort linkages with each of the relevant federal state registries have been established on a contractual basis (for details, see *eMethods, eFigure 1*). It is possible that not all incident cancer cases are reported through linkage with cancer registries, e.g., due to incomplete registry coverage (< 5%) (12) or lack of consent in relation to NAKO (8% at baseline). NAKO therefore also uses additional data sources to identify incident cancer cases, such as self-reports by the participants and linkage with death registers (see *eMethods*) or with health insurance and pension funds data (not in this article). Linkage with data from health insurance and pension funds falls outside the remit of this article.

### Data processing and statistical methods

After linkage procedures, individual-level data from the registries were combined and inconsistencies resolved. In addition, self-reported incident cancers were coded using ICD-10 and merged with cancer registry data. Matching of self-reported cases to registry cases was based on:

- ICD-10 code
- Age at diagnosis
- Topography
- Morphology

The matching process started with exact agreements, and subsequently the criteria were relaxed. Furthermore, data from local mortality registries were added. Non-melanoma skin cancer (C44) was excluded from all analyses.

Prevalence of cancers derived from cancer registry data is shown only for cancers diagnosed up to 5 years prior to recruitment; data over a longer retrospective period were less complete because the various cancer registries were founded at different times. The incidence of cancer sites was derived from cancer registry data, from self-reports, and from mortality registries, in terms of total numbers as well as stratified by sex and year of follow-up.

We calculated for each cancer site the expected number of new cancer cases and the ratio of observed to expected cases (O/E) with the corresponding 95% confidence interval (95% CI). To this end, we multiplied age- and sex-specific incidence rates from the German cancer registries covered by the Center for Cancer Registry Data (ZfKD) by the number of NAKO participants in identical sex and age-group strata, using ZfKD data on cancers diagnosed in the period 2014–2021 (13). The O/E ratios were calculated only for the first 2 years of prospective follow-up, because at the time this analysis was conducted, case ascertainment for the longer follow-up times was still incomplete.

## Results

Based on two rounds of linkage per cancer registry, 4295 new cases of invasive cancer were recorded up to a maximum of 5 years after recruitment. The most common were cancer of the female breast (N = 882; 44% of cancers in women), prostate cancer (N = 880; 38% of cancers in men), colorectal cancer (N = 343), lung cancer (N = 271), and malignant melanoma of the skin (N = 274; *Table 1, Figure 1 a and b*). As shown in *Table 1*, annual numbers of incident cases declined after the first years of follow-up. Within the first 2 years of follow-up, the following numbers of cases were reported through cancer registries:

- 149 colorectal cancers
- 110 lung cancers
- 135 cutaneous malignant melanomas
- 353 prostate cancers
- 404 female breast cancers

In addition to invasive cancers, 706 in situ tumors (484 in women, of which 77% affected the breast and genital organs), 106 benign neoplasms, and 123 tumors of uncertain behavior were recorded (not shown in the table).

Within the first 2 years of follow-up, 56% (N = 1273) of self-reported incident cancers could be matched with cancer registry data. The remaining self-reports, without corresponding cancer registry records, were predominantly for prostate cancer, breast cancer, and skin cancer *(eFigure 2)*. Overall, 82.7% (N = 1890) of confirmed cancer cases were derived from cancer registries and 15.6% (N = 357) from self-reports. A further 1.7% (N = 39) were documented exclusively from death certificates *(Table 2)*. Participants' self-reports played a substantial part in the documentation of some cancer types, such as bladder cancer (N = 21; 35%) or melanoma (N = 52; 28%), whereas additional

DCO cases were most relevant for cancers of the pancreas (N = 6; 12%) and lung (N = 7; 6%).

Compared with the expected numbers of new cancers, the observed numbers, based on registry linkage, were lower overall in the first 2 years of follow-up (O/E = 0.80, [0.76; 0.83]; *Table 2*). However, the ratio of observed to expected cases varied by cancer site, ranging from 0.38 [0.31; 0.46] for lung cancer to 1.18 [0.94; 1.45] for renal carcinoma. Within these limits, the ratios of observed to expected cases were 0.62 [0.52; 0.73] for colorectal, 1.02 [0.93; 1.13] for breast, and 1.12 [1.01; 1.25] for prostate cancer. The combination of registry data, self-reports, and documentation on death certificates only resulted in higher ratios of observed to expected cases than registry data alone. The ratios were as follows:

- Overall: 0.96 [0.92; 1.00]
- Lung cancer: 0.44 [0.36; 0.52]
- Colorectal cancer: 0.68 [0.58; 0.80]
- Breast cancer: 1.11 [1.01; 1.22]
- Prostate cancer 1.31 [1.18; 1.44]

In total, 2774 cancer registry-derived cases (excluding ICD-10 diagnostic code C44) were diagnosed within the 5 years immediately preceding NAKO recruitment (1.5% of participants, *Figure 1a and eTable 1*). These prevalent cancer cases were predominantly neoplasms with high long-term survival probabilities (e.g., prostate cancer N = 454 [35% of prevalent cancers in male participants] and female breast cancer N = 758 [51% of prevalent cancers in female participants]). Only small numbers of these prevalent cancer cases were characterized by low survival probabilities, e.g., cancer of the pancreas (N = 14), liver (N = 4), or ovaries (N = 32) (14).

Selected variables, e.g., topography and morphology, are shown in *Table 3*. They serve as criteria for data quality and are important for the majority of future epidemiological analyses, Complete data were obtained from all cancer registries on the primary tumor (ICD-10) and date of diagnosis, while morphology data were available for 96% of incident cases, and most diagnoses were based on histology or cytology (94%). By contrast, the data for tumor, lymph nodes, and metastases (TNM) were complete for a lower proportion of incident cancers (70–78%).

## Discussion

The primary—and thus most important—source of high-quality cancer data for the NAKO study, with its 205 053 participants, are the population-based cancer registries of the German federal states. Based on two rounds of registry linkage, almost 2800 existing and 4300 newly occurring cases of cancer were documented in the 5 years immediately before and the 5 years after recruitment, respectively. Overall, the observed number of incident cancer cases was lower than expected on the basis of nationwide cancer registry data, although the ratio of observed to expected cases varied by tumor site. NAKO supplemented the cancer registry data with participants' self-reported cancer diagnoses. This approach to ascertainment resulted in additional potential incident cancer cases, which, however, require validation via medical record review.

The reasons why fewer cases than expected were observed for some kinds of cancer are likely multifactorial. They may include healthy volunteer bias (e.g., fewer smokers in the general population: lung cancer O/E = 0.44), incomplete linkage, and time lags in cancer registration. Higher than average rates of participation in cancer screening may explain ratios above 1.0 for prostate cancer (E/O = 1.31), malignant melanoma (E/O = 1.53), and breast cancer (O/E = 1.11), and well as the ratio below 1.0 for colorectal cancer (E/O = 0.68); however, this needs to be investigated further. Discrepancies in observed versus expected case numbers probably do not affect internal validity and relative risk estimates, but may hamper external validity, especially for the estimation of absolute risks and attributable/preventable fractions when extrapolating to the general German population. To date, scientific use of NAKO data is affected not so much by imperfect ratios of observed to expected cases as by limited case numbers for some cancer sites. All these aspects need to be carefully and clearly considered for studies within NAKO.

NAKO is the first large-scale population-based study in Germany using extensive nationwide linkage of individual-level data from a number of registries for outcome ascertainment. Following the first two rounds of linkage, this is now a well-established process for all participating registries. Establishment of associations between characteristics and behavior patterns of NAKO participants prior to disease onset with occurrence of incident cancers is the key approach for identifying possible causes of disease development.

The key aspects of data quality with respect to cancer registration data, as described in detail by Bray & Parkin (15, 16) and by Arndt et al. (9), comprise:

- Comparability
- Validity
- Timeliness
- Completeness

In Germany, physicians are required to report case between 4 weeks and 6 months after diagnosis, after which cancer registries process and verify the cases within 6 weeks. In practice, the time taken for reporting and verification can vary between registries, and lag times between the date of cancer diagnosis and the transfer of data to NAKO via linkage may be as long as 2 years. In general, data quality—and especially the timely, correct, and complete reporting of cancers—depends crucially on having motivated and continuously trained physicians. Evaluations by the ZfKD indicate that population-based cancer registries in Germany capture over 95% of overall cancer incidence (12), which is comparable with the findings from cancer registries in other countries (17). As our project demonstrates, most cancer registries provide highly complete information on ICD-10-based variables, whereas stage information is less complete and varies between registries, cancer sites, and years of diagnosis. The impact of incomplete data items—e.g., TNM, ranging from 70.1% to 78.3% completeness—is currently a limitation but is expected to be resolved over the next few years, as item completeness in registries is rapidly increasing. This lack of completeness was due to the fact that some registries were recently founded or reorganized after the introduction of new federal legislation mandating clinical cancer registration. Prospectively, we expect data completeness for newly occurring tumors to be sufficient for most scientific evaluations in NAKO that require TNM data.

Complementing cancer registry data in NAKO with the participant's self-reports increased the overall incidence in the first 2 years by 16% and the overall ratio of observed to expected cases to 0.96. The quality of self-reported cancer data is low relative to cancer registry data, as the self-reports are limited to cancer site and year of diagnosis, with a degree of imprecision in both items. Hence, self-reports require extensive clinical validation with

medical records—not only for verification purposes, but also to increase the precision of those cancer notifications (18).

In conclusion, linkages to German cancer registries covering all NAKO recruitment areas have been successfully set up and performed. As of 2024, completeness of cancer data for the entire cohort over a full 5-year period has not yet been attained, nor is there satisfactory item completeness for all of the relevant data elements, e.g., information on TNM. However, regular linkages will result in complete data on all aspects of cancer in subsequent years. Incident case numbers will increase as participants age. Verification of self-reports can be used to complement the cancer registry data, and item completeness will automatically increase in the coming years, mirroring the completeness of cancer registry data. We therefore expect that the next few years will see a highly comprehensive and complete dataset with rapidly growing case numbers for the most frequent cancers. This will allow researchers to address important questions on organ-specific cancer etiology in a large, well characterized prospective cohort.

**Remaining authors**
Karin Halina Greiser, Florian Karpa, Dorothee Zoller, Renée Fortner, Karen Steindorf, Michael Hoffmeister, Hermann Brenner, Peter Schirmacher, Michael Leitzmann, Katharina Nimptsch, Ulrike Haug, Katharina Hofmann, Christoph Stallmann, Ulrich Mueller, Andrea Werdecker, Iris Pigeot, Enno Swart, Wolfang Ahrens, Martin Meyer, Sabine Luttmann, Alice Nennecke, Anne von Rüsten, Joachim Kieschke, Tobias Hartz, Andreas Stang, Wolfgang Hoffmann, Bernd Holleczek, Hans Gert Fabian, Annette Peters, Stefan N. Willich, Lilian Krist, Matthias B. Schulze, Kathrin Guenther, Hajo Zeeb, Nina Ebert, Börge Schmidt, Anna Köttgen, Alexander Kluttig, Rafael Mikolajczyk, Volker Harth, Nadia Obi, Carolina Klett-Tammen, Manuela Harries, Wolfgang Lieb, Heiko Becher, Heike Minnerup, André Karch, Claudia Meinke-Franze, Hansjörg Baurecht, Ute Mons, Lena Koch-Gallenkamp, Klaus Berger, Henry Völzke, Tobias Pischon, Alexander Katalinic

**Affiliations of the remaining authors**
Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg: Dr. med. Karin Halina Greiser, Florian Karpa, Dorothee Zoller, Dr. Renée Fortner

Division of Physical Activity, Cancer Prevention and Survivorship, German Cancer Research Center (DKFZ), Heidelberg: Prof. Dr. Karen Steindorf

Division of Clinical Epidemiology of Early Cancer Detection, German Cancer Research Center (DKFZ), Heidelberg: Prof. Dr. Michael Hoffmeister, Prof. Dr. emeritus Hermann Brenner, Dr. Lena Koch-Gallenkamp

BioMaterialBank Heidelberg, University Hospital Heidelberg: Prof. Dr. med. Peter Schirmacher, Dr. rer. nat. Katharina Hofmann

Institute for Epidemiology and Preventive Medicine, University of Regensburg: Prof. Dr. Dr. emeritus Michael Leitzmann, Dr. Hansjörg Baurecht

Department of Molecular Epidemiology, Max Delbrück Center for Molecular Medicine in the Helmholtz Society (MDC), Berlin: Dr. Katharian Nimptsch, Prof. Dr. Tobias Pischon

Leibniz Institute for Prevention Research and Epidemiology – BIPS, Bremen: Prof. Dr. Ulrike Haug, Prof. Dr. rer. nat. Iris Pigeot, Prof. Dr. Wolfgang Arens, Dr. Sabine Luttmann, Dr. Kathrin Guenther, Prof. Dr. med. Hajo Zeeb

Institute for Social Medicine and Health System Research (ISMG), Faculty of Medicine, University of Magdeburg: Dr. Christoph Stallmann, Prof. Dr. Enno Swart

Center for Population and Health e.V., Wiesbaden: Prof. Dr. Dr. med. Ulrich Mueller

Federal Institute for Population Research (BiB), Wiesbaden: Dr. rer. med. Andrea Werdecker

Bavarian State Office for Health and Food Safety, Data Trust Center of the Bavarian State Cancer Registry, Nürnberg: Dr. Martin Meyer

Bremen State Cancer Registry, Bremen: Dr. Sabine Luttmann

Hamburg Cancer Registry (HKR), Authority for Science, Research, Equality, and District Affairs, Hamburg: Dr. Alice Nennecke

Clinical–Epidemiological Cancer Registry Brandenburg–Berlin gGmbH, Registration Office Berlin: Anne von Rüsten

Lower Saxony State Epidemiological Cancer Registry, Lower Saxony State Health Office, Hanover: Joachim Kieschke

Lower Saxony Clinical Cancer Registry (KKN), Hanover: Dipl.-Math. Tobias Hartz

North Rhine–Westphalia State Cancer Registry, Bochum; Institute for Medical Informatics, Biometrics, and Epidemiology, University Hospital Essen: Prof. Dr. Andreas Stang

Institute for Community Medicine, Department of Healthcare Epidemiology and Community Health, University Medical Center Greifswald, Public Corporation, Greifswald; Mecklenburg–West Pomerania State Cancer Registry, Greifswald: Prof. Dr. med. Wolfgang Hoffmann

Saarland State Cancer Registry: PD Dr. Bernd Holleczek

Saxony State Cancer Registry: Hans Gert Fabian

Institute for Epidemiology, Helmholtz Centre Munich – Environmental Health Center, Munich: Prof. Dr. Annette Peters

Institute for Social Medicine, Epidemiology, and Health Economics, Charité – University Medical Center Berlin: Prof. Dr. Stefan N. Willich, PD Dr. Lilian Krist

Department of Molecular Epidemiology, German Institute of Human Nutrition, Nuthetal: Prof. Dr. Matthias B. Schulze

Institute for Biometrics and Epidemiology, German Diabetes Center (DDZ), Leibniz Center for Diabetes Research, University of Düsseldorf: Nina Ebert

Institute for Medical Informatics, Biometrics, and Epidemiology, University Hospital Essen: Prof. Dr. Börge Schmidt

Institute for Epidemiology and Prevention, University Hospital Freiburg: Prof. Dr. med. Anna Köttgen

Institute for Medical Epidemiology, Biometrics, and Informatics, Faculty of Medicine, University of Halle–Wittenberg, Halle; Saxony–Anhalt State Cancer Registry gGmbH, Halle: Dr. rer. medic. Alexander Kluttig

Medical Epidemiology, Biometrics, and Informatics, University of Halle–Wittenberg, Halle (Saale): Prof. Dr. Rafael Mikolajczyk

Central Institute for Occupational and Maritime Medicine (ZfAM), University Hospital Hamburg-Eppendorf, Hamburg: Prof. Dr. Volker Harth, Dr. Nadia Obi

Department of Epidemiology, Helmholtz Centre for Infection Research (HZI), Braunschweig: Dr. Caroline Klett-Tammen, Manuela Harries

Institute for Epidemiology, University of Kiel: Prof. Dr. Wolfgang Lieb

Heidelberg Institute for Global Health, University Hospital Heidelberg: Prof. Dr. Heiko Becher

Institute for Epidemiology and Social Medicine, University of Münster: Prof. Dr. med. Heike Minnerup, Prof. Dr. André Karch, Prof. Dr. med. Klaus Berger

Institute for Community Medicine, University Medical Center Greifswald: Dr. rer. med. Claudia Meinke-Franze, Prof. Dr. med. Henry Völzke

Division of Primary Cancer Prevention, German Cancer Research Center (DKFZ), Heidelberg: Prof. Dr. Ute Mons

Institute for Social Medicine and Epidemiology, University Hosptal Schleswig–Holstein, Lübeck: Prof. Dr. med. Alexander Katalinic

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**Conflict of interest statement**
André Karch is president of the German Society for Epidemiology (DGEpi).

The remaining authors declare that no conflict of interest exists.

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**Corresponding author**
Dr. sc. hum. Verena A. Katzke
v.katzke@dkfz.de

**Supplementary material**
**Complete list of full references incl. eReferences, eMethods, eTables, eFigures:**
**www.aerzteblatt-international.de/m2026.0061**

## CLINICAL SNAPSHOT

# Blue-Tinted Glasses in Photosensitive Epilepsy in Road Traffic: Protection or Risk?

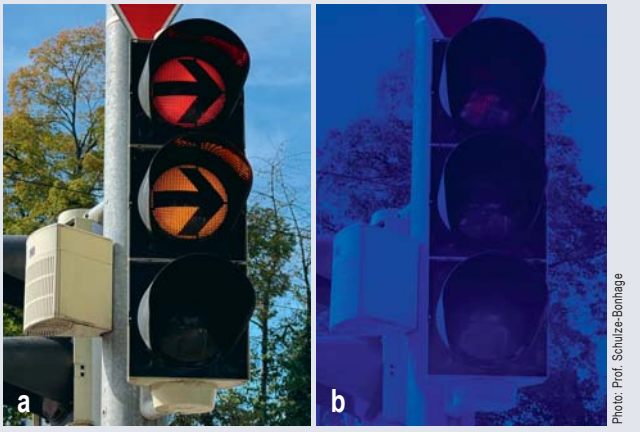


Photo: Prof. Schulze-Bonhage

**Figure:** a) Photo taken without the lens; b) photo taken with the anti-seizure blue-tinted lens in place

A patient in his 20s with juvenile myoclonic epilepsy who was receiving anti-seizure medication experienced epileptic reflex seizures triggered exclusively by flickering light. Blue lenses can prevent seizures in up to 90% of cases in patients with photosensitive epilepsy. Consistent with this, wearing blue polarized glasses during EEG photostimulation in this patient resulted in complete suppression of epileptic activity ("photoparoxysmal response"). As a result, blue Z1 lenses were prescribed. This raises the question: Is this patient permitted to resume driving if he remains seizure-free? This is due to the fact that blue lenses reduce the red spectral component of light by 80–90%, thereby impairing the recognition of red traffic signals *(Figure)*. Therefore, international and German guidelines for glasses (DIN EN ISO 12312–1:2022–08) do not permit lenses that reduce the red spectral component by more than 80% or have a light transmittance of less than 92% in road traffic. According to the regulations of the German Federal Highway Research Institute (*Bundesanstalt für Straßenwesen*), fitness to drive a motor vehicle can only be certified after 1 year of freedom from spontaneous seizures. The risk of reflex seizures must be assessed by a neurologist. Irrespective of whether seizure freedom is achieved, patients who wear the tinted glasses discussed here are not permitted to drive a motor vehicle.

**Dr. med. Lena Bender, Prof. Dr. med. Andreas Schulze-Bonhage,** Epilepsiezentrum, Medizinische Fakultät, Universitätsklinikum Freiburg, lena.bender@uniklinik-freiburg.de

**Prof. Dr. med. Wolf Alexander Lagrèze**, Neuroophthalmologie, Klinik für Augenheilkunde, Universitätsklinikum Freiburg

**Conflict of interest statement:** The authors declare that no conflict of interest exists.

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**Supplementary material** to accompany the article

# Ascertainment of Cancer Cases in the German National Cohort (NAKO)

## Methods and Initial Results

by Verena A. Katzke, Volker Arndt, [...]* and Rudolf Kaaks

Dtsch Arztebl Int 2026; 123: 439–46. DOI: 10.3238/arztebl.m2026.0061

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## eMETHODS

### NAKO

Baseline information was obtained at recruitment by means of highly standardized face-to-face interviews, questionnaires, a wide range of biomedical examinations, and collection of biological samples such as blood, urine, saliva, nasal swabs, and stool. A subset of 59 971 participants took part in an intensified baseline examination program, and of these, 30 861 participants additionally underwent whole-body magnetic resonance imaging using dedicated 3-T scanners. Regular re-examinations and follow-up questionnaires are planned to collect longitudinal information on changes in risk factors, functional health tests, and incident events. Furthermore, all NAKO participants were asked to sign, and regularly reconfirm, separate informed consent for the collection of health record data. This consent covered both acquisition of data from their treating physicians and data collection through linkages with cancer registries, local mortality registries, and secondary data sources (health insurance claims, medical rehabilitation data from the German federal pension authority).

### Cancer registration in Germany

The federal state cancer registries in Germany collect data on date of diagnosis, histology and topography, tumor stage, vital status, date and cause of death, treatment, and disease trajectories, together with more detailed tumor characteristics (e1). These data are coded in accordance with the ICD-10 classification (e2). Cancer registries provide information on invasive malignant neoplasms, their precursors, neoplasms of uncertain or unknown behavior, and benign neoplasms of the central nervous system as outlined in the Manual for Cancer Registration (*Manual der Krebsregistrierung*) (e3). On a yearly basis, all federal state registries transmit pseudonymized data on cancer cases to the German Center for Cancer Registry Data (ZfKD), which estimates cancer frequencies for Germany and publishes the findings under the title of Cancer in Germany (*Krebs in Deutschland*).

### Procedures for record linkage between NAKO and the cancer registries

The 18 NAKO study centers are distributed across 13 federal states and are covered by 12 of the 15 state cancer registries. A schematic overview of the process for record linkage between NAKO and the state cancer registries is shown in *eFigure 1*. The NAKO study filed official requests for cohort data linkage at each of the respective cancer registries that required approval by regional authorities, ethics boards, scientific advisory boards, or other responsible bodies. Upon approval, contracts for record linkage and data transfer were signed if needed. Starting in 2017, all registries have given their approval and/or concluded a data usage agreement by 2024. The actual record linkage for NAKO participants with registries and other data owners is operated through the central NAKO data center. At 2-year intervals, one designated representative of each cancer registry receives access to person-related data of NAKO participants. The registries perform in-house linkage, compile medical information for participant matching, and send this information to the NAKO integration center. Quality control is performed by NAKO tumor documentation assistants. The NAKO integration center links all cancer-registry data to individuals' primary identification numbers, after which the data are integrated into the overall NAKO research database, which forms the basis for scientific use of NAKO data (e4). The first wave of cancer registry linkages with individual registries was initiated in 2019, with most linkages being completed by 2020. A second wave was launched in 2022. By mid-2024, all registries had transferred the cancer-related data of NAKO participants from both linkage waves, with the processing taking on average 8 months (range 2–17 months) to complete.

### Self-reports by study participants with subsequent clinical validation

At baseline, all NAKO participants completed a standardized computer-based personal interview including questions about physician-diagnosed cancer, such as number and type of cancer diagnoses (including in-situ neoplasms) for up to four cancers, year of or age at diagnosis, treating physician or hospital, and treatment during the past 12 months (e5). Incident cancer cases occurring after baseline are recorded at every consecutive visit to the study center (at intervals of 4–5 years) or are obtained through self-administered health follow-up questionnaires every 2.5–3 years between the visits *(eTable 2)*. Subsequently, the participant's primary care physician is asked to complete a standardized questionnaire and to provide additional medical records that are used for algorithm-based verification or otherwise of an incident event. For cancer, active verification of a self-report through treating physicians is initiated only when confirmation cannot be obtained through linkage with cancer registries.

eFigure 1

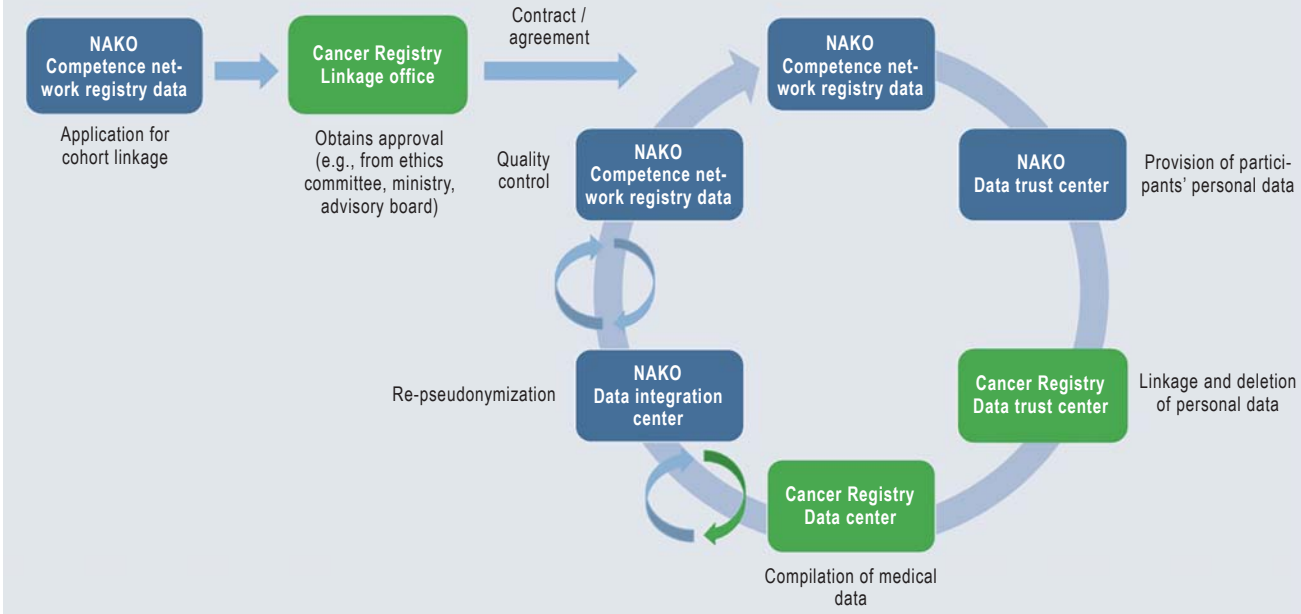
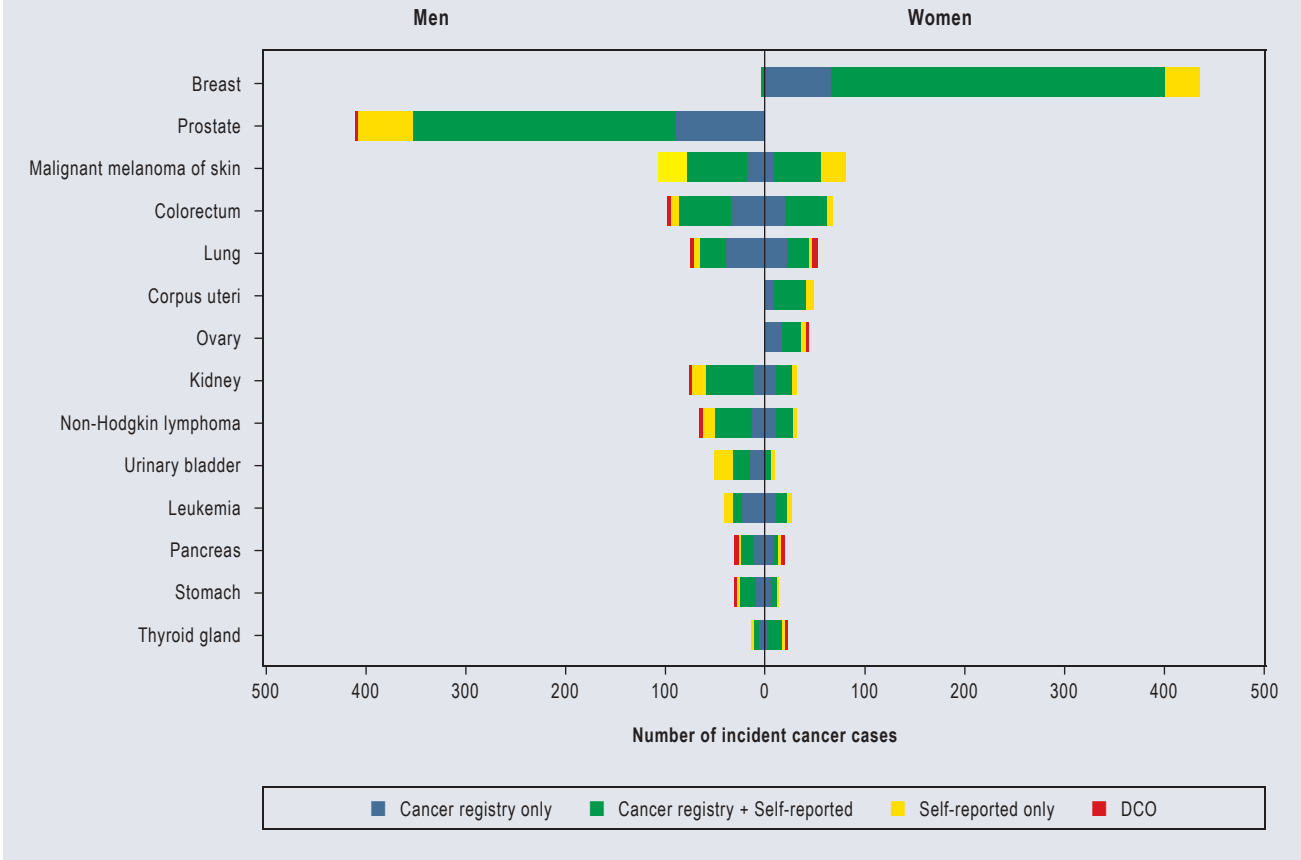



**Chart showing the data flow** between the NAKO and the state cancer registries

eFigure 2




**The cancers most often diagnosed** in the first 2 years of the NAKO study
DCO, Death certificate only

**eTable 1**

**Selected data for the 5-year prevalence of cancer in NAKO (diagnoses C00–C96, without C44)**

| Prevalent cancer | | Observed cases by number of years before baseline | | | | | Men | | Women | |
|---|---|---|---|---|---|---|---|---|---|---|
| ICD-10 code | Oncological diagnosis | 5 – > 4 years | 4 – > 3 years | 3 – > 2 years | 2 – > 1 years | 1 – > 0 years | N | Age at diagnosis (median) | N | Age at diagnosis (median) |
| **C00–C14** | Lip, oral cavity, pharynx | 10 | 10 | 26 | 20 | 18 | 64 | 58.8 | 20 | 52.9 |
| **C15–C26** | Digestive organs | 58 | 64 | 67 | 97 | 70 | 206 | 58.9 | 150 | 58.1 |
| C18–C20 | Colon, rectum | 39 | 40 | 39 | 60 | 39 | 116 | 60.0 | 101 | 58.3 |
| **C30–C39** | Respiratory organs, other intrathoracic organs | 23 | 27 | 24 | 31 | 36 | 79 | 60.0 | 62 | 61.0 |
| C33–C34 | Trachea, bronchi, lung | 14 | 20 | 16 | 30 | 29 | 54 | 60.2 | 55 | 61.1 |
| **C43** | Malignant melanoma of skin | 51 | 49 | 45 | 60 | 50 | 130 | 57.3 | 125 | 53.2 |
| **C50** | Breast | 149 | 152 | 175 | 183 | 103 | 4 | 46.7 | 758 | 54.0 |
| **C51–C58** | Female genital organs | 20 | 22 | 33 | 35 | 32 | — | — | 142 | 55.3 |
| C54–C55 | Corpus uteri | 12 | 9 | 13 | 18 | 18 | — | — | 70 | 59.4 |
| **C60–C63** | Male genital organs | 72 | 97 | 99 | 126 | 104 | 498 | 61.9 | — | — |
| C61 | Prostate | 65 | 84 | 91 | 117 | 97 | 454 | 62.6 | — | — |
| **C64–C68** | Urinary organs | 21 | 26 | 29 | 33 | 28 | 102 | 60.6 | 35 | 59.0 |
| C64 | Kidney, except renal pelvis | 12 | 18 | 17 | 19 | 19 | 61 | 59.5 | 24 | 58.7 |
| **C73–C75** | Thyroid gland, other endocrine glands | 17 | 21 | 25 | 11 | 20 | 23 | 45.0 | 71 | 51.0 |
| C73 | Thyroid gland | 17 | 20 | 25 | 11 | 19 | 22 | 44.8 | 70 | 51.2 |
| **C81–C96** | Lymphoid/hematopoetic/related tissue | 35 | 40 | 49 | 60 | 44 | 134 | 59.8 | 94 | 55.8 |
| C82–C88 | Non-Hodgkin lymphoma | 19 | 19 | 29 | 26 | 21 | 68 | 60.2 | 46 | 56.4 |
| C91–C95 | Leukemia | 8 | 11 | 13 | 18 | 19 | 41 | 62.4 | 28 | 56.9 |
| **Other** | Other, unspecific, unknown sites | 9 | 14 | 16 | 20 | 18 | 50 | 47.1 | 27 | 51.0 |
| **Total (2774)** | | **465** | **522** | **588** | **676** | **523** | **1290** | **60.2** | **1484** | **54.9** |

* Obtained through linkage with federal state cancer registries 2019 – 2024; prevalence in 1-year intervals, starting 5 years before study baseline (0 = baseline)

**eTable 2**

**Self-reported cancer information in NAKO**

| Type of tool | Assessment year participants, N | Question | Assessment | Other information collected |
|---|---|---|---|---|
| Recruitment examination | 2014–2019<br>N = 205 053 | Has a doctor ever diagnosed a malignant tumor (cancer), including in situ? | Topographic region (22 in men, 21 in women)<br>– e.g., mouth, stomach, intestine, breast, skin, prostate | • Age at first, second, third, and last cancer diagnosis<br>• Name and address of treating person |
| First written follow-up (2.5–3 years after recruitment) | 2016–2022<br>N = 170 226 | Has a doctor diagnosed a malignant tumor (cancer) since the last study visit? | Free text field to enter tumor type | • Year of diagnosis<br>• Name and address of treating person |
| Second examination | 2018–2024<br>N = 137 277 | Has a doctor diagnosed a malignant tumor (cancer) since the last study visit? | Topographic region comparable with recruitment examination | • Year of diagnosis<br>• Name and address of treating person |
| Second written follow-up 2.5–3 years after second examination | 2023–2026 | Has a doctor diagnosed a malignant tumor (cancer) since the last study visit? | Free text field to enter tumor type | • Year of diagnosis<br>• Name and address of treating person |
| Third examination | 2024–2028<br>N = 85 000 (planned) | Has a doctor diagnosed a malignant tumor (cancer) since the last NAKO examination? | Topographic region identical with recruitment examination | • Year of diagnosis<br>• Name and address of treating person |