BMJ Open

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| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2020-045491 |
| Article Type: | Original research |
| Date Submitted by the Author: | 04-Oct-2020 |
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| Keywords: | EPIDEMIOLOGY, Breast tumours < ONCOLOGY, Gynaecological oncology < ONCOLOGY |
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# Validity of self-reported diagnoses of gynecological and breast cancers in the Japan Nurses' Health Study

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## ABSTRACT

**Background** The validity of self-reported diagnoses of gynecological and breast cancers is controversial. We investigated it in a nationwide prospective cohort study of nursing professionals: the Japan Nurses' Health Study (JNHS)

**Methods** Data were reviewed for 15,717 subjects. The mean age at baseline was 41.6±8.3 years (median: 41), and the mean follow-up period was 10.5±3.8 years (median: 12). Participants are regularly mailed a follow-up questionnaire once every 2 years. Respondents who self-reported a positive cancer diagnosis were sent an additional confirmation questionnaire and contacted the diagnosing facility to confirm the diagnosis based on medical records. A review panel of experts verified the disease status. Regular follow-up, confirmation questionnaires, and expert review were validated for their positive predictive value (PPV) and negative predictive value (NPV).

**Results** New incidences were verified in 37, 47, 26, and 300 cervical, endometrial, ovarian, and breast cancer cases, respectively. The estimated incidence rates were 22.0, 25.4, 13.8 and 160.4 per 100,000 person-years. These were comparable to those of national data from regional cancer registries in Japan. For regular follow-up, the corresponding PPVs for cervical, endometrial, ovarian, and breast cancer were 16.9%, 54.2%, 45.1%, and 81.4%, and the NPVs were 100%, 99.9%, 99.9%, and 99.9%,

respectively. Adding the confirmation questionnaire improved the PPVs to 31.5%, 88.9%, 76.7%, and 99.9%; the NPVs were uniformly 99.9%. Expert review yielded PPVs and NPVs that were all ~100%.

**Conclusion** Gynecological cancer cannot be accurately assessed by self-reporting alone. Additionally, the external validity of cancer incidence in this cohort was confirmed.



## Strengths and limitations of this study

▸ This study investigated the validity of self-reporting of gynecologic and breast cancers in a large, nationwide prospective cohort study of nursing professionals, the Japan Nurses' Health Study (JNHS).

▸ Participants of JNHS cohort, which was composed entirely of female nursing professionals, are likely to answer the cancer history more accurately than general population.

▸ Periodic questionnaires, meticulous review of subjects' medical records and death-certificate surveys were employed to establish self-report validity, circumventing the limitations presented by Japan's lack of complete national cancer registries.

▸ Not all answer for confirmation questionnaire was sent back.

▸ There was relatively small number of young skew of the participants' ages in this cohort.

## INTRODUCTION

Self-reporting is frequently used to assess disease status in cohort research. The methodology's cost-effectiveness and feasibility make it an attractive approach in countries without comprehensive national disease registries such as Japan. However, the unreliability of self-reported information is problematic and can introduce errors into epidemiological investigations of risk factors, especially for new cancer incidences in a cohort. Self-reporting appears to accurately reflect diabetes status and surgical history of hysterectomies [1, 2]; however, body weight is often under-reported [3]. Regarding patients' cancer history, healthcare providers must consider that an affirmative response on a questionnaire is not equivalent to a definitive medical diagnosis because patients may remember incorrectly. Ideally, their answers should be corroborated against their medical records, but these typically cannot be acquired for an entire cohort. Additionally, validity can depend on background factors, such as ethnicity and cohort-specific characteristics, which further complicates interpreting self-report data.

The Japan Nurses' Health Study (JNHS) is a nationwide prospective cohort study of over 15,000 female nurses, which began in 2001 to ascertain how women's health is affected by lifestyle factors, healthcare practices, and physical status over their lifetime [4]. Here, we investigated the validity of self-reported diagnoses of three gynecological

cancers (i.e., cervical, endometrial, and ovarian) and breast cancer in our cohort. Also, we checked the external validity of our cohort by confirming the cancer incidence.

## METHODS

### Subjects

The JNHS is an ongoing prospective cohort study investigating the association between lifestyle, health care practices and women's health in Japan. Detailed information on its design, population, protocol, and sample-size calculations were published previously [4, 5]. Briefly, the baseline survey was conducted from 2001–2007, with planned follow-up for 30 years. In total, 15,019 women agreed to follow-up, signing and returning the informed-consent form with the completed survey. At the time of the baseline survey, the study population consisted of female licensed nursing professionals, including registered nurses, licensed practical nurses, public health nurses, and midwives, aged ≥25 years, and residing in Japan. Follow-up is currently ongoing; subjects are regularly mailed a self-administered questionnaire once every 2 years to complete and return by post.

Before initiating the JNHS, the feasibility of its research strategy and the validity of its questionnaires were investigated and confirmed in a pilot cohort study started in 1999 (the Gunma Nurses' Health Study; GNHS, n=698) [6, 7]. We combined the JNHS and

GNHS datasets in the present work as JNHS cohort (n=15,717). Table 1 shows the number of subjects in each age group. Women had a mean age at baseline of 41.6 (8.3) years (mean (SD) ; median: 41 years) and a mean follow-up of 10.5 (3.8) years (median: 12 years).

The JNHS Coordination and Data Center is located in the Epidemiological Research Office of the School of Health Sciences at Gunma University. This study was performed under the Declaration of Helsinki, the Guidelines for Good Epidemiology Practices [8], and the Japanese Ethical Guidelines for Epidemiological Research [9]. The GNHS study protocol was approved by the institutional review board of Gunma University, Japan (approval # 3, 1999), and the JNHS study protocol was approved by the institutional review board of Gunma University, Japan (approval #101, 2001) and the ethics review board of Japan's National Institute of Public Health, Japan (approval # 03007, 2003).

**Patient and Public Involvement statement**

This research was done without involving participants in defining the research question, outcome measures or study design. Participants were recruited with the study information to nursing society. They were not invited to comment on the design and to

interpret the results, and were not invited to contribute to the writing or editing of the manuscript. The results will be reported to participants in the JNHS newsletter, and also be posted on the Website of JNHS.

**Data collection and corroboration**

In the baseline and regular biennial follow-up questionnaires, women were asked, "Have you ever been diagnosed with breast cancer (cervical cancer, endometrial cancer, or ovarian cancer) by a medical doctor?", and if so, what was their age at first diagnosis. We identified and isolated those women who self-reported new incidences of one of the cancers of interest in the regular follow-up by July 2017.

To corroborate the self-reported positive cases, an additional confirmation questionnaire was sent to those women who affirmed a new cancer diagnosis in the regular follow-up. Subjects were again asked the same question as above and to provide details about their date of/age at diagnosis, method of detection, tumor stage, and treatment history. We also asked for permission to access their medical records; if they consented, we reviewed the records to obtain accurate clinical information on their condition. For gynecological cancers, the data collected included date of diagnosis, clinical stage, histological type, treatments, and concomitant cancer(s). For breast cancer,

the data included date of diagnosis, tumor site, invasivity, Tumor-Node-Metastasis classification (Union for International Cancer Control, 7th ed.) [10], diagnostic method(s), tumor size, mammography category, surgical procedure, histological classification, and pathological classification (i.e., regional lymph node involvement (pN) and hormone receptor positivity for estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor type2 (HER2)). This clinical information was furnished to an expert review panel comprising specialists on gynecological and breast cancers to verify each self-reported positive diagnosis.

In Japan, the clinical reporting of gynecologic cancers follows the Japan Society of Obstetrics and Gynecology (JSOG) staging system, which is based on the internationally recognized surgical staging system published by the International Federation of Gynecology and Obstetrics (FIGO). When the FIGO criteria were updated during the study period in 2011 [11], the JSOG system was revised in tandem to remove Stage 0 lesions from the corresponding definitions, i.e., cervical carcinoma *in situ* (CIS) and atypical endometrial hyperplasia from cervical and endometrial cancer, respectively. Therefore, stage 0 cancers were not considered positive in our primary analysis, and all medical records were double-checked for patients who self-reported a new incidence of gynecological cancer before 2011. These borderline cases were excluded.

If a subject was reported as deceased or inexplicably failed to complete any recent study activities, we established a cause of death by checking it against death certificate-related information in Japan's National Vital Statistics database.

**Validation**

Regular follow-up, confirmation questionnaires, and expert review were validated for their positive predictive value (PPV) and negative predictive value (NPV) for new incidences of each cancer.

For the first two sources, the validation sample included all members of the study cohort (n=15,717) who reported no past history of the cancer in question at baseline. The PPV of the regular follow-up was calculated as the number of verified positive cases of the cancer, i.e., cases whose self-reported positive diagnosis was verified by medical-record review or cause-of-death investigation, divided by all cases of self-reported new incidences of the cancer in the regular follow-up. The NPV was calculated as the number of suspected negative cases, divided by all members of the validation sample who self-reported no new cancer incidence in the regular follow-up. Here, the suspected negative cases consisted of all members of the validation sample for the cancer in question minus A) cases who self-reported new incidences in the regular follow-up and B) positive cases

whose status was established only by death certificate (DCO).

The PPV of the combined regular follow-up and confirmation questionnaire was calculated as the number of verified positive cases of the cancer divided by all cases who corroborated their positive diagnosis on the confirmation questionnaire. The NPV was calculated as the number of suspected negative cases divided by all members of the validation sample except those who self-reported their positive diagnosis on the confirmation questionnaire. Here, the suspected negative cases consisted of all members of the validation sample minus A) cases who self-reported their positive diagnosis on the confirmation questionnaire, B) cases ruled positive by DCO, C) cases ruled positive by cause-of-death investigation, and D) contradictory cases (i.e., women confirmed by expert review but self-reported a negative status on the confirmation questionnaire or left the field blank).

The expert review panel's judgments were also validated for comparison. In this analysis, the validation sample consisted of all participants who A) returned the confirmation questionnaire, B) permitted the research team to contact their diagnosing facility, and C) their provider agreed to respond to the team's inquiry. The PPV was calculated as the number of cases verified as positive by the diagnosing facility, divided by the number of cases ruled positive by the expert review panel. The NPV was calculated

as the number of cases verified as negative by the diagnosing facility, divided by the number of cases ruled negative by the panel.

After fixing the cancer cases, the incidence rate of each cancer was estimated from the observed events and person-time at risk for 10 years of observation. Because of the total numbers and events of the patients during the observation period, the 30–60 year-old age group was used. We calculated the 95% confidence intervals of the incidence rates based on the exact Poisson confidence interval in accordance with known methods [12].

## RESULTS

### Verified cases of each cancer type

The flow diagram illustrating the validation process of each cancer is listed in the Web Appendices. The numbers of new cases of self-reported cancers in the regular follow-up (and incidences in the respective validation sample) were cervical cancer: 219 (1.4%), endometrial cancer: 83 (0.5%), ovarian cancer: 51 (0.3%), and breast cancer: 365 (2.3%). New incidence was verified by expert review in 37, 45, 23, and 297 of these cases, respectively. Some subjects sent the confirmation questionnaire corroborating their positive diagnosis but were ruled negative by the expert panel (72.1%, 11.1%, 30.3%, and

1.0%, respectively), while 37.6%, 33.8%, 25.6%, and 8.3% of subjects, respectively, responded with negative diagnosis on the confirmation questionnaire.

For all observed cases of mortality, cause of death was established as being cervical cancer (n=4, DCO=0), endometrial cancer (n=7, DCO=2), ovarian cancer (n=3, DCO=3), or breast cancer (n=16, DCO=3). New incidences of the four cancers were verified in 37, 47, 26, and 300 cases, respectively.

In the JNHS cohort, the estimated incidence rates for patients aged 30–60 years were 22.0/100,000; 25.4/100,000; 13.8/100,000; and 160.4/100,000 person-years for cervical, endometrial, ovarian, and breast cancer, respectively (Table 2). Considering the lack of heterogeneity between this cohort and Japanese women overall, the incidence rates for each age group were compared with the national data from regional cancer registries in the 2015 statistics published by Japan's National Cancer Center [13] (Figure 1). For all four cancers, the cohort data did not deviate from the national data.

**Self-reported PPV/NPV for each cancer**

Table 3 summarizes the PPVs and NPVs for the regular follow-up, regular follow-up plus confirmation questionnaire, and expert review for the new incidence of each cancer.

Expert review achieved 100% accuracy for each cancer except cervical (PPV:

92.3%) because of a single false-positive case, which the participant's provider clarified to be a different condition.

Self-reporting achieved NPVs near 100% for all cancers for both the regular follow-up and the regular follow-up plus confirmation questionnaire. However, the corresponding PPVs tended to be somewhat lower and variable across cancers. The PPVs were worse for gynecological cancers than for breast cancer (breast > endometrial > ovarian > cervical, in descending order) for both follow-up sources. The PPV for uterine cancer, which included cervical and endometrial cancers, was 27.2%.

The regular follow-up plus confirmation questionnaire achieved higher PPVs in all cases than did regular follow-up alone; however, while it achieved 99.0% accuracy for breast cancer, the estimates were lower for endometrial (88.9%) and ovarian (76.7%) cancer and poor for cervical cancer (31.5%).

Considering the changes to the official JSOG clinical staging system during the survey period, we calculated a similar summary for PPVs and NPVs, adding cases of cervical CIS, atypical endometrial hyperplasia, and borderline ovarian tumors (Table 4).

The resulting PPVs were uniformly higher when all three cancers were included than when they were excluded. For endometrial and ovarian cancer, the improvements ranged from 3.3%–6.7%, but for cervical cancer, their inclusion almost doubled the

predictive value for both the regular follow-up and regular follow-up plus confirmation questionnaire, at +20.1% and +37.9%, respectively.

## DISCUSSION

In the JNHS cohort, self-reporting in regular follow-up achieved a PPV of 81.4% for breast cancer but performed poorer for gynecological cancers, especially uterine cancers (PPV: 27.2%) and cervical cancer alone (PPV: 16.9%). Our PPVs were higher than the corresponding values reported by the Japan Public Health Center (JPHC) Study, a population-based prospective cohort study (all cancers in women: 54.2%, breast: 58.4%, uterine: 21.7%) [14]. The validity of self-reporting is associated with individual characteristics [15], and our cohort consisted entirely of nursing professionals. While evidence suggests that educational level has a negligible association with validity [16], we partially attribute the high self-reporting accuracy to the uniformly high level of medical education and deeper knowledge of cancer in our cohort than in the general population. Other studies support this argument [17]. However, sizeable percentages of nurses who affirmed new incidences of cancer in the regular follow-up gave the opposite response on the confirmation questionnaire (gynecological cancer: 25.6%–37.6%, breast cancer:

8.3%). Similarly, considerable percentages of respondents to the confirmation questionnaire were verified not to have cancer (gynecological cancer: 41.2%–81.2%, breast cancer: 9.2%). Many who corroborated their self-reported positive diagnosis were eventually ruled negative by expert review, especially for cervical cancer (72.1%), followed by ovarian (30.3%), endometrial (11.1%) and breast (1.0%). In summary, self-reporting alone apparently fails to capture the real cancer incidence, even for this cohort of nursing professionals with uniformly high medical knowledge. Additional inquiries to confirm the details are needed.

Compared to PPVs of self-report validity in other prospective cohort study datasets [16, 18, 19], our PPVs were comparable to the literature values for breast cancer but lower than these values for uterine cancers. Many studies have shown that self-reporting of breast cancer has high PPVs [10, 16, 19]. Some evidence has linked higher educational levels with a greater risk of breast cancer [20], which may also be true for our cohort. Additionally, breast cancer diagnoses included ductal carcinoma *in situ*, which may have led to less confusion than with gynecological cancers that excluded stage 0 cases and borderline tumors.

Studies outside of Japan have also found self-reporting to yield lower PPVs for uterine cancers than for other cancers [18, 21], for several possible reasons. One is inaccurate

memory of precancerous cervical lesions, which are rarely addressed immediately by surgical intervention. Additionally, age and sex may have some association; for example, participants >50 years old in a Native American cohort were more likely to report incorrectly [22]. Further, a study from Australia found that self-reported breast cancer had lower PPVs in women aged 70–75 years [23]. Disease-specific considerations may also be relevant. One study noted that many cases of women's cancers, especially cervical cancer, are not recorded in cancer registries [22], while another estimated false-negative rates of 43.8%, 28.6%, and 20.8% for self-reports of uterine, ovarian, and breast cancers, respectively [24]. Differences in incidence must also be considered. Because gynecological cancers are >5 times less prevalent than breast cancer, a difference of one case would produce a proportionally larger change in PPV.

One problem specific to Japan regarding the self-reporting of women's cancers is how the results of cytological screening tests are reported for cervical and endometrial cancers. Today, Pap smear results are recorded using the Bethesda system, the standard international format, but these results previously followed a class-based system. Class II status, which shows within the normal range is sometimes confused with stage II cervical cancer. Similarly, atypical endometrial hyperplasia was previously classified as stage 0 endometrial cancer, which may be confused with non-atypical endometrial hyperplasia.

We suspect that another reason the self-report validity in our cohort was so poor for certain cancers was that subjects were recalling their past medical history during the regular follow-up, rather than the new incidence as intended. Additionally, ambiguous language in the questionnaire, such as “dysplasia” or “precancerous lesions”, may have reduced the self-report validity, as evidenced by the higher PPVs for borderline forms, such as cervical CIS, atypical endometrial hyperplasia, and borderline ovarian tumors included in the analysis. Among the three borderline forms, classifying cervical CIS as cervical cancer led to a greater increase in PPVs than did other cancers. Manjer et al. also found that self-reporting of malignant cervical cancer was less sensitive when the definition included cervical CIS [25]. These considerations suggest that compared with other cancers, diagnoses of cervical cancer and precancerous lesions have a greater risk of being inaccurately communicated or negatively interpreted by patients.

One of this study’s strengths was our meticulous review of subjects’ medical records and death-certificate surveys to establish self-report validity, circumventing the limitations presented by Japan’s lack of complete national cancer registries. Additionally, we believe that our data better reflect the general Japanese population than did past findings for other regional cohorts because the nationwide scope of the JNHS minimizes the geographical variation. Moreover, our cohort was relatively homogenous in terms of

sex and occupation, consisting entirely of female nursing professionals.

The study also had some limitations. Cohort-specific characteristics may limit the generalizability of our findings, especially the relatively young skew of the participants' ages. However, when converted to incidence rates, our rates seem most consistent with the 2015 statistics published by Japan's National Cancer Center [13]. Additionally, self-reported diagnoses could not be verified in some cases. Our expert panel made their judgments based on the specific language nurses used in the questionnaire to describe their treatments such as "hysterectomy" and "chemotherapy", but the panel still encountered cases that were difficult to definitively verify. However, we established a conclusive diagnosis based on all available information such as postmortem exam findings and supplemental details from primary-care providers. No indeterminate cases were found among those lacking medical records for verification.

The JNHS database covers all of Japan. The confirmation of external validity of these cancer incidence in this cohort will allow the further investigation of risk factors for different cancers such as menopausal hormone therapy and lifestyle factors and their associations, with unaffected by information bias. We plan to continue our work by analyzing the respective contributions of different risk factors among confirmed cases of gynecological and breast cancer, as verified above.

**Acknowledgments** The authors appreciate the cooperation of the Japanese nurses who participate in the JNHS and the GNHS. We also thank Ms. Satomi Shimizu at the JNHS Data Center for her help with data management.

**Contributors** KT was the panel member and wrote the initial draft of the paper to which all authors contributed. YI, NM, and KN collected data and analyzed. MK and TY were panel members and revised manuscript. KH designed the study, raised funding, and directed its implementation including quality assurance and control.

**Funding** This work was partly supported by a grant from the Japan Society for the Promotion of Science (JSPS KAKENHI Grant Number: 18H04069).

**Competing interests** None declared.

**Patient consent for publication** Not required.

**Data sharing statement** The data are not publically available due to data transfer agreements. No additional data is available.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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## Figure and table legends

**Figure 1** Estimated incidence rates for each age group in the JNHS cohort and the national data from regional cancer registries.

(error bars shows the 95% confidence intervals)

A. cervical cancer

B. endometrial cancer

C. ovarian cancer

D. breast cancer

**Table 1** Numbers and percentages of subjects in each age group at baseline in the JNHS cohort

**Table 2** Estimated incidence rate of each cancer in patients aged 30–60 years in the JNHS cohort

**Table 3** PPVs/NPVs for regular follow-up, regular follow-up plus confirmation questionnaire, and expert review for new incidences of gynecological and breast cancers in the JNHS cohort

**Table 4** Corresponding PPVs/NPVs including those of cervical CIS, atypical endometrial hyperplasia, and borderline ovarian tumor in the JNHS cohort

**Appendix legends**

**Appendix Figure 1** Flow diagram illustrating the validation process for self-reported cervical cancer (BL: baseline, CIS: carcinoma in situ, DCO: death certificate only)

**Appendix Figure 2** Flow diagram illustrating the validation process for self-reported endometrial cancer (BL: baseline, aEmH: atypical endometrial hyperplasia, DCO: death certificate only)

**Appendix Figure 3** Flow diagram illustrating the validation process for self-reported ovarian cancer (BL: baseline, DCO: death certificate only)

**Appendix Figure 4** Flow diagram illustrating the validation process for self-reported breast cancer (BL: baseline, CIS: carcinoma in situ, DCO: death certificate only)

**Table 1** Numbers and percentages of subjects in each age group at baseline in the JNHS cohort

| Age (years) | n | (%) |
|---|---|---|
| < 30 | 692 | (4.4) |
| 30 – 34 | 2,955 | (18.8) |
| 35 – 39 | 3,176 | (20.2) |
| 40 – 44 | 3,133 | (19.9) |
| 45 – 49 | 2,767 | (17.6) |
| 50 – 54 | 2,012 | (12.8) |
| 55 – 59 | 797 | (5.1) |
| 60 – 64 | 143 | (0.9) |
| ≥ 65 | 42 | (0.3) |

**Table 2** Estimated incidence rate of each cancer in patients aged 30 to 60 years in the JNHS cohort

| | Cancer cases | Person-years | Incidence rate (per 100,000 person-years) | Lower limit of 95% confidence interval | Upper limit of 95% confidence interval |
|---|---|---|---|---|---|
| Cervical cancer | 29 | 131,658.50 | 22.0 | 14.8 | 31.6 |
| Endometrial cancer | 32 | 126041.0 | 25.4 | 17.4 | 35.8 |
| Ovarian cancer | 18 | 130662.5 | 13.8 | 8.2 | 21.8 |
| Breast cancer | 210 | 130960.5 | 160.4 | 139.4 | 183.6 |

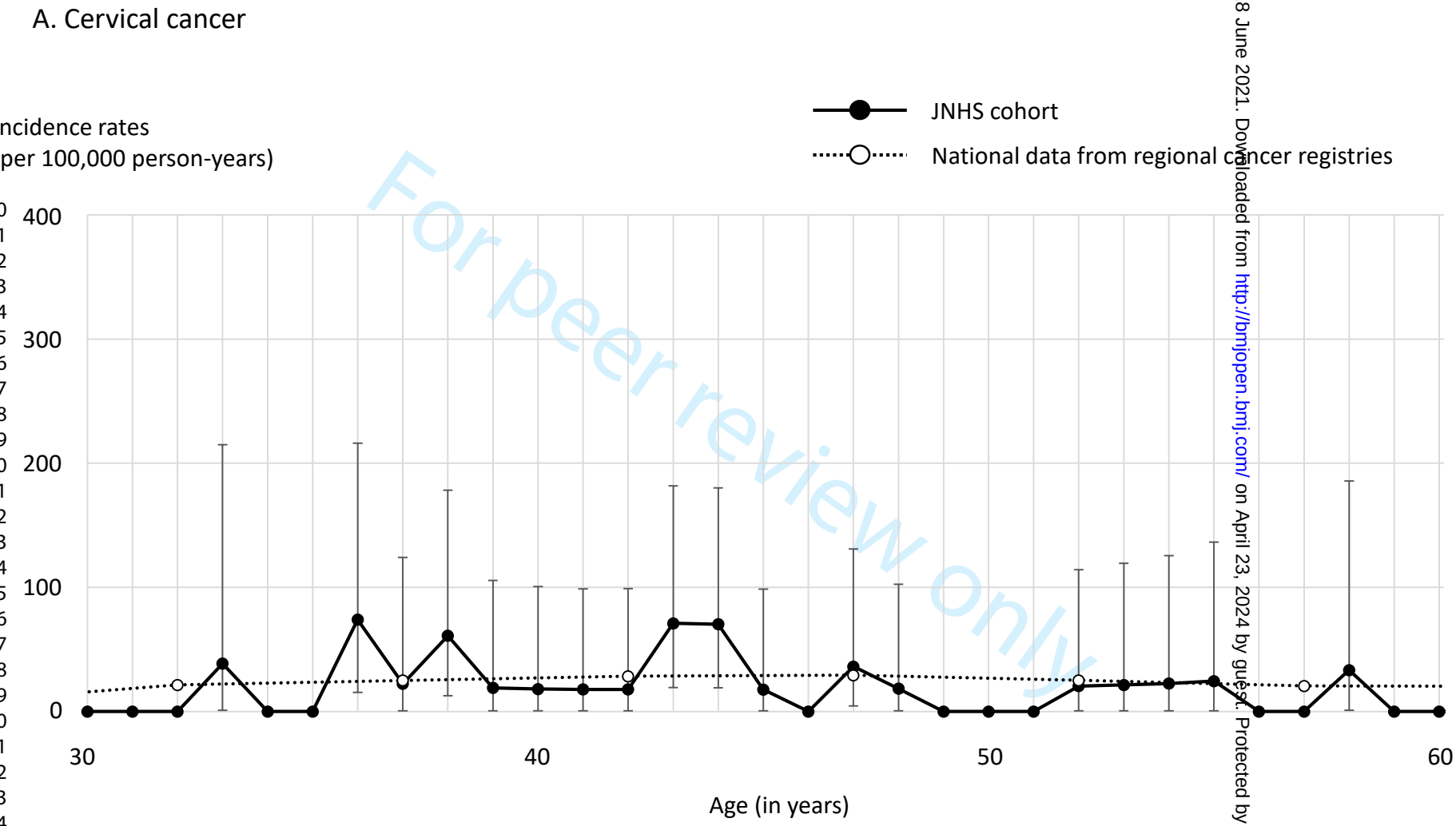
**Table 3** PPVs/NPVs of regular follow-up, regular follow-up plus confirmation questionnaire, and expert review for new incidences of gynecological and breast cancers in the JNHS cohort

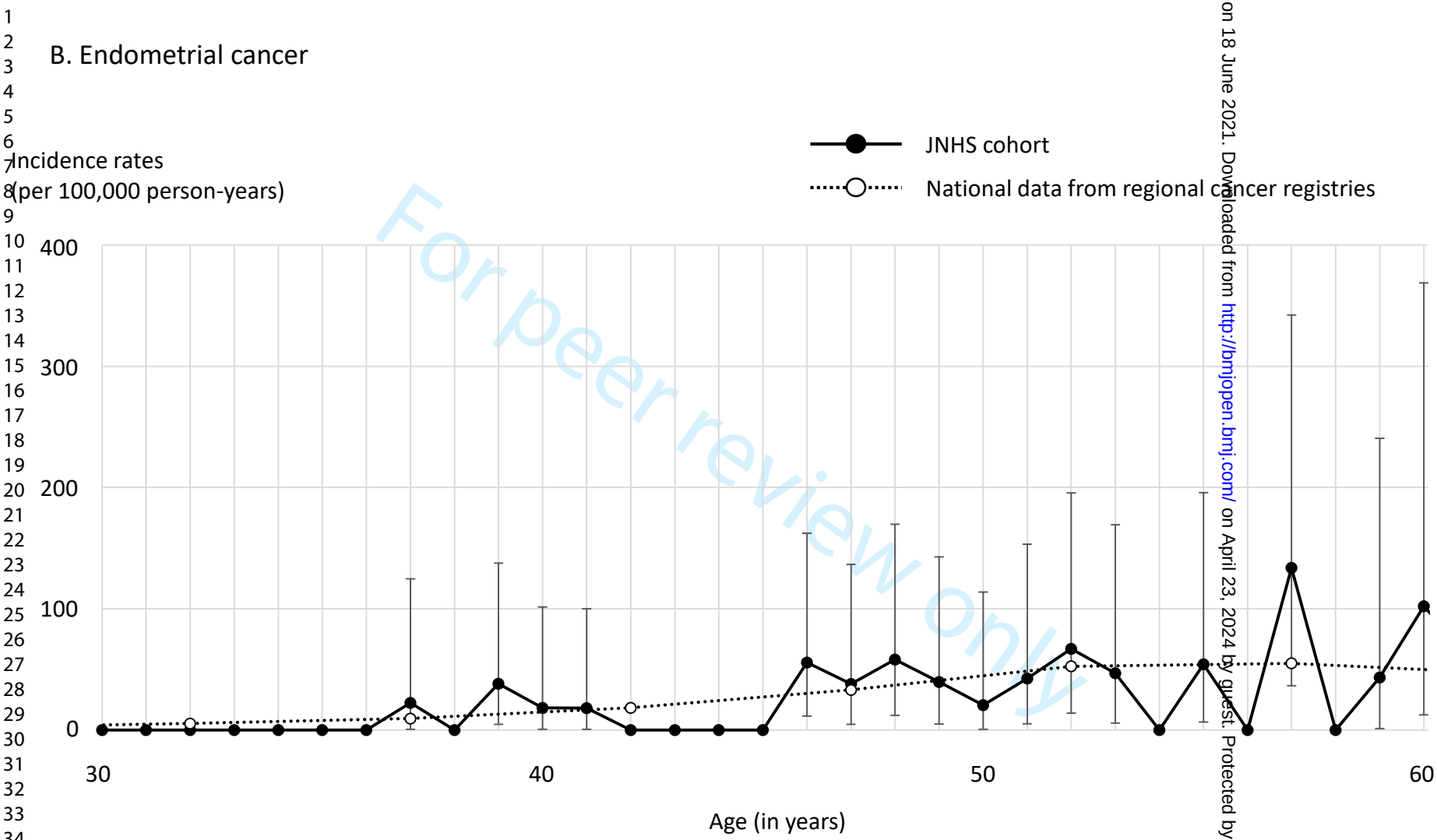
| | Positive history self-reported at baseline | Validation sample | Positive diagnosis self-reported in regular follow-up | Positive status established by cause-of-death investigation (incl. DCO cases) | Regular follow-up | | Regular follow-up plus confirmation questionnaire | | Expert review | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | PPV | NPV | PPV | NPV | PPV | NPV |
| Cervical cancer | 167 | 15,550 | 219 | 2 (0) | 16.9% | 100.0% | 31.5% | 99.9% | 92.3% | 100.0% |
| Endometrial cancer | 31 | 15,686 | 83 | 7 (2) | 54.2% | 99.9% | 88.0% | 99.9% | 100.0% | 100.0% |
| Ovarian cancer | 37 | 15,680 | 51 | 3 (3) | 45.1% | 99.9% | 76.5% | 99.9% | 100.0% | 100.0% |
| Breast cancer | 138 | 15,579 | 365 | 5 (3) | 81.4% | 99.9% | 99.2% | 99.9% | 100.0% | 100.0% |

**Table 4** Corresponding PPVs/NPVs including cervical CIS, atypical endometrial hyperplasia, and borderline ovarian tumors in the JNHS cohort

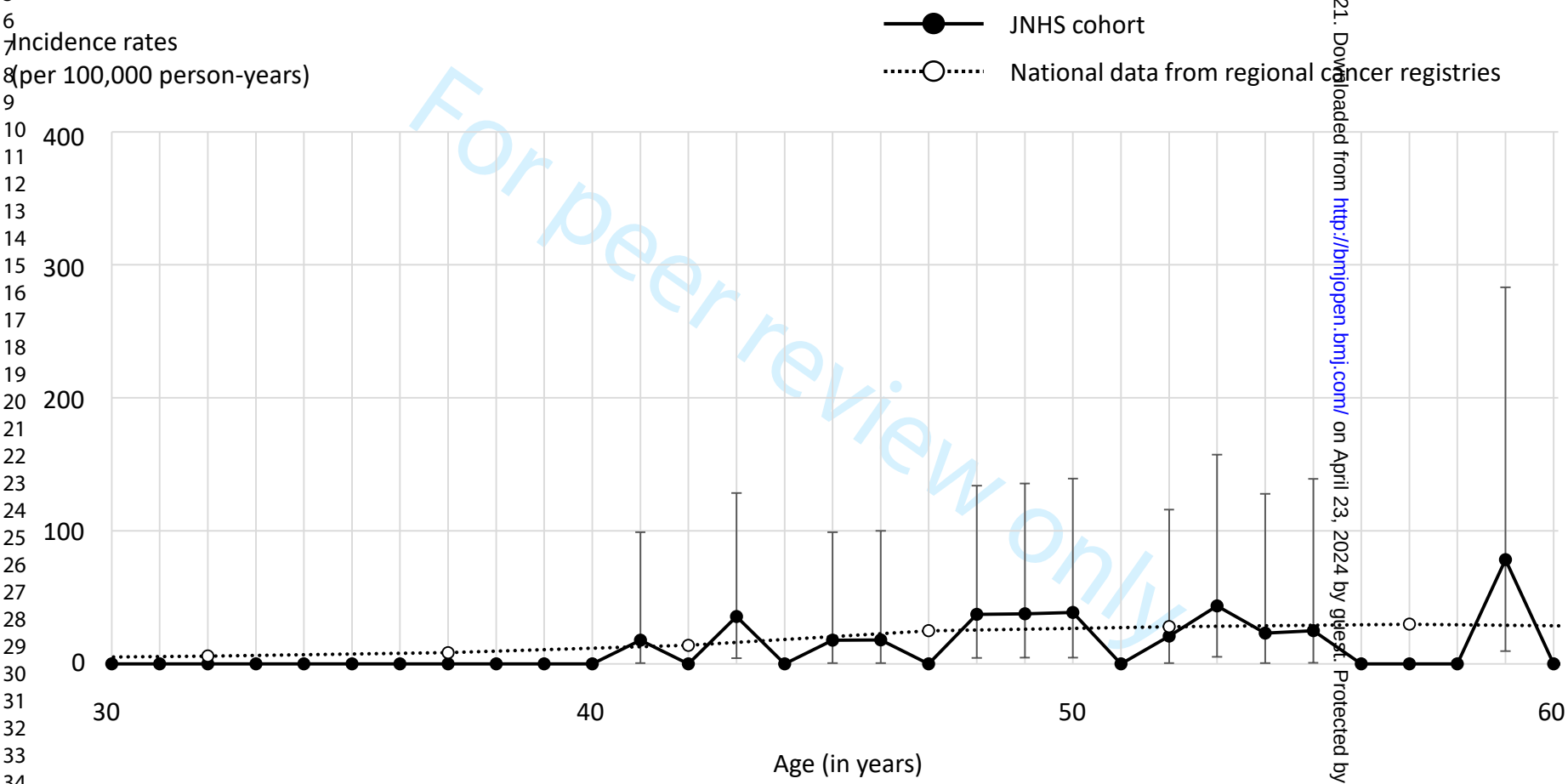
| | Positive history self-reported at baseline | Validation sample | Positive diagnosis self-reported in regular follow-up | Positive status established by cause-of-death investigation (incl. DCO cases) | Regular follow-up | | Regular follow-up plus confirmation questionnaire | |
|---|---|---|---|---|---|---|---|---|
| | | | | | PPV | NPV | PPV | NPV |
| Cervical cancer | 167 | 15,550 | 219 | 2 (0) | 37.0% | 100.0% | 69.4% | 99.9% |
| Endometrial cancer | 31 | 15,686 | 83 | 7 (2) | 57.8% | 99.9% | 95.6% | 99.9% |
| Ovarian cancer | 37 | 15,680 | 51 | 3 (3) | 49.0% | 99.9% | 80.0% | 99.9% |

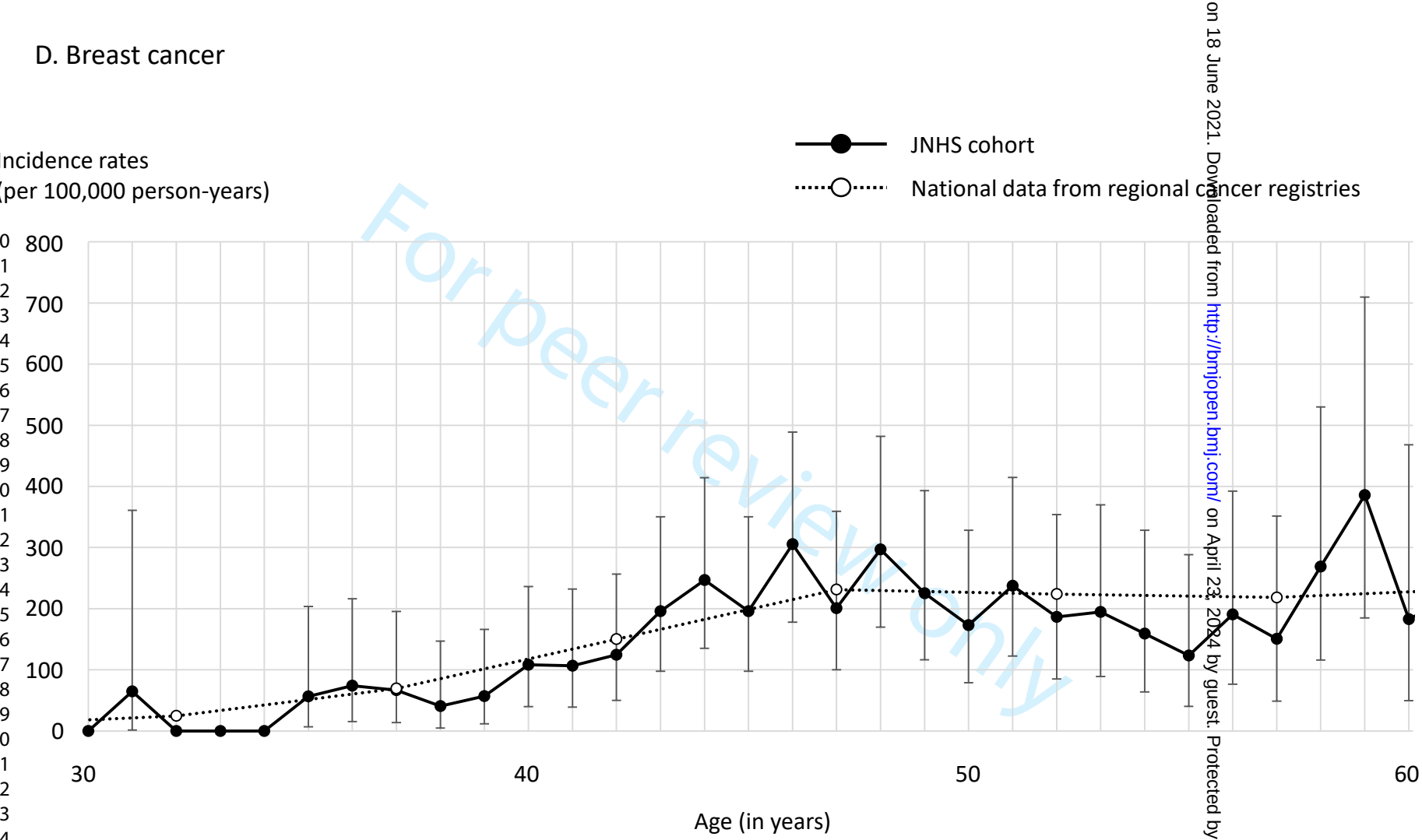
**Figure 1** Estimated incidence rates for each age group in the JNHS cohort and the national data from regional cancer registries (error bars shows 95% confidence intervals)



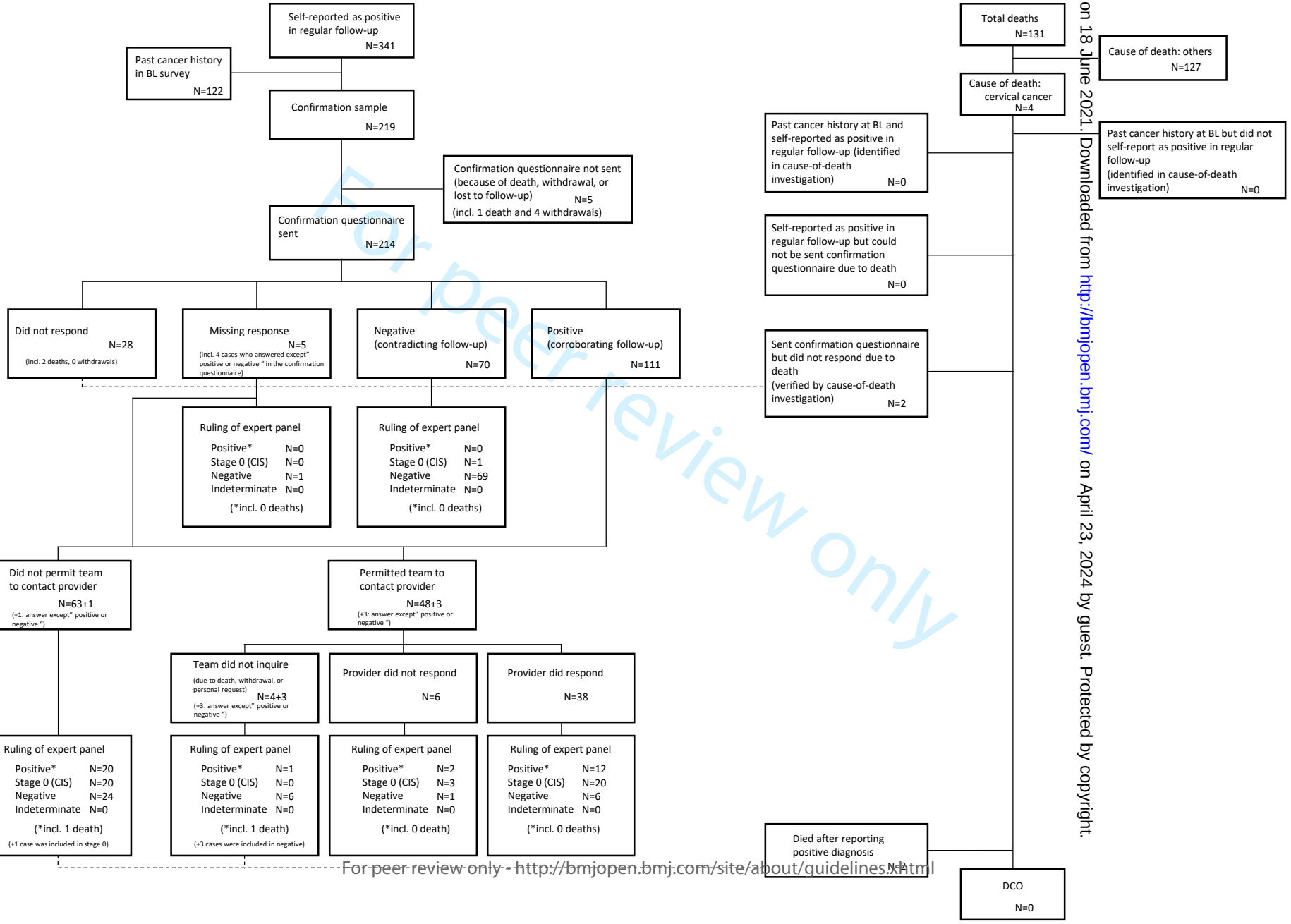


C. Ovarian cancer

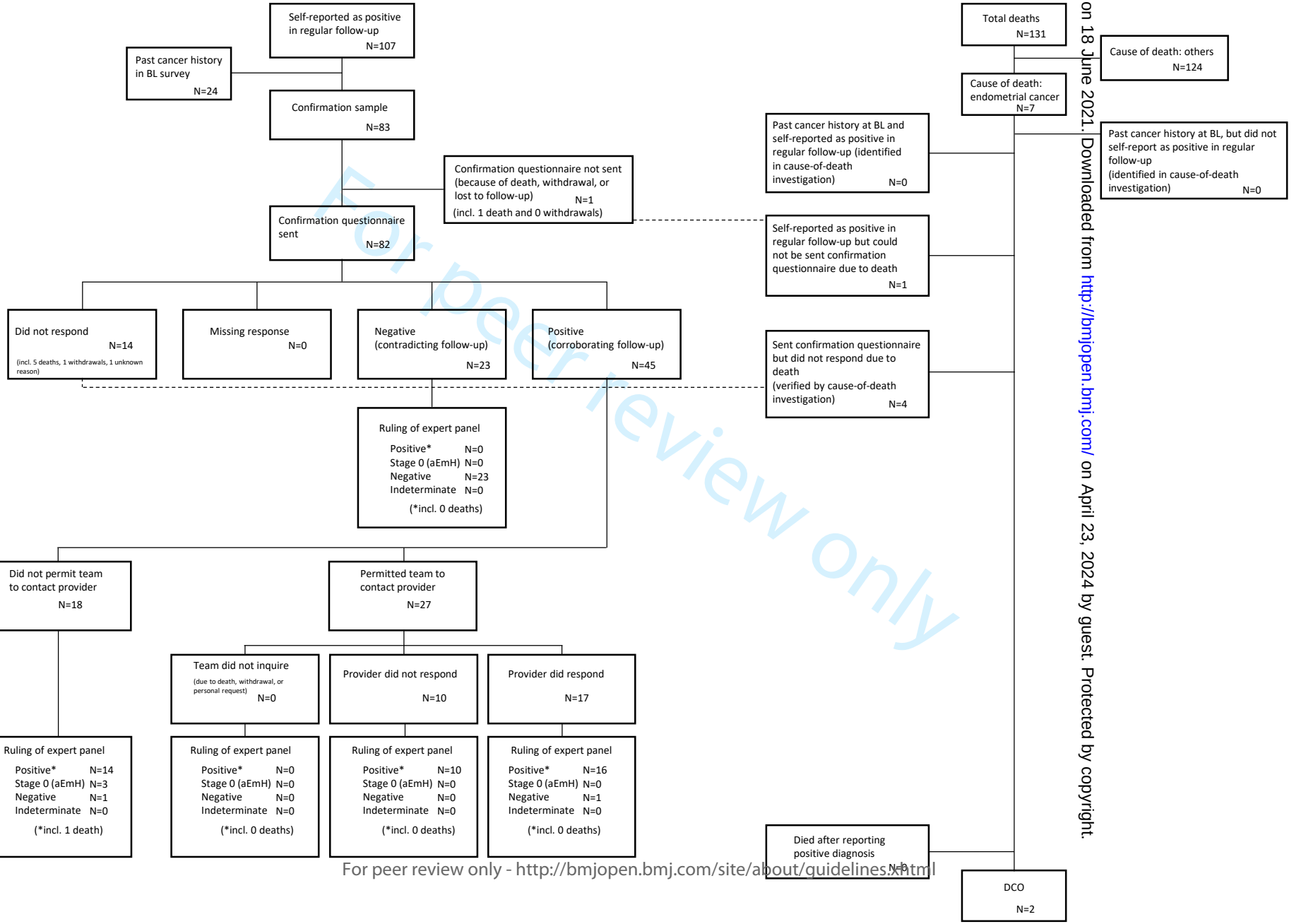




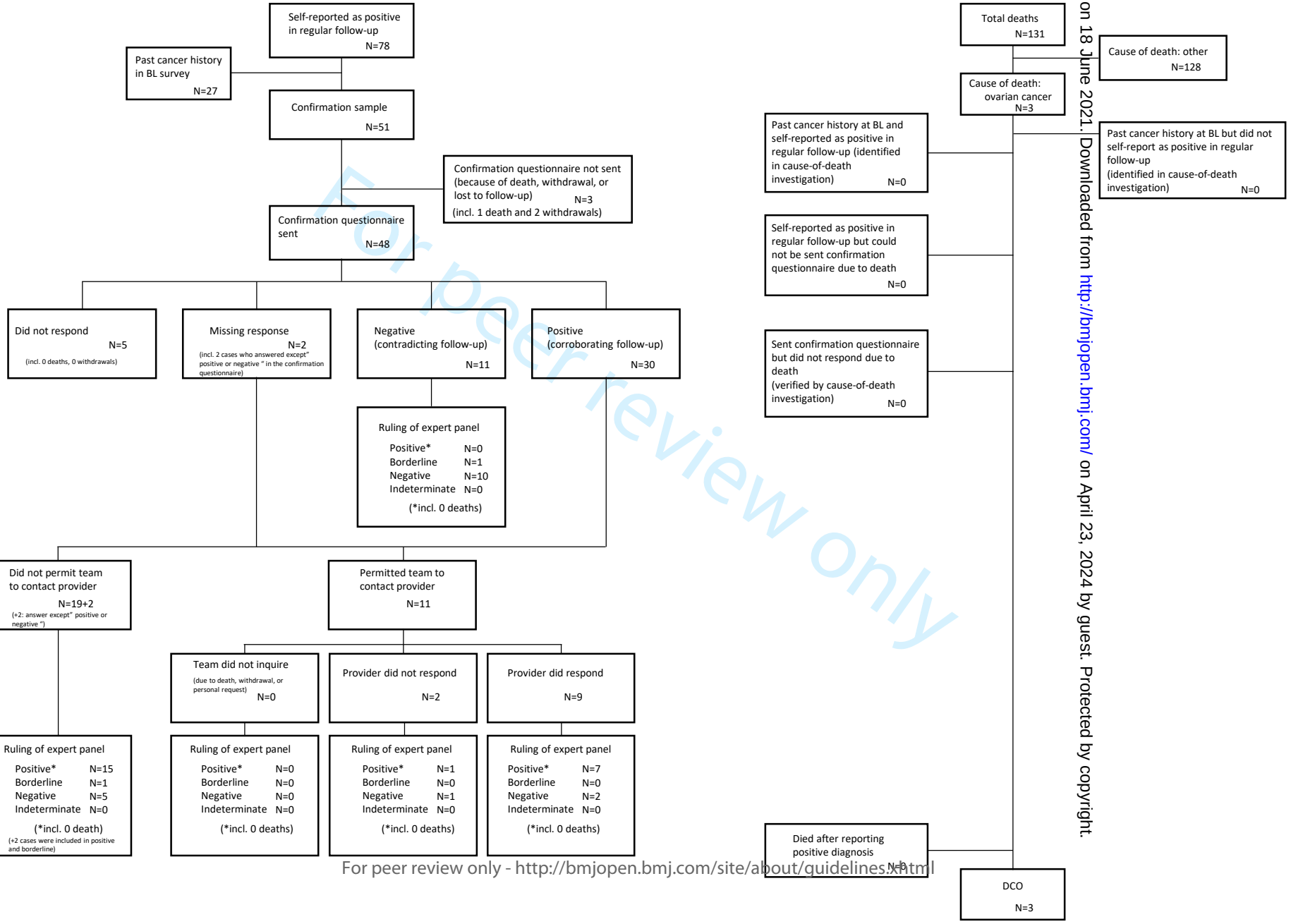
**Appendix Figure 1** Flow diagram illustrating the validation process for self-reported cervical cancer (BL: baseline, CIS: carcinoma in situ, DCO: death certificate only)



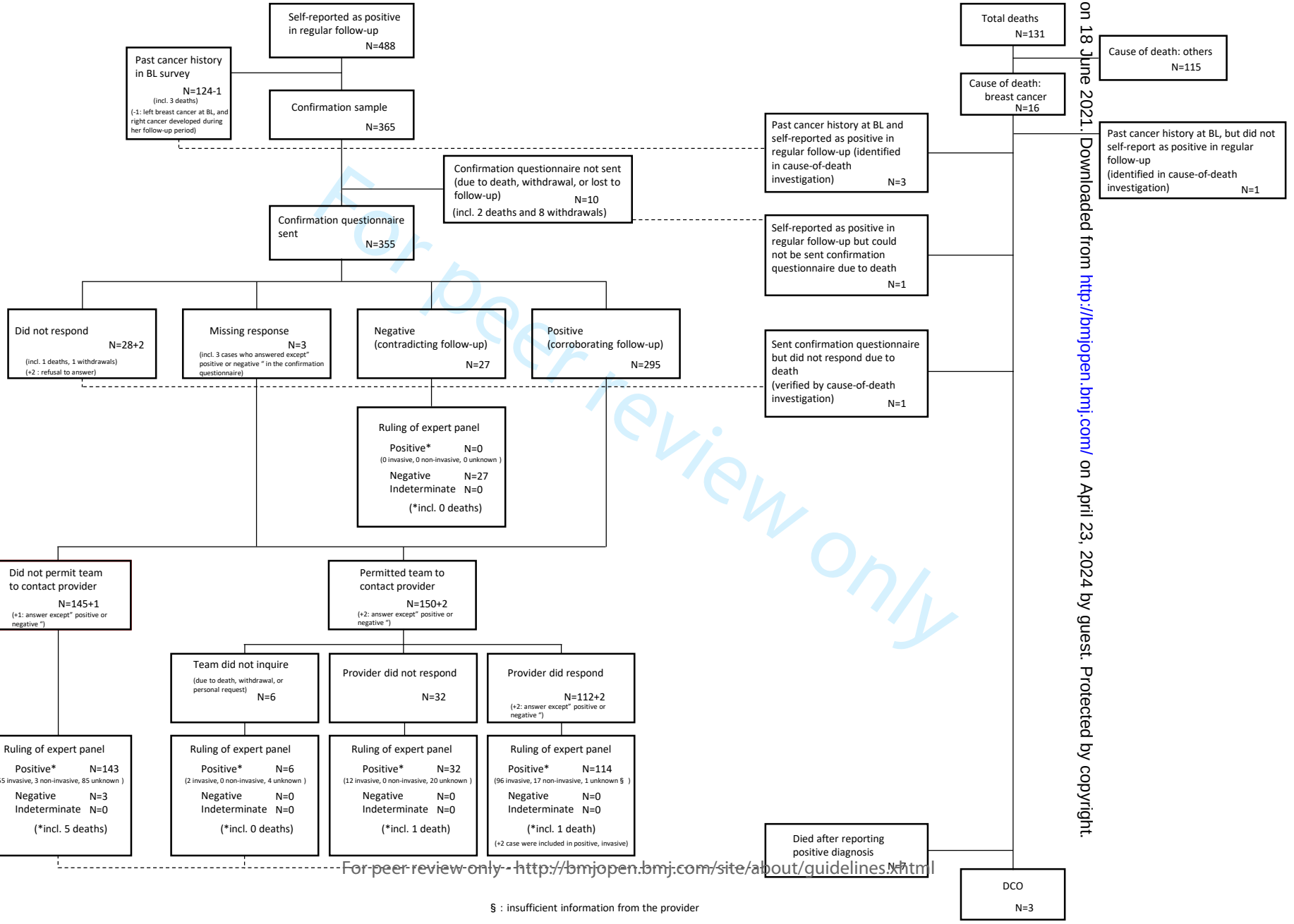
**Appendix Figure 2** Flow diagram illustrating the validation process for self-reported endometrial cancer (BL: baseline, aEmH: atypical endometrial hyperplasia, DCO: death certificate only)



**Appendix Figure 3** Flow diagram illustrating the validation process for self-reported ovarian cancer (BL: baseline, DCO: death certificate only)



**Appendix Figure 4** Flow diagram illustrating the validation process for self-reported breast cancer (BL: baseline, CIS: carcinoma in situ, DCO: death certificate only)



BMJ Open

# Validity of self-reported diagnoses of gynecological and breast cancers in a prospective cohort study: the Japan Nurses' Health Study

| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2020-045491.R1 |
| Article Type: | Original research |
| Date Submitted by the Author: | 04-Mar-2021 |
| Complete List of Authors: | Takamatsu, Kiyoshi; Tokyo Dental College Ichikawa General Hospital, Obstetrics and Gynecology<br>Ideno, Yuki; Gunma University, Center for Mathematics and Data Science<br>Kikuchi, Mami; Gunma University Hospital, Center of Regional Medical Research and Education<br>Yasui, Toshiyuki; University of Tokushima Graduate School of Biomedical Sciences, Department of Reproductive and Menopausal Medicine<br>Maruoka, Naho; Gunma University Graduate School of Health Sciences, Department of International/Community Health Laboratory Sciences<br>Nagai, Kazue; Gunma University Graduate School of Health Sciences, Gunma University, Department of International/Community Health Laboratory Sciences<br>Hayashi, Kunihiko; Gunma University Graduate School of Health Sciences, Department of International/Community Health Laboratory Sciences |
| Primary Subject Heading: | Epidemiology |
| Secondary Subject Heading: | Obstetrics and gynaecology |
| Keywords: | EPIDEMIOLOGY, Breast tumours < ONCOLOGY, Gynaecological oncology < ONCOLOGY |
| | |

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# Validity of self-reported diagnoses of gynecological and breast cancers in a prospective cohort study: the Japan Nurses' Health Study

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## ABSTRACT

**Objectives** To validate the self-reported diagnoses of gynecological and breast cancers in a nationwide prospective cohort study of nursing professionals: the Japan Nurses' Health Study (JNHS)

**Design and setting** Retrospective analysis of the Japan Nurses' Health Study (JNHS)

**Participants and measures** Data were reviewed for 15,717 subjects. The mean age at baseline was 41.6±8.3 years (median: 41), and the mean follow-up period was 10.5±3.8 years (median: 12). Participants are regularly mailed a follow-up questionnaire once every 2 years. Respondents who self-reported a positive cancer diagnosis were sent an additional confirmation questionnaire and contacted the diagnosing facility to confirm the diagnosis based on medical records. A review panel of experts verified the disease status. Regular follow-up, confirmation questionnaires, and expert review were validated for their positive predictive value (PPV) and negative predictive value (NPV).

**Results** New incidences were verified in 37, 47, 26, and 300 cervical, endometrial, ovarian, and breast cancer cases, respectively. The estimated incidence rates were 22.0, 25.4, 13.8 and 160.4 per 100,000 person-years. These were comparable to those of national data from regional cancer registries in Japan. For regular follow-up, the corresponding PPVs for cervical, endometrial, ovarian, and breast cancer were 16.9%,

54.2%, 45.1%, and 81.4%, and the NPVs were 100%, 99.9%, 99.9%, and 99.9%, respectively. Adding the confirmation questionnaire improved the PPVs to 31.5%, 88.9%, 76.7%, and 99.9%; the NPVs were uniformly 99.9%. Expert review yielded PPVs and NPVs that were all ~100%.

**Conclusions** Gynecological cancer cannot be accurately assessed by self-reporting alone. Additionally, the external validity of cancer incidence in this cohort was confirmed.



**Strengths and limitations of this study**

- This study investigated the validity of self-reporting of gynecologic and breast cancers in a large, nationwide prospective cohort study of nursing professionals, the Japan Nurses' Health Study (JNHS).
- Participants of JNHS cohort, which was composed entirely of female nursing professionals, are likely to answer the cancer history more accurately than general population.
- Periodic questionnaires, meticulous review of subjects' medical records and death-certificate surveys were employed to establish self-report validity, circumventing the limitations presented by Japan's lack of complete national cancer registries.
- Not all answers for confirmation questionnaire were obtained.

▸ There was relatively small number of young participants in this cohort.

## INTRODUCTION

Self-reporting is frequently used to assess disease status in cohort research. The methodology's cost-effectiveness and feasibility make it an attractive approach in countries without comprehensive national disease registries such as Japan. However, the unreliability of self-reported information is problematic and can introduce errors into epidemiological investigations of risk factors, especially for new cancer incidences in a cohort. Self-reporting appears to accurately reflect diabetes status and surgical history of hysterectomies [1, 2]; however, body weight is often under-reported [3]. Regarding patients' cancer history, healthcare providers must consider that an affirmative response on a questionnaire is not equivalent to a definitive medical diagnosis because patients may remember incorrectly. Ideally, their answers should be corroborated against their medical records, but these typically cannot be acquired for an entire cohort. Additionally, validity can depend on background factors, such as ethnicity and cohort-specific characteristics, which further complicates interpreting self-report data. In this sense, validation of self-reported diagnoses of gynecological and breast cancers is not clear in Japan.

The Japan Nurses' Health Study (JNHS) is a nationwide prospective cohort study

of over 15,000 female nurses, which began in 2001 to ascertain how women's health is affected by lifestyle factors, healthcare practices, and physical status over their lifetime [4]. Here, we investigated the validity of self-reported diagnoses of three gynecological cancers (i.e., cervical, endometrial, and ovarian) and breast cancer in our cohort. Also, we checked the external validity of our cohort by confirming the cancer incidence.

## METHODS

### Subjects

The JNHS is an ongoing prospective cohort study investigating the association between lifestyle, health care practices and women's health in Japan. Detailed information on its design, population, protocol, and sample-size calculations were published previously [4, 5]. Briefly, the baseline survey was conducted from 2001–2007, with planned follow-up for 30 years. In total, 15,019 women agreed to follow-up, signing and returning the informed-consent form with the completed survey. At the time of the baseline survey, the study population consisted of female licensed nursing professionals, including registered nurses, licensed practical nurses, public health nurses, and midwives, aged ≥25 years, and residing in Japan. Follow-up is currently ongoing; subjects are regularly mailed a self-administered questionnaire once every 2 years to complete and return by post.

Before initiating the JNHS, the feasibility of its research strategy and the validity of its questionnaires were investigated and confirmed in a pilot cohort study started in 1999 (the Gunma Nurses' Health Study; GNHS, n=698) [6, 7]. We combined the JNHS and GNHS datasets in the present work as JNHS cohort (n=15,717). Table 1 shows the number of subjects in each age group. Women had a mean age at baseline of 41.6 (8.3) years (mean (SD) ; median: 41 years) and a mean follow-up of 10.5 (3.8) years (median: 12 years).

The JNHS Coordination and Data Center is located in the Epidemiological Research Office of the School of Health Sciences at Gunma University. This study was performed under the Declaration of Helsinki, the Guidelines for Good Epidemiology Practices [8], and the Japanese Ethical Guidelines for Epidemiological Research [9]. The GNHS study protocol was approved by the institutional review board of Gunma University, Japan (approval # 3, 1999), and the JNHS study protocol was approved by the institutional review board of Gunma University, Japan (approval #101, 2001) and the ethics review board of Japan's National Institute of Public Health, Japan (approval # 03007, 2003).

**Patient and Public Involvement statement**

This research was done without involving participants in defining the research question, outcome measures or study design. Participants were recruited with the study information to nursing society. They were not invited to comment on the design and to interpret the results, and were not invited to contribute to the writing or editing of the manuscript. The results will be reported to participants in the JNHS newsletter, and also be posted on the Website of JNHS.

**Data collection and corroboration**

In the baseline and regular biennial follow-up questionnaires, women were asked, "Have you ever been diagnosed with breast cancer (cervical cancer, endometrial cancer, or ovarian cancer) by a medical doctor?", and if so, what was their age at first diagnosis. We identified and isolated those women who self-reported new incidences of one of the cancers of interest in the regular follow-up by July 2017.

To corroborate the self-reported positive cases, an additional confirmation questionnaire was sent to those women who affirmed a new cancer diagnosis in the regular follow-up. Subjects were again asked the same question as above and to provide details about their date of/age at diagnosis, method of detection, tumor stage, and treatment history. We also asked for permission to access their medical records; if they

consented, we reviewed the records to obtain accurate clinical information on their condition. For gynecological cancers, the data collected included date of diagnosis, clinical stage, histological type, treatments, and concomitant cancer(s). For breast cancer, the data included date of diagnosis, tumor site, invasivity, Tumor-Node-Metastasis classification (Union for International Cancer Control, 7th ed.) [10], diagnostic method(s), tumor size, mammography category, surgical procedure, histological classification, and pathological classification (i.e., regional lymph node involvement (pN) and hormone receptor positivity for estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor type2 (HER2)). This clinical information was furnished to an expert review panel comprising specialists on gynecological and breast cancers to verify each self-reported positive diagnosis.

In Japan, the clinical reporting of gynecologic cancers follows the Japan Society of Obstetrics and Gynecology (JSOG) staging system, which is based on the internationally recognized surgical staging system published by the International Federation of Gynecology and Obstetrics (FIGO). When the FIGO criteria were updated during the study period in 2011 [11], the JSOG system was revised in tandem to remove Stage 0 lesions from the corresponding definitions, i.e., cervical carcinoma *in situ* (CIS) and atypical endometrial hyperplasia from cervical and endometrial cancer, respectively. Therefore,

stage 0 cancers were not considered positive in our primary analysis, and all medical records were double-checked for patients who self-reported a new incidence of gynecological cancer before 2011. These borderline cases were excluded.

If a subject was reported as deceased or inexplicably failed to complete any recent study activities, we established a cause of death by checking it against death certificate-related information in Japan's National Vital Statistics database.

**Validation**

Regular follow-up, confirmation questionnaires, and expert review were validated for their positive predictive value (PPV) and negative predictive value (NPV) for new incidences of each cancer.

For the first two sources, the validation sample included all members of the study cohort (n=15,717) who reported no past history of the cancer in question at baseline. The PPV of the regular follow-up was calculated as the number of verified positive cases of the cancer, i.e., cases whose self-reported positive diagnosis was verified by medical-record review or cause-of-death investigation, divided by all cases of self-reported new incidences of the cancer in the regular follow-up. The NPV was calculated as the number of suspected negative cases, divided by all members of the validation sample who self-

reported no new cancer incidence in the regular follow-up. Here, the suspected negative cases consisted of all members of the validation sample for the cancer in question minus A) cases who self-reported new incidences in the regular follow-up and B) positive cases whose status was established only by death certificate (DCO).

The PPV of the combined regular follow-up and confirmation questionnaire was calculated as the number of verified positive cases of the cancer divided by all cases who corroborated their positive diagnosis on the confirmation questionnaire. The NPV was calculated as the number of suspected negative cases divided by all members of the validation sample except those who self-reported their positive diagnosis on the confirmation questionnaire. Here, the suspected negative cases consisted of all members of the validation sample minus A) cases who self-reported their positive diagnosis on the confirmation questionnaire, B) cases ruled positive by DCO, C) cases ruled positive by cause-of-death investigation, and D) contradictory cases (i.e., women confirmed by expert review but self-reported a negative status on the confirmation questionnaire or left the field blank).

The expert review panel's judgments were also validated for comparison. In this analysis, the validation sample consisted of all participants who A) returned the confirmation questionnaire, B) permitted the research team to contact their diagnosing

facility, and C) their provider agreed to respond to the team's inquiry. The PPV was calculated as the number of cases verified as positive by the diagnosing facility, divided by the number of cases ruled positive by the expert review panel. The NPV was calculated as the number of cases verified as negative by the diagnosing facility, divided by the number of cases ruled negative by the panel.

After fixing the cancer cases, the incidence rate of each cancer was estimated from the observed events and person-time at risk for 10 years of observation. Because of the numbers of participants aged age <30 and ≥60 years were small, the 30–60 year-old age group was used. We calculated the 95% confidence intervals of the incidence rates based on the exact Poisson confidence interval in accordance with known methods [12].

## RESULTS

### Verified cases of each cancer type

The flow diagram illustrating the validation process of each cancer is listed in the Web Appendices (Appendix 1-4). The numbers of new cases of self-reported cancers in the regular follow-up (and incidences in the respective validation sample) were cervical cancer: 219 (1.4%), endometrial cancer: 83 (0.5%), ovarian cancer: 51 (0.3%), and breast

cancer: 365 (2.3%). New incidence was verified by expert review in 37, 45, 23, and 297 of these cases, respectively. Some subjects sent the confirmation questionnaire corroborating their positive diagnosis but were ruled negative by the expert panel (72.1%, 11.1%, 30.3%, and 1.0%, respectively), while 37.6%, 33.8%, 25.6%, and 8.3% of subjects, respectively, responded with negative diagnosis on the confirmation questionnaire.

For all observed cases of mortality, cause of death was established as being cervical cancer (n=4, DCO=0), endometrial cancer (n=7, DCO=2), ovarian cancer (n=3, DCO=3), or breast cancer (n=16, DCO=3). New incidences of the four cancers were verified in 37, 47, 26, and 300 cases, respectively.

In the JNHS cohort, the estimated incidence rates for patients aged 30–60 years were 22.0/100,000; 25.4/100,000; 13.8/100,000; and 160.4/100,000 person-years for cervical, endometrial, ovarian, and breast cancer, respectively (Table 2). Considering the lack of heterogeneity between this cohort and Japanese women overall, the incidence rates for each age group were compared with the national data from regional cancer registries in the 2015 statistics published by Japan's National Cancer Center [13] (Figure 1-4). For all four cancers, the cohort data did not deviate from the national data.

**Self-reported PPV/NPV for each cancer**

Table 3 summarizes the PPVs and NPVs for the regular follow-up, regular follow-up plus confirmation questionnaire, and expert review for the new incidence of each cancer.

Expert review achieved 100% accuracy for each cancer except cervical (PPV: 92.3%) because of a single false-positive case, which the participant's provider clarified to be a different condition.

Self-reporting achieved NPVs near 100% for all cancers for both the regular follow-up and the regular follow-up plus confirmation questionnaire. However, the corresponding PPVs tended to be somewhat lower and variable across cancers. The PPVs were worse for gynecological cancers than for breast cancer (breast > endometrial > ovarian > cervical, in descending order) for both follow-up sources. The PPV for uterine cancer, which included cervical and endometrial cancers, was 27.2%.

The regular follow-up plus confirmation questionnaire achieved higher PPVs in all cases than did regular follow-up alone; however, while it achieved 99.0% accuracy for breast cancer, the estimates were lower for endometrial (88.9%) and ovarian (76.7%) cancer and poor for cervical cancer (31.5%).

Considering the changes to the official JSOG clinical staging system during the survey period, we calculated a similar summary for PPVs and NPVs, adding cases of cervical CIS, atypical endometrial hyperplasia, and borderline ovarian tumors (Table 4).

The resulting PPVs were uniformly higher when all three cancers were included than when they were excluded. For endometrial and ovarian cancer, the improvements ranged from 3.3%–6.7%, but for cervical cancer, their inclusion almost doubled the predictive value for both the regular follow-up and regular follow-up plus confirmation questionnaire, at +20.1% and +37.9%, respectively.

## DISCUSSION

In the JNHS cohort, self-reporting in regular follow-up achieved a PPV of 81.4% for breast cancer but performed poorer for gynecological cancers, especially uterine cancers (PPV: 27.2%) and cervical cancer alone (PPV: 16.9%). Our PPVs were higher than the corresponding values reported by the Japan Public Health Center (JPHC) Study, a population-based prospective cohort study (all cancers in women: 54.2%, breast: 58.4%, uterine: 21.7%) [14]. The validity of self-reporting is associated with individual characteristics [15], and our cohort consisted entirely of nursing professionals. While evidence suggests that educational level has a negligible association with validity [16], we partially attribute the high self-reporting accuracy to the uniformly high level of medical education and deeper knowledge of cancer in our cohort than in the general population.

Other studies support this argument [17]. However, sizeable percentages of nurses who affirmed new incidences of cancer in the regular follow-up gave the opposite response on the confirmation questionnaire (gynecological cancer: 25.6%–37.6%, breast cancer: 8.3%). Similarly, considerable percentages of respondents to the confirmation questionnaire were verified not to have cancer (gynecological cancer: 41.2%–81.2%, breast cancer: 9.2%). Many who corroborated their self-reported positive diagnosis were eventually ruled negative by expert review, especially for cervical cancer (72.1%), followed by ovarian (30.3%), endometrial (11.1%) and breast (1.0%). In summary, self-reporting alone apparently fails to capture the real cancer incidence, even for this cohort of nursing professionals with uniformly high medical knowledge. Additional inquiries to confirm the details are needed.

Compared to PPVs of self-report validity in other prospective cohort study datasets [16, 18, 19], our PPVs were comparable to the literature values for breast cancer but lower than these values for uterine cancers. Many studies have shown that self-reporting of breast cancer has high PPVs [10, 16, 19]. Some evidence has linked higher educational levels with a greater risk of breast cancer [20], which may also be true for our cohort. Additionally, breast cancer diagnoses included ductal carcinoma *in situ*, which may have led to less confusion than with gynecological cancers that excluded stage 0 cases and borderline

tumors.

Studies outside of Japan have also found self-reporting to yield lower PPVs for uterine cancers than for other cancers [18, 21], for several possible reasons. One is inaccurate memory of precancerous cervical lesions, which are rarely addressed immediately by surgical intervention. Additionally, age and sex may have some association; for example, participants >50 years old in a Native American cohort were more likely to report incorrectly [22]. Further, a study from Australia found that self-reported breast cancer had lower PPVs in women aged 70–75 years [23]. Disease-specific considerations may also be relevant. One study noted that many cases of women's cancers, especially cervical cancer, are not recorded in cancer registries [22], while another estimated false-negative rates of 43.8%, 28.6%, and 20.8% for self-reports of uterine, ovarian, and breast cancers, respectively [24]. Differences in incidence must also be considered. Because gynecological cancers are >5 times less prevalent than breast cancer, a difference of one case would produce a proportionally larger change in PPV.

One problem specific to Japan regarding the self-reporting of women's cancers is how the results of cytological screening tests are reported for cervical and endometrial cancers. Today, Pap smear results are recorded using the Bethesda system, the standard international format, but these results previously followed a class-based system. Class II

status, which shows within the normal range is sometimes confused with stage II cervical cancer. Similarly, atypical endometrial hyperplasia was previously classified as stage 0 endometrial cancer, which may be confused with non-atypical endometrial hyperplasia.

We suspect that another reason the self-report validity in our cohort was so poor for certain cancers was that subjects were recalling their past medical history during the regular follow-up, rather than the new incidence as intended. Additionally, ambiguous language in the questionnaire, such as "dysplasia" or "precancerous lesions", may have reduced the self-report validity, as evidenced by the higher PPVs for borderline forms, such as cervical CIS, atypical endometrial hyperplasia, and borderline ovarian tumors included in the analysis. Among the three borderline forms, classifying cervical CIS as cervical cancer led to a greater increase in PPVs than did other cancers. Manjer et al. also found that self-reporting of malignant cervical cancer was less sensitive when the definition included cervical CIS [25]. These considerations suggest that compared with other cancers, diagnoses of cervical cancer and precancerous lesions have a greater risk of being inaccurately communicated or negatively interpreted by patients.

One of this study's strengths was our meticulous review of subjects' medical records and death-certificate surveys to establish self-report validity, circumventing the limitations presented by Japan's lack of complete national cancer registries. Additionally,

we believe that our data better reflect the general Japanese population than did past findings for other regional cohorts because the nationwide scope of the JNHS minimizes the geographical variation. Moreover, our cohort was relatively homogenous in terms of sex and occupation, consisting entirely of female nursing professionals.

The study also had some limitations. Cohort-specific characteristics may limit the generalizability of our findings, especially the relatively young skew of the participants' ages. However, when converted to incidence rates, our rates seem most consistent with the 2015 statistics published by Japan's National Cancer Center [13]. Additionally, self-reported diagnoses could not be verified in some cases. Our expert panel made their judgments based on the specific language nurses used in the questionnaire to describe their treatments such as "hysterectomy" and "chemotherapy", but the panel still encountered cases that were difficult to definitively verify. However, we established a conclusive diagnosis based on all available information such as postmortem exam findings and supplemental details from primary-care providers. No indeterminate cases were found among those lacking medical records for verification.

## CONCLUSION

In Japan, gynecological cancer also cannot be accurately assessed by self-reporting

alone. However, external validity of these cancer incidence in JNHS with our method was confirmed. As the JNHS database covers all of Japan, this results allow the further investigation of risk factors for different cancers such as menopausal hormone therapy and lifestyle factors and their associations, with unaffected by information bias. We plan to continue our work by analyzing the respective contributions of different risk factors among confirmed cases of gynecological and breast cancer, as verified above.

**Acknowledgments** The authors appreciate the cooperation of the Japanese nurses who participate in the JNHS and the GNHS. We also thank Ms. Satomi Shimizu at the JNHS Data Center for her help with data management.

**Contributors** KT was the panel member and wrote the initial draft of the paper to which all authors contributed. YI, NM, and KN collected data and analyzed. MK and TY were panel members and revised manuscript. KH designed the study, raised funding, and directed its implementation including quality assurance and control.

**Funding** This work was partly supported by a grant from the Japan Society for the Promotion of Science (JSPS KAKENHI Grant Number: 18H04069).

**Competing interests** None declared.

**Patient consent for publication** Not required.

**Data sharing statement** The data are not publically available due to data transfer agreements. No additional data is available.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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## Figure and table legends

**Figure 1** Estimated incidence rates of cervical cancer for each age group in the JNHS cohort and the national data from regional cancer registries.

(error bars shows the 95% confidence intervals)

**Figure 2** Estimated incidence rates of endometrial cancer for each age group in the JNHS cohort and the national data from regional cancer registries.

(error bars shows the 95% confidence intervals)

**Figure 3** Estimated incidence rates of ovarian cancer for each age group in the JNHS cohort and the national data from regional cancer registries.

(error bars shows the 95% confidence intervals)

**Figure 4** Estimated incidence rates of breast cancer for each age group in the JNHS cohort and the national data from regional cancer registries.

(error bars shows the 95% confidence intervals)

**Table 1** Numbers and percentages of subjects in each age group at baseline in the JNHS cohort

**Table 2** Estimated incidence rate of each cancer in patients aged 30–60 years in the JNHS cohort

**Table 3** PPVs/NPVs for regular follow-up, regular follow-up plus confirmation questionnaire, and expert review for new incidences of gynecological and breast cancers in the JNHS cohort

**Table 4** Corresponding PPVs/NPVs including those of cervical CIS, atypical endometrial hyperplasia, and borderline ovarian tumor in the JNHS cohort

**Appendix legends**

**Appendix Figure 1** Flow diagram illustrating the validation process for self-reported cervical cancer (BL: baseline, CIS: carcinoma in situ, DCO: death certificate only)

**Appendix Figure 2** Flow diagram illustrating the validation process for self-reported endometrial cancer (BL: baseline, aEmH: atypical endometrial hyperplasia, DCO: death certificate only)

**Appendix Figure 3** Flow diagram illustrating the validation process for self-reported ovarian cancer (BL: baseline, DCO: death certificate only)

**Appendix Figure 4** Flow diagram illustrating the validation process for self-reported breast cancer (BL: baseline, CIS: carcinoma in situ, DCO: death certificate only)

Table 1 Numbers and percentages of subjects in each age group at baseline in the JNHS cohort

| Age (years) | n | (%) |
|---|---|---|
| < 30 | 692 | (4.4) |
| 30 – 34 | 2,955 | (18.8) |
| 35 – 39 | 3,176 | (20.2) |
| 40 – 44 | 3,133 | (19.9) |
| 45 – 49 | 2,767 | (17.6) |
| 50 – 54 | 2,012 | (12.8) |
| 55 – 59 | 797 | (5.1) |
| 60 – 64 | 143 | (0.9) |
| ≥ 65 | 42 | (0.3) |

Table 2 Estimated incidence rate of each cancer in patients aged 30 to 60 years in the JNHS cohort

| | Cancer cases | Person-years | Incidence rate (per 100,000 person-years) | Lower limit of 95% confidence interval | Upper limit of 95% confidence interval |
|---|---|---|---|---|---|
| Cervical cancer | 29 | 131,658.50 | 22.0 | 14.8 | 31.6 |
| Endometrial cancer | 32 | 126041.0 | 25.4 | 17.4 | 35.8 |
| Ovarian cancer | 18 | 130662.5 | 13.8 | 8.2 | 21.8 |
| Breast cancer | 210 | 130960.5 | 160.4 | 139.4 | 183.6 |

Table 3 PPVs/NPVs of regular follow-up, regular follow-up plus confirmation questionnaire, and expert review for new incidences of gynecological and breast cancers in the JNHS cohort

| | | | | | Regular follow-up | | Regular follow-up plus confirmation questionnaire | | Expert review | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Positive history self-reported at baseline | Validation sample | Positive diagnosis self-reported in regular follow-up | Positive status established by cause-of-death investigation (incl. DCO cases) | PPV | NPV | PPV | NPV | PPV | NPV |
| Cervical cancer | 167 | 15,550 | 219 | 2 (0) | 16.9% | 100.0% | 31.5% | 99.9% | 92.3% | 100.0% |
| Endometrial cancer | 31 | 15,686 | 83 | 7 (2) | 54.2% | 99.9% | 88.9% | 99.9% | 100.0% | 100.0% |
| Ovarian cancer | 37 | 15,680 | 51 | 3 (3) | 45.1% | 99.9% | 76.7% | 99.9% | 100.0% | 100.0% |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Breast cancer | 138 | 15,579 | 365 | 5 (3) | 81.4% | 99.9% | 99.0% | 99.9% | 100.0% | 100.0% |

Table 4 Corresponding PPVs/NPVs including cervical CIS, atypical endometrial hyperplasia, and borderline ovarian tumors in the JNHS cohort

| | | | | | Regular follow-up | | Regular follow-up plus confirmation questionnaire | |
|---|---|---|---|---|---|---|---|---|
| | Positive history self-reported at baseline | Validation sample | Positive diagnosis self-reported in regular follow-up | Positive status established by cause-of-death investigation (incl. DCO cases) | PPV | NPV | PPV | NPV |
| Cervical cancer | 167 | 15,550 | 219 | 2 (0) | 37.0% | 100.0% | 69.4% | 99.9% |
| Endometrial cancer | 31 | 15,686 | 83 | 7 (2) | 57.8% | 99.9% | 95.6% | 99.9% |
| Ovarian cancer | 37 | 15,680 | 51 | 3 (3) | 49.0% | 99.9% | 80.0% | 99.9% |

**Figure 1** Estimated incidence rates of cervical cancer for each age group in the JNHS cohort and the national data from regional cancer registries (error bars shows the 95% confidence intervals)

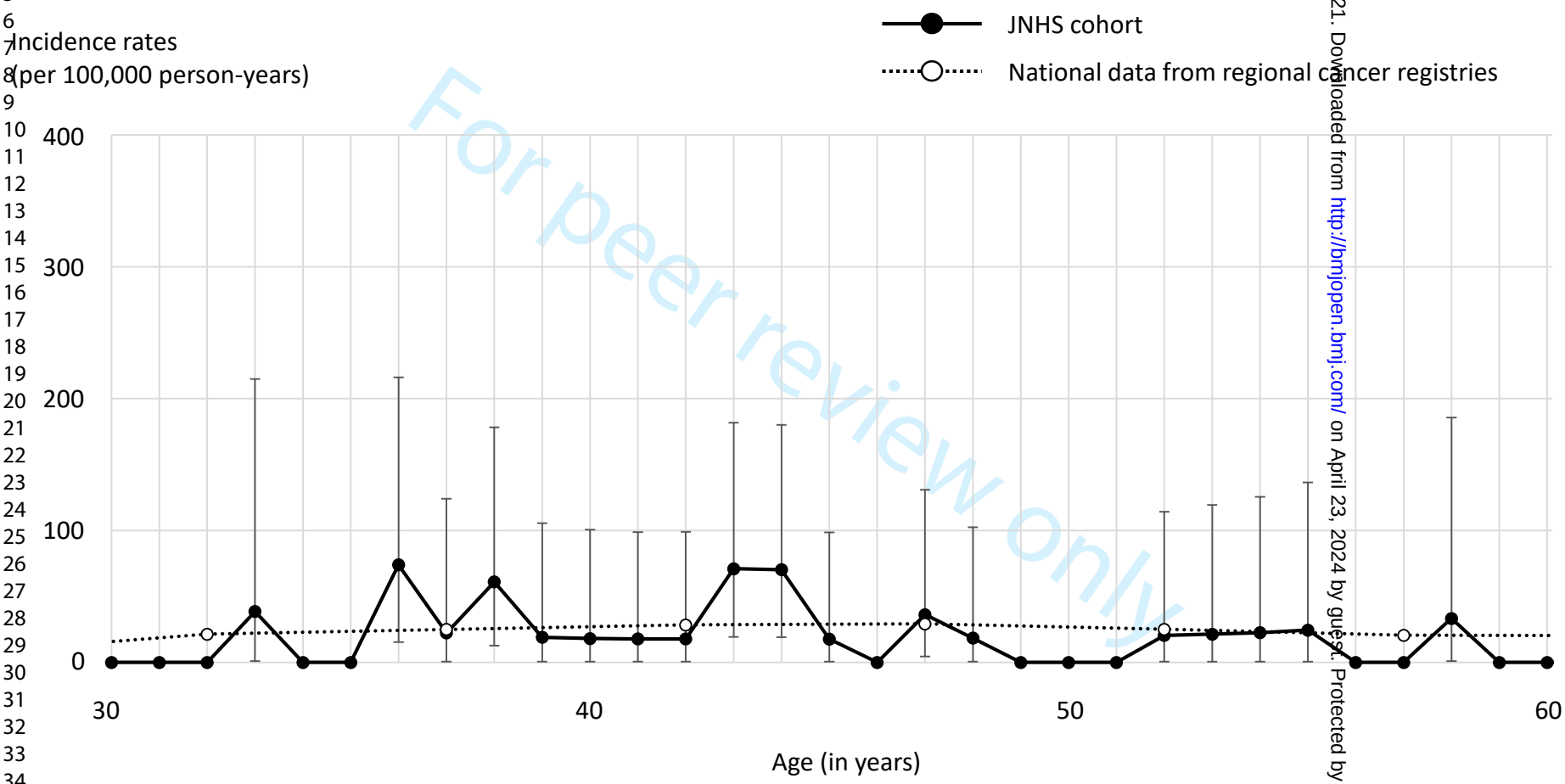


**Figure 2** Estimated incidence rates of endometrial cancer for each age group in the JNHS cohort and the national data from regional cancer registries
(error bars shows the 95% confidence intervals)

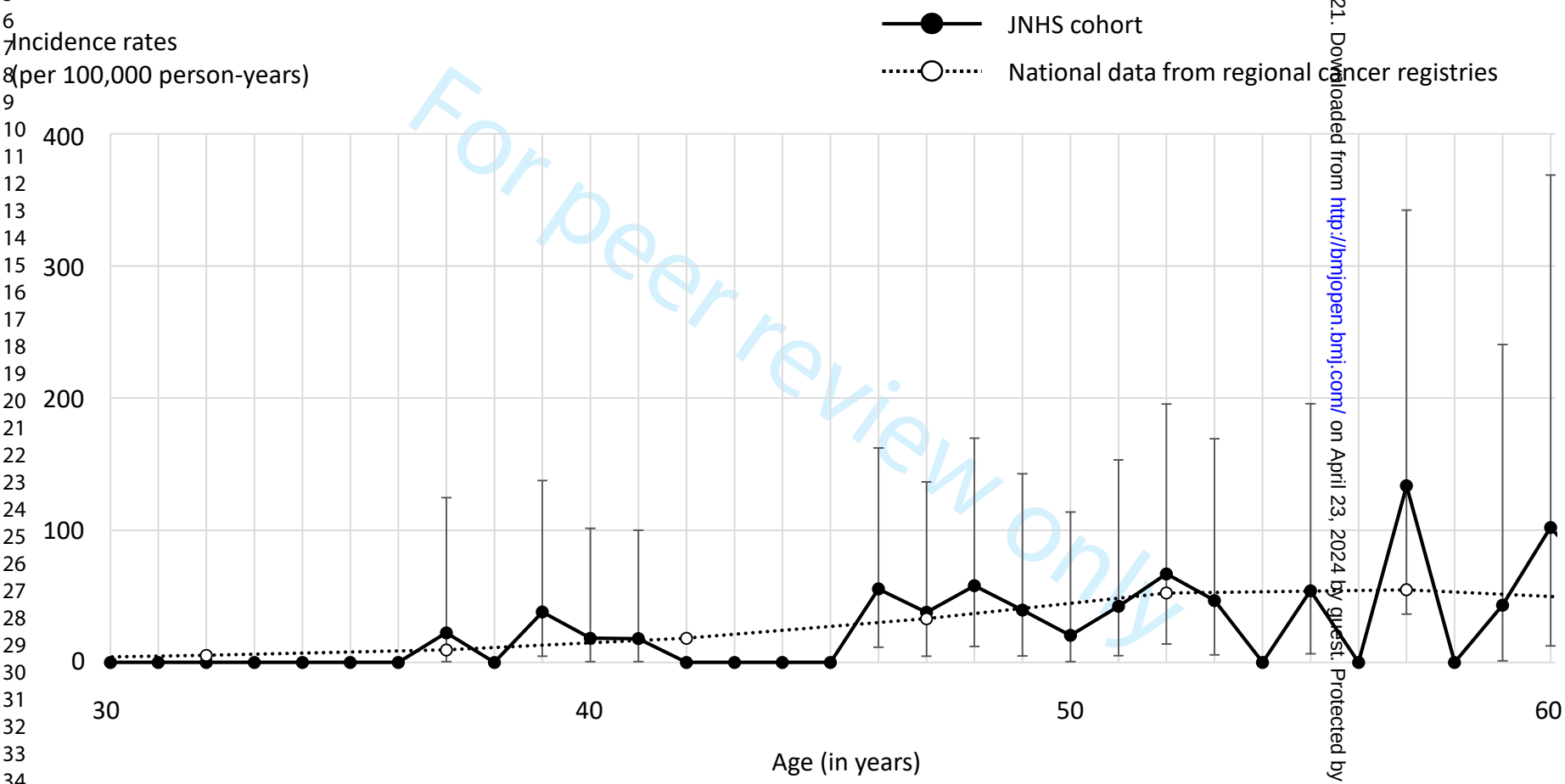


**Figure 3** Estimated incidence rates of ovarian cancer for each age group in the JNHS cohort and the national data from regional cancer registries (error bars shows the 95% confidence intervals)

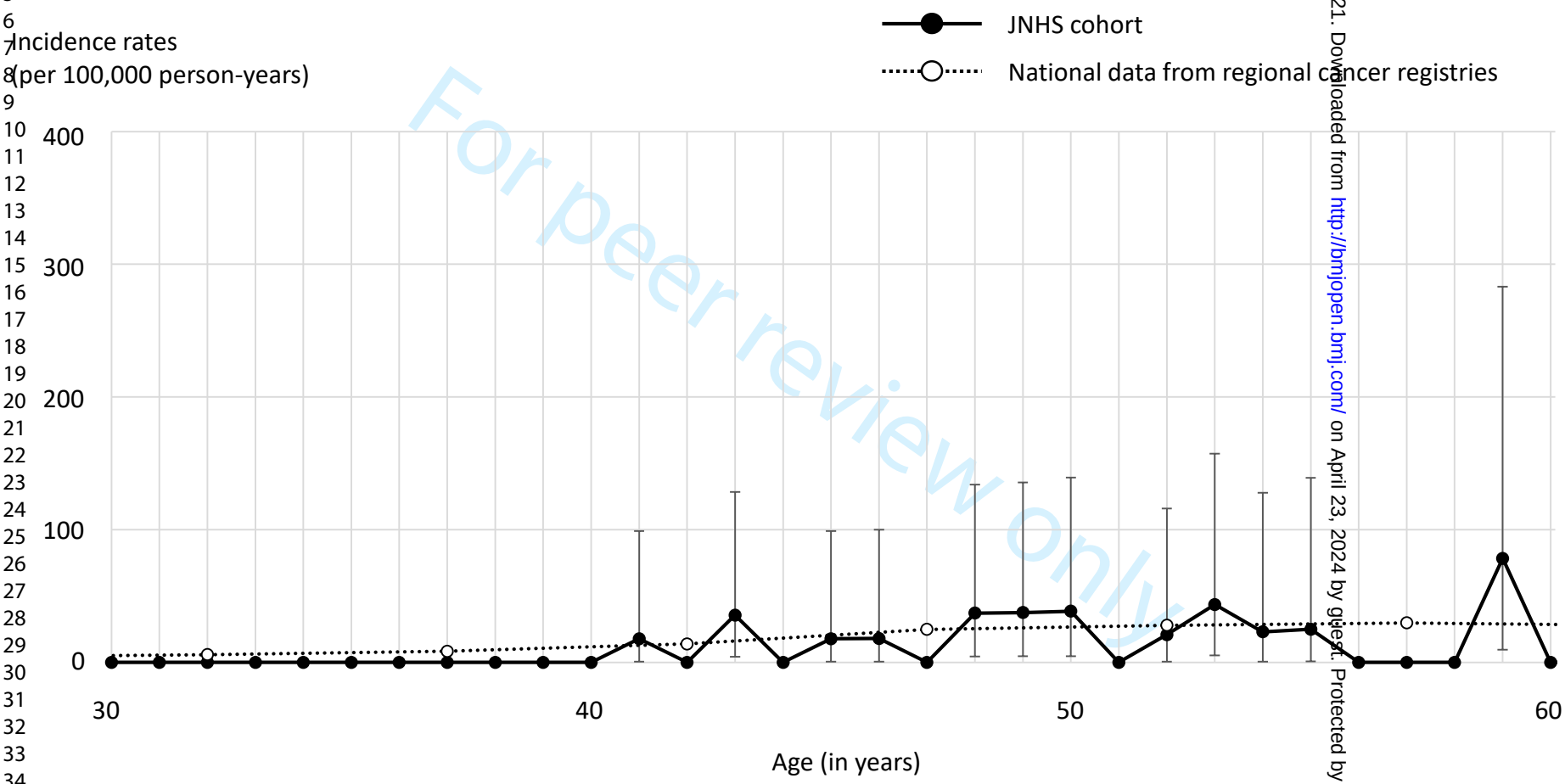
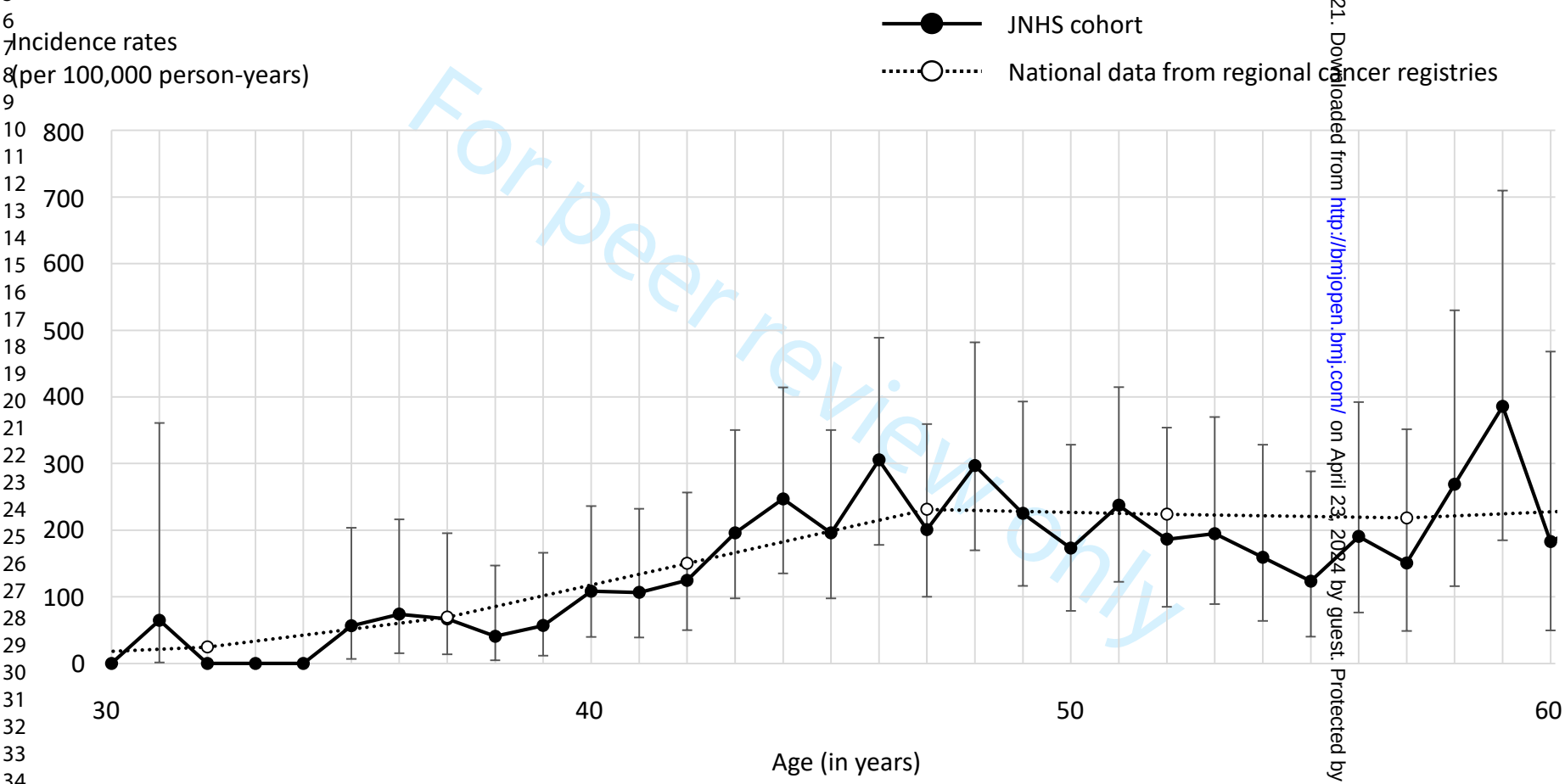
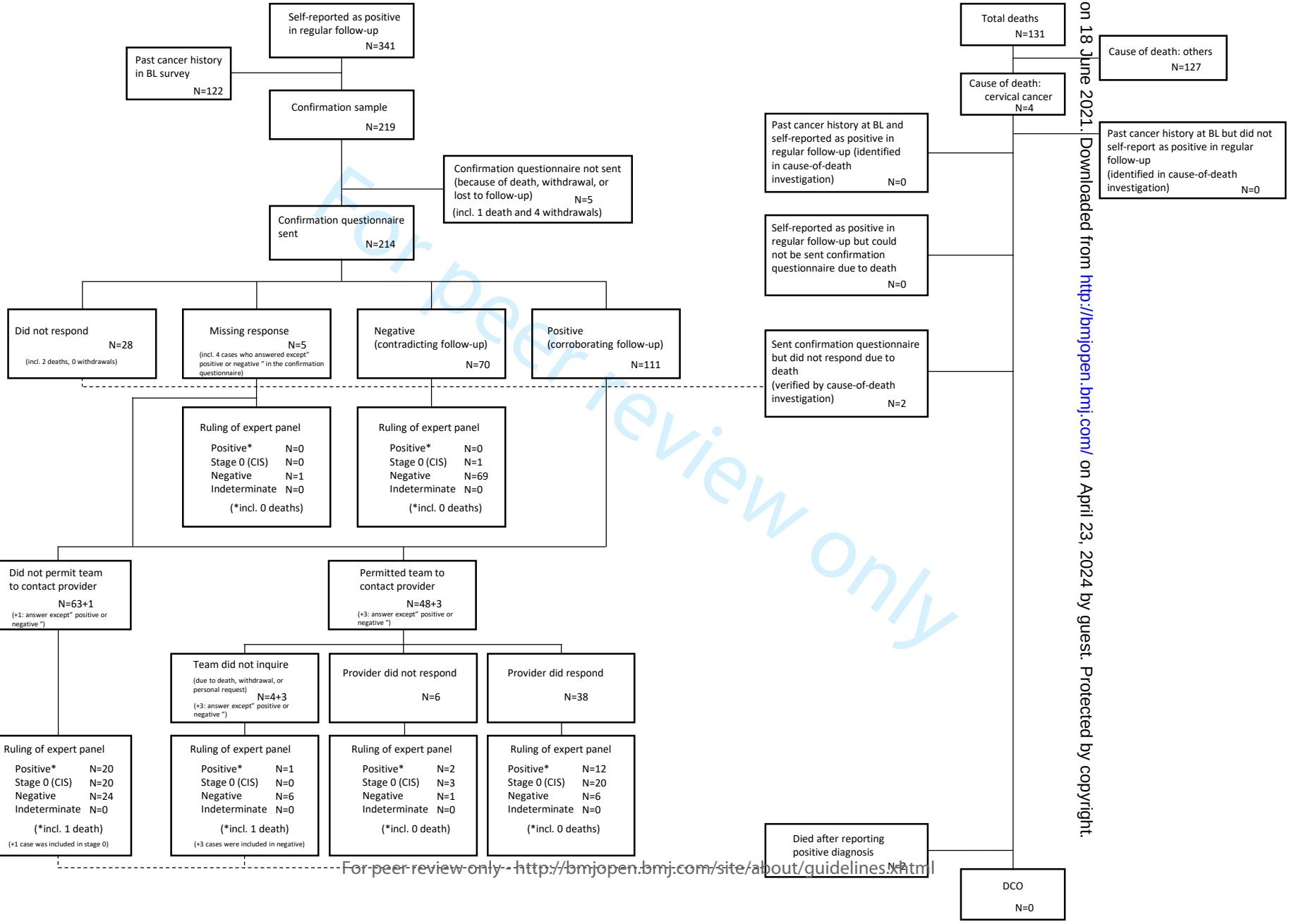


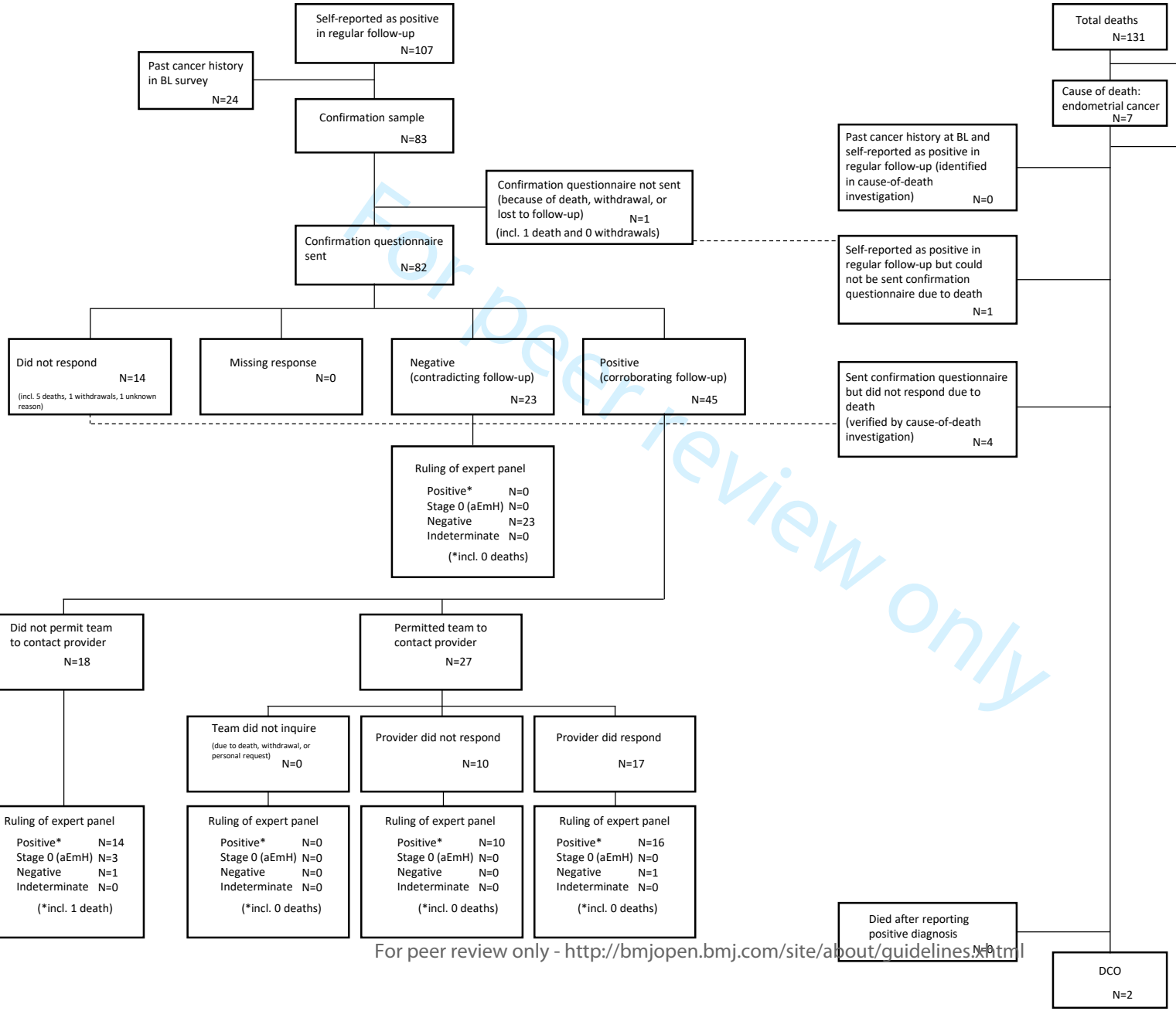
**Figure 4** Estimated incidence rates of breast cancer for each age group in the JNHS cohort and the national data from regional cancer registries (error bars shows the 95% confidence intervals)



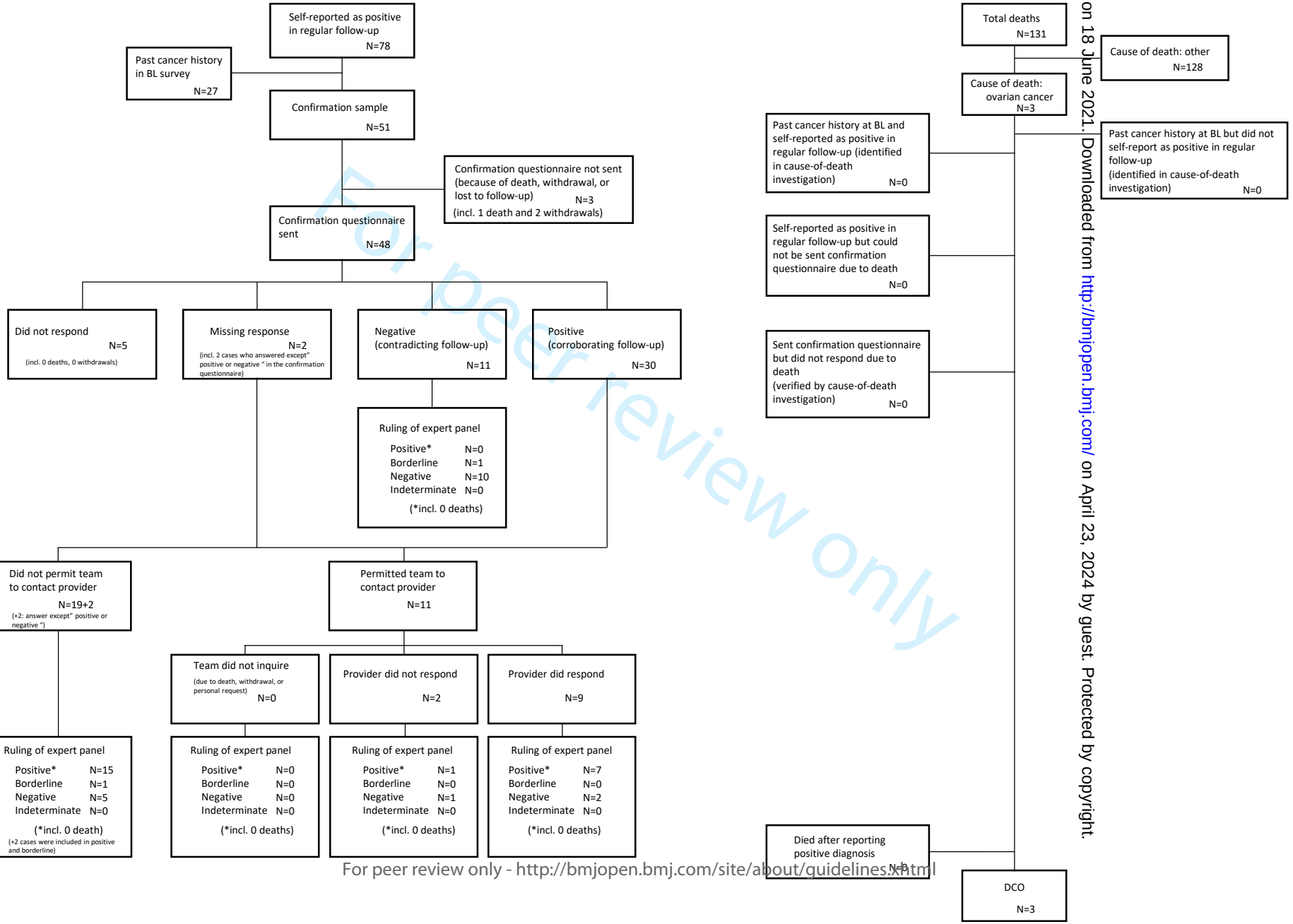
**Appendix Figure 1** Flow diagram illustrating the validation process for self-reported cervical cancer (BL: baseline, CIS: carcinoma in situ, DCO: death certificate only)



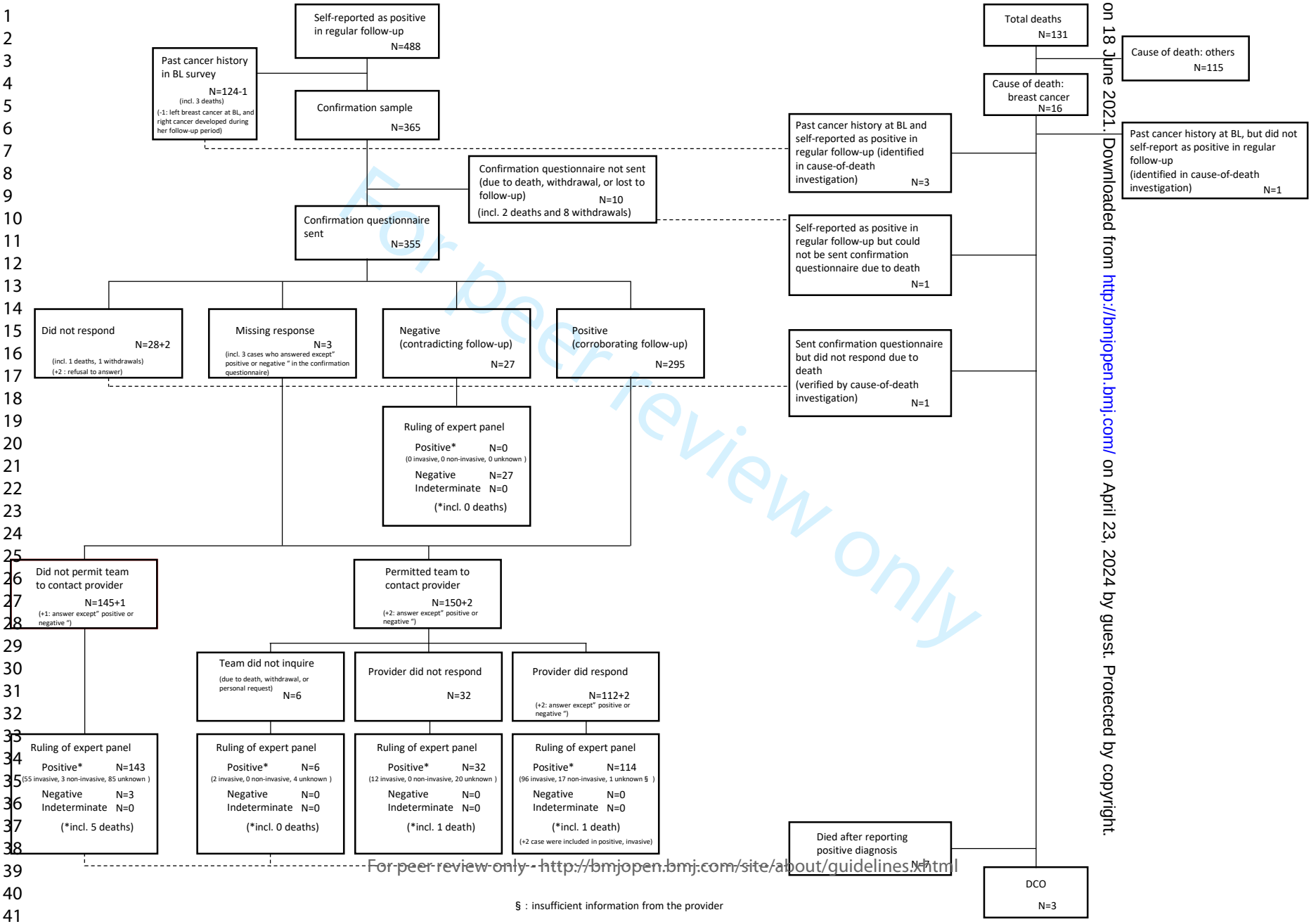
**Appendix Figure 2** Flow diagram illustrating the validation process for self-reported endometrial cancer (BL: baseline, aEmH: atypical endometrial hyperplasia, DCO: death certificate only)



**Appendix Figure 3** Flow diagram illustrating the validation process for self-reported ovarian cancer (BL: baseline, DCO: death certificate only)



**Appendix Figure 4** Flow diagram illustrating the validation process for self-reported breast cancer (BL: baseline, CIS: carcinoma in situ, DCO: death certificate only)



**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies***

| Section/Topic | Item # | Recommendation | Reported on page # |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 1 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 2-3 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 4 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 5 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 4-5 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 5-6 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 5-6 |
| | | (*b*) For matched studies, give matching criteria and number of exposed and unexposed | N/A |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 9-11 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 12 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 7-9 |
| Study size | 10 | Explain how the study size was arrived at | 5-6 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 9-11 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 11 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 12 |
| | | (*c*) Explain how missing data were addressed | 11-12, Appendix 1-4 |
| | | (*d*) If applicable, explain how loss to follow-up was addressed | 11-12, Appendix 1-4 |
| | | (*e*) Describe any sensitivity analyses | N/A |
| **Results** | | | |

| | | | |
|---|---|---|---|
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 11-12, Appendix 1-4 |
| | | (b) Give reasons for non-participation at each stage | N/A |
| | | (c) Consider use of a flow diagram | Appendix 1-4 |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 5-6 |
| | | (b) Indicate number of participants with missing data for each variable of interest | 11-12, Appendix 1-4 |
| | | (c) Summarise follow-up time (eg, average and total amount) | 7 |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | 11-12, Appendix 1-4 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 12-14 |
| | | (*b*) Report category boundaries when continuous variables were categorized | N/A |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | N/A |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | N/A |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 14 |
| **Limitations** | | | |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 15-18 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 17-18 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 19 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.