Research Article

Surveillance of Second-Degree Relatives from Melanoma Families with a CDKN2A Germline Mutation

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Abstract

Background: Lifetime melanoma risk of mutation carriers from families with a germline mutation in the CDKN2A gene is estimated to be 67%. The necessity to include family members in a melanoma surveillance program is widely endorsed, but there is no consensus on which family members should be invited.

Methods: In a retrospective follow-up study, we investigated the yield of surveillance of first- and second-degree relatives of melanoma and pancreatic cancer patients from 21 families with the “p16-Leiden” CDKN2A mutation. Melanoma incidence rates were compared with the general population.

Results: Three-hundred and fifty-four first-degree relatives and 391 second-degree relatives were included. Forty-five first-degree relatives and 11 second-degree relatives were diagnosed with melanoma. Most (72%) of second-degree relatives diagnosed with melanoma had become a first-degree relative before diagnosis, due to the occurrence of a melanoma in a parent or sibling. Overall, melanoma incidence rate was 2.1 per 1,000 person years [95% confidence interval (CI), 1.2–3.8] in family members still being second-degree relatives at diagnosis, compared with 9.9 per 1,000 person years (95% CI, 7.4–13.3) in first-degree relatives. The standardized morbidity ratio for melanoma of second-degree relatives compared with the general population was 12.9 (95% CI, 7.2–23.4).

Conclusion: Second-degree relatives from families with the p16-Leiden mutation in CDKN2A have a considerably increased melanoma risk compared with the general population.

Impact: This study provides justification for the surveillance of second-degree relatives from families with a CDKN2A germline mutation. Cancer Epidemiol Biomarkers Prev; 22(10); 1771–7. ©2013 AACR.

Introduction

Familial melanoma is one of the strongest risk factors for cutaneous melanoma. Approximately 10% of melanoma cases are found in families with two or more patients with melanoma (1). In up to 40% of families with three or more melanoma cases, a mutation in the high penetrance melanoma susceptibility gene CDKN2A (MIM# 600160) is found (2). With respect to melanomagenesis, CDKN2A has an incomplete penetrance that has been estimated to be 0.67 by age 80 years (3). In the Netherlands, by far the most prevalent CDKN2A germline mutation is a specific founder mutation (c.225-243del19; ref. 4), known as the p16-Leiden mutation. The p16-Leiden mutation is associated with a very high melanoma risk, comparable with other CDKN2A mutations, and with a cumulative risk of pancreatic cancer of 17% by age 75 (5).

Because of the increased melanoma risk and expected benefit of surveillance (6, 7), regular surveillance of members of familial melanoma families is widely advocated (8, 9). In the Netherlands, the first surveillance program for familial melanoma was initiated at the Leiden University Medical Center (LUMC, Leiden, the Netherlands) in 1981. Individuals that were invited to the program encompassed patients with melanoma, their first-degree relatives (parents, siblings, and children) as well as their second-degree relatives (grandparents, uncles, aunts, nieces, nephews, and grandchildren). Assuming an autosomal dominant pattern of inheritance (as was later proven to be the case for CDKN2A germline mutations), first and second-degree relatives have a 50% and 25% chance of carrying the genetic risk factor.

The 1981 surveillance guidelines were based on the estimation that lifetime melanoma risk of mutation...
carriers approximated 100%, implying an almost 25% lifetime melanoma risk for second-degree relatives. Since 1981, the recommendation for surveillance of second-degree relatives has remained unchanged (10).

Since the year 2000 (predictive, CDKN2A), DNA testing of asymptomatic family members is available in the Netherlands. Predictive DNA testing facilitates the selective offering of surveillance to those family members at highest risk of melanoma and therefore has the potential to greatly increase surveillance (cost-) effectiveness. An earlier study at our institution suggested however that the majority of relatives either do not opt for genetic testing, or at an age (i.e., average age 48 years) that lies considerably beyond the young age of onset (i.e. median age of melanoma diagnosis 39 years) in CDKN2A-mutated families (11, 12). As a consequence, second-degree relatives have continued to present for surveillance.

To the best of our knowledge, surveillance of second-degree relatives has not been addressed in (familial) melanoma guidelines from other countries and is unusual for other types of hereditary cancer syndromes as well. Given this discrepancy between Dutch and foreign guidelines, and to evaluate current surveillance recommendations, we conducted a retrospective follow-up study to evaluate the yield of surveillance of second-degree relatives in families with a founder mutation in CDKN2A (the p16-Leiden mutation).

Materials and Methods

Family ascertainment and data collection

Families were ascertained through the pigmented lesion clinic of the department of dermatology of the Leiden University Medical Centre (LUMC) from 1980 onward. At the clinic, family trees were constructed and family members were invited to participate in annual total skin examinations. Since 1985, a decade before the identification of the p16-Leiden mutation, blood samples have been collected for research purposes. Patients consented to this, knowing that carrier information would not be transmitted back to them. Clinicians were also kept unaware of gene carrier status.

Pedigree information was updated on a regular basis. Follow-up data were collected, both during clinic visits, and in several research projects. Confirmation of melanoma diagnoses was gathered through pathology reports and medical records. In 2007 at the event of an earlier study, melanomas of mutation-negative family members and all tumors with missing data, in situ melanomas and lentigo malignas were revised by one of us, a member of the pathology panel of the Dutch Melanoma Working Party (7). Further details on family ascertainment and the collection of follow-up data have been described elsewhere (5).

Inclusion

Inclusion of family members was based on the presence of the p16-Leiden mutation in their family and independent of personal CDKN2A mutation status (mutated, wild-type or unknown). In the study model all relatives with melanoma or pancreatic cancer were regarded (probable) mutation-carriers and mutation status of all other relatives was regarded to be unknown.

First- and second-degree relatives of family members with a medical history of invasive melanoma, melanoma in situ, or pancreatic cancer, were included. A minimum age of 12 years was required. To minimize selection bias, not only family members undergoing regular skin check-ups and participants in research projects at the LUMC dermatology department, but also relatives that had not visited the LUMC clinic thus far, were included in the study. Data on non-visiting family members were obtained from their parents, siblings or children that did visit the clinic and was collected through questionnaires at the occasion of an earlier study (5). No data were available on the extent of participation of family members at skin examinations by general practitioners or clinicians at other hospitals than the LUMC.

Analysis of melanoma incidence

Melanoma incidence was analyzed in two ways. In the first analysis we used a model in which calculation of follow-up was independent of actual participation in the surveillance program. Follow-up times for all relatives started as soon as their family fulfilled the criteria for familial melanoma, which was defined as: a minimum of two first-degree relatives with either invasive melanoma, or one with invasive melanoma and one with pancreatic cancer, or three (non-first degree) relatives with invasive melanoma or two with invasive melanoma and one with pancreatic cancer. End of follow-up was defined as: (i) occurrence of an event, i.e., the diagnosis of an invasive or in situ melanoma; (ii) end of follow-up due to closure of the study (Jan 1 2004, based on completeness of data collected for an earlier study), lost to follow-up, death, a diagnosis of pancreatic cancer (indicating a probable p16-Leiden mutation carrier), or having a child or grandchild diagnosed with melanoma or pancreatic cancer (indicating a high likelihood of being a p16-Leiden mutation carrier). An additional reason for end of follow-up for second-degree relatives consisted of the reclassification as first-degree relative. Subsequent follow-up of these relatives was included in the calculation of the melanoma incidence rate of first-degree relatives. For relatives with multiple primary melanomas, only the first melanoma was included in the analysis.

A second analysis was conducted to calculate the melanoma incidence in first- and second-degree relatives during actual participation in the surveillance program at the LUMC dermatology department. It was anticipated that this subpopulation was enriched for individuals with an increased likelihood of being diagnosed with melanoma, as it was expected that family members with a suspicious nevus or large numbers of (atypical) nevi were more likely to attend surveillance. For this subanalysis, we used data on clinic visits spanning from 1993 till 2004, as
from 1993 onwards clinic appointments were recorded in the LUMC hospital information system.

**Statistical analysis**

Person years were calculated separately for each category (first- and second-degree relatives) and used to compute overall incidence rates and incidence rates per 10 years age groups. For second-degree relatives that became first-degree relatives during follow-up, subsequent follow-up was added to the person years for first-degree relatives, as described earlier. The overall HR for first-degree relatives to develop a melanoma compared with second-degree relatives corrected for age was estimated using a Cox proportional hazard analysis.

Standardized morbidity ratios (SMR) were calculated to estimate the increase in melanoma risk in first- and second-degree relatives compared with the general population. The SMR was computed as the ratio of the observed number of cases in either the first- or second-degree relatives over the number of cases expected based on the case rate in the general population, after standardization for age and incidence year distribution. General population data were based on the reported melanoma incidence for age and incidence year distribution. The SMR was computed as the ratio of the observed melanoma incidences [with (near) completeness of data both for invasive and in situ melanomas] per gender and 5-years age categories between 1989 and 2003 at the Netherlands Cancer Registry (13).

To analyze the probability of second-degree relatives to become a first-degree relative before melanoma diagnosis a multistate analysis was conducted with age as time scale (14). Four states are considered: (i) second-degree relative without melanoma, (ii) first-degree relative without melanoma, (iii) second-degree relative with melanoma, and (iv) first-degree relative with melanoma. Transitions are possible from state 1 to 2 and 3, and from state 3 to 4. Nonparametric estimates of the transition hazards were obtained using the package mstate, version 0.2.6 for R (15). Subsequently, state occupation probabilities (of the four states) over time were calculated, given second-degree relatives without melanoma, first-degree relatives without melanoma, (ii) first-degree relative without melanoma at the moment of melanoma detection could not be verified. For second-degree relatives, the moment of melanoma detection was; 1 (9%) first clinic visit, 9 (82%) during surveillance and 1 (9%) unverifiable.

**Melanoma incidence**

Overall, melanoma incidence rate was 9.9 per 1,000 person years (95% CI, 7.4–13.3) in first-degree relatives and 2.1 per 1,000 person years (95% CI, 7.4–13.3) in second-degree relatives (Table 2). Overall HR of first-degree relatives to develop a melanoma compared with

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**Table 1. Data characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>First-degree relatives</th>
<th>Second-degree relatives</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of relatives in the pedigrees</td>
<td>364 (286 + 78)*</td>
<td>503</td>
<td>867 (789)*</td>
</tr>
<tr>
<td>Number of relatives included in the study</td>
<td>354 (97%)</td>
<td>391 (78%)</td>
<td>745 (667)*</td>
</tr>
<tr>
<td>Total follow-up (person years)</td>
<td>4,531</td>
<td>5,280</td>
<td>9,811</td>
</tr>
<tr>
<td>Number of relatives with complete follow-up</td>
<td>319</td>
<td>331</td>
<td>650</td>
</tr>
<tr>
<td>Length of follow-up median (range)</td>
<td>12.8 y (0.0–36.4)</td>
<td>14.9 y (0.0–25.7)</td>
<td>—</td>
</tr>
<tr>
<td>Age at inclusion median (range)</td>
<td>33 y (12–78)</td>
<td>19 y (12–71)</td>
<td>—</td>
</tr>
<tr>
<td>Gender</td>
<td>177 males (49.7%)</td>
<td>203 males (52.2%)</td>
<td>—</td>
</tr>
</tbody>
</table>

*Seventy-eight individuals changed from second- to first-degree relative during follow-up. Their person years as second-degree relatives were added to the totals of second-degree relatives and person years as first-degree relative to the totals of the first-degree relatives.

Analyses were conducted with STATA (version 11), SPSS (version 17), and R (version 2.15.0).

**Results**

**Data characteristics**

A total of 21 families was included in the study. Twelve families were included with two first-degree relatives with melanoma, 2 families with three (non-first degree) relatives with melanoma, 5 families with two first-degree relatives, one with melanoma and one with pancreatic cancer, and 2 families with two relatives with melanoma and one or more relatives with pancreatic cancer.

On the basis of the pedigrees of these 21 families there were 789 eligible family members. Of these, 667 could be included: 354 first-degree relatives (including 78 relatives that turned from second into first-degree relative during follow-up) and 391 second-degree relatives. Data characteristics are reported in Table 1.

A total of 56 relatives (45 first-degree, 11 second-degree relatives) were diagnosed with melanoma during follow-up; 50 invasive and 6 in situ melanomas (5 in first-degree, 1 in second-degree relatives). Three additional lesions initially diagnosed as in situ melanoma were excluded, as they were reclassified as benign melanocytic lesions after histologic revision. Median age of melanoma diagnosis was 39 years (range 15–72) in first-degree relatives and 26 years (range 16–44) in second-degree relatives.

In case of the first-degree relatives, 13 patients were diagnosed with melanoma (29%) at their first clinic visit, 22 patients (49%) during surveillance, and for 10 patients (22%) the moment of melanoma detection could not be verified. For second-degree relatives, the moment of melanoma detection was; 1 (9%) first clinic visit, 9 (82%) during surveillance and 1 (9%) unverifiable.

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Second-degree relatives, adjusted for age, was found to be 5.1 (95% CI: 2.6–10.0; P < 0.001).

Overall SMR for melanoma compared with the general population was 101.0 (95% CI: 55.9–182.3) in first-degree relatives (observed: 45, expected: 0.76), and 12.9 (95% CI, 7.2–23.4) in second-degree relatives (observed: 11, expected: 0.53).

Melanoma detection rates during surveillance

We conducted a subanalysis of relatives that had been under surveillance at the LUMC dermatology clinic. A total of 128 of 277 first-degree relatives (46%) and 113 of 286 second-degree relatives (40%) with follow-up data between 1993 and 2004, attended the surveillance program at least once within this period.

The number of clinic visits per year was 1.12 for first-degree relatives (705 clinic visits in 627 person years) and 0.91 for second-degree relatives (536 clinic visits in 588 person years). Median age of first- and second-degree relatives was 32.6 years and 28.8 years, respectively. Melanoma incidence rate was calculated to be 22.3/1,000 person years (95% CI, 13.2–37.7) in first-degree relatives and 8.5/1,000 person years (95% CI, 3.5–20.4) in second-degree relatives. Overall HR of first-degree relatives to develop a melanoma compared with second-degree relatives, adjusted for age, was found to be 2.6 (95% CI: 0.9–7.6, P = 0.070).

In family members that had not been under surveillance at the LUMC between 1993 and 2004, in this period one melanoma was diagnosed in first-degree relatives (n = 149) and one melanoma in second-degree relatives (n = 173).

Second- to first-degree relative transition

During follow-up 20% (78/391) of the second-degree relatives became first-degree relatives as the result of a new diagnosis of melanoma or pancreatic cancer in one of their family members. Median age of transition from second- to first-degree relative was 30 years (range 12–67).

Besides the 11 second-degree relatives that were diagnosed with melanoma while (still) being a second-degree relative [median age of diagnosis: 26 years (range 16–44)], there were 11 relatives, who started out as second-degree relative at inclusion, and were diagnosed with melanoma after they had become a first-degree relatives [median age of diagnosis: 35 years (range 16–46)]. There were no differences between these two groups concerning age at inclusion; [median 15.1 years (range 12.0–28.4) versus 17.4 years (range 12.0–39.3)], number of first degree relatives (parent and siblings); 4 relatives (range 3–6) versus 3 relatives (range 1–8), or number of first degree relatives older than themselves; 2 relatives (range 1–4) versus 3 relatives (range 1–4).

In Fig. 1 the probabilities of second-degree relatives to become a first-degree relative and to develop a melanoma as a first- or second-degree relative, according to age, are presented. Overall 20.8% of individuals that entered follow-up as second-degree relatives were estimated to be diagnosed with melanoma at age 80 years, 72.2% of whom had been transformed to first-degree relative, before melanoma diagnosis.

Discussion

The goal of this study was to evaluate the yield of surveillance of second-degree relatives in melanoma families with the p16-Leiden mutation in CDKN2A. In the Netherlands, historically all first- and second-degree relatives of patients with melanoma with familial melanoma have been recommended to undergo regular skin examinations. Given the expected high lifetime risk and relatively simple, noninvasive screening procedure at hand, inclusion of second-degree relatives in the surveillance program seemed logical at the time. An intensive literature study suggested that inclusion of second-degree relatives is unusual in other countries and for other types of hereditary cancer (16, 17), but we did not encounter evidence against inclusion of second-degree relatives either.

We report a melanoma incidence rate of 2.1/1000 person years for second-degree relatives. The relative risk of first-degree relatives (incidence rate: 9.9/1,000 person

| Table 2. Incidence rates of melanoma in first- and second-degree relatives according to age |
|----------------------------------------|----------------------|----------------------|
| Age band | No. of melanoma case patients | No. of person years | Incidence rate/1,000 person years (95% CI) |
| A. Incidence rates of melanoma in first-degree relatives: | | | |
| 10–19 | 4 | 407.1 | 9.8 (3.7–26.2) |
| 20–29 | 7 | 801.5 | 8.7 (4.2–18.3) |
| 30–39 | 14 | 967.1 | 14.5 (8.6–24.4) |
| 40–49 | 8 | 777.3 | 10.3 (5.1–20.6) |
| 50–59 | 6 | 682.5 | 8.8 (3.9–19.6) |
| 60–69 | 5 | 574.0 | 8.7 (3.6–20.9) |
| 70–79 | 1 | 253.8 | 9.9 (0.6–28.0) |
| 80–89 | 0 | 53.1 | 0 (0–69.0) |
| 90–99 | 0 | 14.6 | 0 (0–252.7) |
| Total | 45 | 4,531.0 | 9.9 (7.4–13.3) |

B. Incidence rates of melanoma in second-degree relatives:

<table>
<thead>
<tr>
<th>Age band</th>
<th>No. of melanoma case patients</th>
<th>No. of person years</th>
<th>Incidence rate/1,000 person years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10–19</td>
<td>1</td>
<td>875.8</td>
<td>1.1 (0.2–8.1)</td>
</tr>
<tr>
<td>20–29</td>
<td>6</td>
<td>1,588.9</td>
<td>8.3 (1.7–8.4)</td>
</tr>
<tr>
<td>30–39</td>
<td>2</td>
<td>1,551.4</td>
<td>1.3 (0.3–5.2)</td>
</tr>
<tr>
<td>40–49</td>
<td>2</td>
<td>838.6</td>
<td>2.4 (0.6–9.5)</td>
</tr>
<tr>
<td>50–59</td>
<td>0</td>
<td>267.4</td>
<td>0 (0–13.8)</td>
</tr>
<tr>
<td>60–69</td>
<td>0</td>
<td>112.3</td>
<td>0 (0–32.8)</td>
</tr>
<tr>
<td>70–79</td>
<td>0</td>
<td>38.2</td>
<td>0 (0–96.6)</td>
</tr>
<tr>
<td>80–89</td>
<td>0</td>
<td>5.0</td>
<td>0 (0–737.8)</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>5,280.2</td>
<td>2.1 (1.2–3.8)</td>
</tr>
</tbody>
</table>
years) compared with second-degree relatives was 5.1, which was considerably higher than anticipated on the basis of Mendelian inheritance (expected RR = 2). To a certain extent this can be explained by our finding that 72% of individuals that entered the study as second-degree relatives that were later diagnosed with melanoma, became a first-degree relative before their melanoma diagnosis. This implies that the majority of melanomas diagnosed in (initially) second-degree relatives were diagnosed after their parent or sibling became melanoma patient, and would not have been missed if only first-degree relatives would have been under surveillance. If transition of second-degree relatives to first-degree relatives was neglected, the overall proportion of second-degree relatives diagnosed with melanoma at age 80 years was estimated to be 20.8%, which is similar to the 17% (a priori) risk that would be expected on Mendelian inheritance (25% of the penetrance for melanoma of proven mutation carriers (67%; ref. 3).

The melanoma detection rate of second-degree relatives that were under surveillance at the LUMC dermatology clinic was considerably higher (8.5/1,000 person years) than the estimate for the second-degree relatives population as a whole (2.1/1,000 person years). It is likely that family members with larger number of (atypical) nevi, who have a higher probability of being a mutation carrier and a higher melanoma risk (18, 19), are more likely to participate in surveillance. However, we have no data on nevus phenotype to support this supposition. In addition, we expect that relatives with a suspicious lesion (i.e., possible melanoma) are more likely to participate in surveillance. This notion is supported by the fact that 25% of the melanomas in our study were detected in family members who presented at the clinic for the first time. Early diagnosis may have accounted for part of the higher melanoma detection rates in relatives that were under surveillance. This is supported by an earlier report that surveillance of these families was associated with lower tumor Breslow thickness (7).

The melanoma risk of second-degree relatives was calculated to be 12.9-fold that of the general population, which is considerably higher than the estimates for individuals with established risk factors such as >5 atypical naevi [relative risk (RR): 6.4] or with >100 melanocytic nevi (RR: 6.9; ref. 20).

On the basis of the incidence rates from our study, the number of patients needed to be screened annually to detect one melanoma (number needed to screen; NNS), was 101 in first and 476 in second-degree relatives. For second-degree relatives that participated in the LUMC surveillance program at the time of diagnosis, the NNS was 118. A recent population-based skin cancer screening intervention study in the German state of Schleswig-Holstein involving 360,288 screened, reported a NNS for malignant melanoma of 620 (21). Taking into consideration that this study involved considerably older subjects (mean age 50 years) that were screened only once, the yield of surveillance of second-degree relatives in our study was considerably higher.

Figure 1. Figure 1 represents the probability of second-degree relatives to belong to one of four states according to their age (12–80 years): 1second-degree relatives who have become first-degree relatives (but were not diagnosed with melanoma); 2second-degree relatives who have become first-degree relatives and were subsequently diagnosed with melanoma (as second-degree relative); 3second-degree relatives diagnosed with melanoma (as second-degree relative); 4second-degree relatives (who remain second-degree relative and were not diagnosed with melanoma).
The ultimate goal of melanoma surveillance and screening is to reduce morbidity and mortality. With the lack of evidence from randomized controlled studies, there is still considerable debate on this subject (22, 23). As there are considerable data that suggests screening for melanoma does save lives, offering surveillance to selected high-risk populations seems justified (8).

Retrospective follow-up studies like ours are at risk of several biases. We dealt with possible family selection bias by excluding probands from the analyses. Consistency of (retrospective and prospective) data could be confirmed in an additional analysis (Cox proportional hazard analysis with delayed entry, data not shown) as from the time families were included in the analysis, melanoma incidence rates were constant over time (a straight line fitting within the 95% confidence intervals) for both first- and second-degree relatives. This was also the case for the probability of second-degree relatives to become first-degree relatives. In an attempt to correct for selection bias of persons at increased risk of melanoma (as described earlier) relatives that had not been screened at the LUMC were included in the analysis.

Our study may have been prone to overdiagnosis and misclassification bias (24, 25). However, as all in situ melanomas and melanomas of proven mutation-negative family members have been revised at the event of an earlier study, we may have reduced misclassification to a minimum. At the same time, surveillance is likely to prevent melanomas as a result of the practice to excise changing and clinically suspicious nevi.

Taking these considerations into account, our results should be viewed with some reserve. It is our overall impression, however, that our data are sound given the fact that the overall cumulative melanoma incidence of second-degree relatives at age 80 years approximated the expected lifetime risk based on data from the literature (see above).

In conclusion, this study provides insights in the family dynamics of surveillance and estimates of melanoma incidence rates and relative risks of second-degree relatives from CDKN2A-mutated families that facilitate the discussion on the selection of relatives for surveillance. We believe our results provide justification for the surveillance of second-degree relatives from these very high-risk melanoma families. Further research is necessary to sort out whether these findings equally apply to families without (or other germline-) mutations in the high-penetrance melanoma susceptibility gene CDKN2A.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
Conception and design: J.I. van der Rhee, N. Kukutsch, W. Bergman
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J.I. van der Rhee, F.A. de Snoo, N.A. Gruis, H.F.A. Vasen, N. Kukutsch, W. Bergman
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.I. van der Rhee, S.E. Boonk, N.A. Gruis, N. Kukutsch
Study supervision: N. Kukutsch, W. Bergman

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References


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